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CHEMISTRY OF ELECTROPHILIC INTERMEDIATES IN THE SULFONATION PROCESS

BY

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Summary

Chemistry of Electrophilic Intermediates in the Sulfonation Process. The study is more specifically concerned with the reactions of aromatic sulfonic anhydrides. The study was carried out in order to gain more knowledge on the reactions and behaviour of aromatic sulfonic anhydrides, and the role they play in the formation of sulfones in the industrial sulfonation process. An introduction to industrial sulfonation as used in the detergent industry is included.

It has been proposed that sulfones are formed in the sulfonation process, by reaction of sulfonic anhydrides with alkylbenzene (starting material). An initial study of the reactions of *p*-toluenesulfonic anhydride with toluene using different catalysts was carried out, providing background knowledge for the more detailed studies that followed.

A number of competition reactions were completed, investigating the influence of substituents in a series of arenes on the relative rates of reaction of *p*-toluenesulfonic anhydride. Studies were carried out using nitromethane as solvent and $AlCl_3$ as catalyst. Included in the study is a review of the synthesis of diaryl sulfones, and the synthesis of a number of unsymmetrical sulfones.

A new route to di-tolyl sulfone was identified from *intra*molecular reaction of *p*-toluenesulfonic anhydride catalysed by $AlCl_3$. The relative rate of formation of sulfones via this route compared to Friedel-Crafts type sulfonylation reactions and was studied. The relative rates were found to be very low.

The synthesis of a series of aromatic sulfonic anhydrides was carried out using direct sulfonation with SO_3. The sulfonic anhydrides were then used to investigate the effect of substituents on the rates of reaction of substituted benzenesulfonic anhydrides

reacting with toluene. The reactions were carried out in nitromethane using $AlCl_3$ as the catalyst.

For My Family

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It is not possible to thank everyone who has helped me along the way, but I will at least attempt in the following few lines to thank some of the most important people.

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CHEMISTRY OF ELECTROPHILIC INTERMEDIATES IN THE SULFONATION PROCESS

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Abbreviations

ABS	Alkylbenzene sulfonate
AE	Alcohol ethoxylate
AES	Alcohol ether sulfate
AMU	Atomic mass unit
AS	Alcohol sulfate
BAB	Branched chain alkylbenzene
BABS	Branched chain alkylbenzene sulfonate
BCME	*Bis*(chloromethyl) ether
FFR	Falling Film Reactor
GC	Gas chromatography
HPLC	High performance liquid chromatography
IR	Infrared spectroscopy
LAB	Linear alkylbenzene
LAS	Linear alkylbenzene sulfonate
LC - MS	Liquid chromatography - mass spectrometry
MO	Molecular orbital
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
ODS	Octadecylsilane
PPA	Polyphosphoric acid
STTAC	Sulfur trioxide trimethylamine complex
TLC	Thin layer chromatography
TPB	Tetrapropylenebenzene
TPBS	Tetrapropylenebenzene sulfonate

Chapter One

Introduction to Industrial Sulfonation

1.1 Detergents and Surfactants

Surfactants or to give them their full name, surface active agents, are a class of compound which exhibit one or more of many possible types of surface activity. The surface activities that they can exhibit include foaming and emulsification. The result is that surfactants are used for polishing, waxing and cleaning. They can also be used as anti-static agents. Cleaning is the area of most interest, since surfactants that display cleaning properties fall into the category of detergents. More specifically detergents are compounds and formulations that display any kind of cleaning properties.

The world-wide use of surfactants in the early 1990s was estimated at 16 million tons per annum, of which less than half (approximately 7 million tons) is of petrochemical or partially synthetic origin. Soap was still the major type of surfactant used.[1]

Details for the manufacture of soap have been found on ancient tablets dating back some 5000 years. It was in the late 18th century following the development of the of the soda ash industry, utilising the Le Blanc process that soap became a major world product. Following each of the two world wars work towards finding alternatives to soaps really took off, due to shortages of fats and high quality suitable alkalies fuelling demand for research.

The development of alkylbenzenesulfonates (ABSs) as detergents can be traced back to 1923 when Adam discovered that it was possible to obtain water-soluble solutions of hexadecyl- and octadecyl- benzene derivatives following their sulfonation. The products were found to display soap-like properties.[2] In 1926 IG-Farbenindustrie (Hoechst) and Chemische Fabrik Pott, Pirna/Sachsen simultaneously discovered the excellent surface-active properties that long-chain ABSs exhibited. The first readily available household detergent based on synthetic surfactants was brought onto the market in 1932 under the name of FEWA (Feinwaschmittel). The product was produced from fatty alcohol sulfonate.[1] The shortage of raw materials after World War II led to further development of products based on more readily available starting materials.

The change of circumstances and development of the chemistry involved led to a large increase in the use of alkylbenzenes in the production of surfactants. The initial trend was towards tetrapropylenebenzene (TPB) as a feedstock, which upon sulfonation gives the tetrapropylenebenzene sulfonate (TPBS). This TPBS showed not only good surface activity, but also good thermal stability. The sulfonate was also easily crystallised enabling washing powders to be produced by the so-called hot spraying process, which allowed significant advances to be made in the industry.

There was a problem with TPBS that was recognised with time. It led to the appearance of large foam build-ups on rivers, in weirs and in locks. This was a particular problem in dry hot summers, when the foam became a common sight. The chemical industry recognised the problem was in the low biodegradability of branched alkylbenzenes (BAB) and branched alkylbenzene sulfonates (BABS). By 1965 legislation was in place in all major European and North American detergent producing countries governing the production of detergents and surfactants. The anionic surfactant content of the detergent had to be at least 80% biodegradable in a standard biological treatment plant in accordance with the predicted analytical method. Replacing the TPB (or BAB) with linear alkylbenzenes (LAB), and the branched chain alkylbenzene sulfonates (BABS) with linear alkylbenzene sulfonates (LAS) achieved this. The linear alkylbenzene sulfonates (LAS) are equally as effective surfactants as BABS, but are highly biodegradable.

Surfactants can be categorised into 4 main classes, cationic, anionic, non-ionic and zwitterionic types. This classification is based on the structure of the surfactant, and more specifically on the presence or lack of any charge types in the hydrophobic part of the molecule (Figure 1).

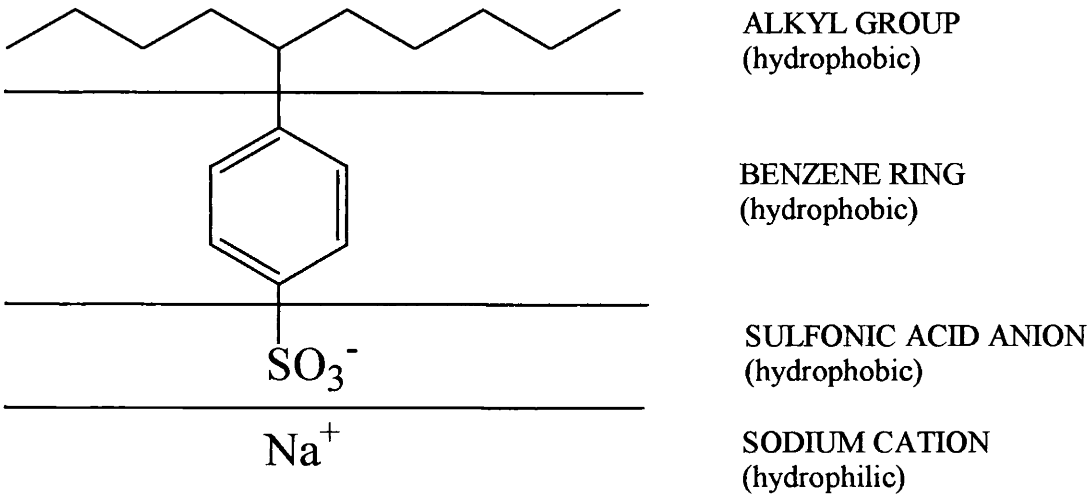


Figure 1

Anionic surfactants (into which category the different alkylbenzenesulfonic acid derivatives fall) are the largest type of manufactured synthetic surfactant. Production of these accounts for approximately 65% of the worldwide production of synthetic or partially synthetic surfactants. Approximately 85% of this figure is used in the manufacture of household detergents. More recent trends however have shown that although anionic surfactants still make up the major market share, the highest rate of growth in this industry is in the non-ionics. Although the non-ionics have the highest rate of growth, it is difficult to see with the favourable price/performance relationship, and good ecotoxicological properties how anionic surfactants will lose the dominant position they currently hold in the market.

Other surfactants are also used quite widely in the production of detergents, including the alcohol-based surfactants that are the main alternatives to LAS. These include alcohol sulfates (AS), alcohol ether sulfates (AES), and alcohol ethoxylates (AE). Many household detergents contain a complex blend containing at least 2 of the given surfactants, and in many cases more. The different types of surfactants each have unique characteristics and advantages.[1, 2]

1.2 LAS Manufacture

Despite the fact that LAS is produced in such large quantities, one of the major steps in the production process, the sulfonation of LAB to form LAS is still not fully understood. What is apparent is that the reactions involved in aromatic sulfonation are more complicated than the explanations offered in the majority of organic textbooks. A detailed explanation of the mechanism is included later in the chapter, however initially the industrial methodology of sulfonation will be considered.

In industrial sulfonation processes, several different reagents can be used to effect the sulfonation. These include SO_3/air from burning sulfur and converting the SO_2 formed into SO_3, SO_3/air from stabilised liquid SO_3, SO_3 stripped from 65% oleum with dried air, 20% oleum and chlorosulfonic acid. The reactions using diluted SO_3 in air are carried out in gas-liquid contact reactors with the liquid being the organic phase. Reactions using oleum and chlorosulfonic acid can be carried out using liquid-liquid contact reactors. It should be noted that both types of reaction are highly exothermic.

In recent years the trend has been towards SO_3/air from burning sulfur as the predominant sulfonating agent.[3] The main reasons for this are detailed below:

1. Versatility

   Many different kinds of organic feedstocks can be successfully converted to high quality sulfonates and sulfonate esters. These include alkylbenzenes, primary alcohols, alcohol ethers and alpha-olefins. Sulfuric acid and oleum are more limited in their applications due to the fact that they can only be used with alkylbenzene feedstocks.

2. Safety

   Liquid SO_3, 65% oleum, 20% oleum and concentrated sulfuric acid are dangerous chemicals to transport and handle. If solid sulfur is used as the starting material for the production of SO_3 then this is far less hazardous to transport.

   Stabilised liquid SO_3 is very difficult to handle and store, as it needs very precise temperature and pressure control. Stabilised liquid SO_3 also contains noxious stabilisers that after evaporation are difficult to handle and dispose of.

3. Costs

   Sulfur is a considerably cheaper starting material to form gaseous SO_3 than liquid SO_3. Oleum is also considerably more expensive than solid sulfur. As well as the raw material being cheaper, the handling, storage and transportation costs are all lower.

4. Availability

   Liquid SO_3, oleum and even concentrated sulfuric acid are not manufactured or available in many parts of the world. Solid sulfur is more readily available.

Figure 3 illustrates the overall SO_3/air sulfonation process as a block diagram.[3] The process is carried out under dry conditions to avoid the formation of sulfuric acid mist or vapour. This is achieved by drying the air used in the process by compressing it, and then cooling it to induce condensation. The water is then removed using a desiccant leaving the air dry.

Molten sulfur is pumped into the furnace where it is converted into SO_2 using an excess of oxygen from the dry air. The output SO_2/air temperature from the furnace is between 600 and 700°C. This is cooled to about 420°C before the SO_2 is then converted into SO_3 using V_2O_5 catalyst on a bed of silica. This is generally carried out over 4 packed silica beds, with cooling in between each due to the highly exothermic nature of the reaction.

Despite the drying of the air that is performed at the start of the overall process, a small amount of concentrated sulfuric acid/oleum mist is formed in the SO_2/SO_3 converter. This is removed as it can affect the product quality of the sulfonation step.

Falling film reactors are now commonly used for the sulfonation step, with the reaction between the SO_3 and organic feedstock being almost instantaneous. The organic acid product that is formed in the sulfonation is of higher viscosity than the organic feedstock. Undesired parallel and consecutive reactions are believed to take place, most notably at high temperatures. These side reactions result in the formation of waste side products that can be costly to remove from the product. Figure 3 illustrates a typical falling film reactor (FFR).

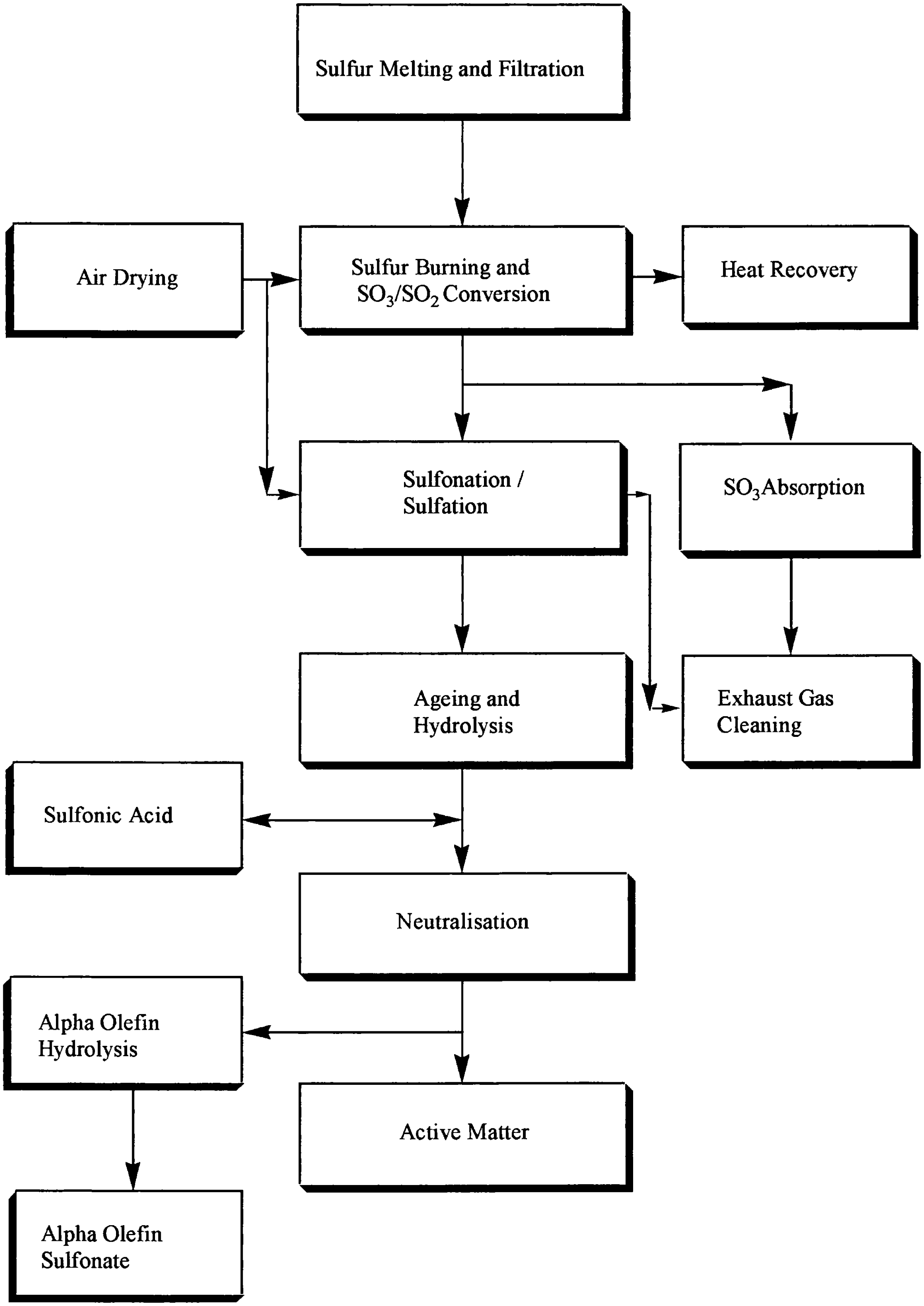


Figure 2 Sulfonation –sulfation plant using burning sulfur.

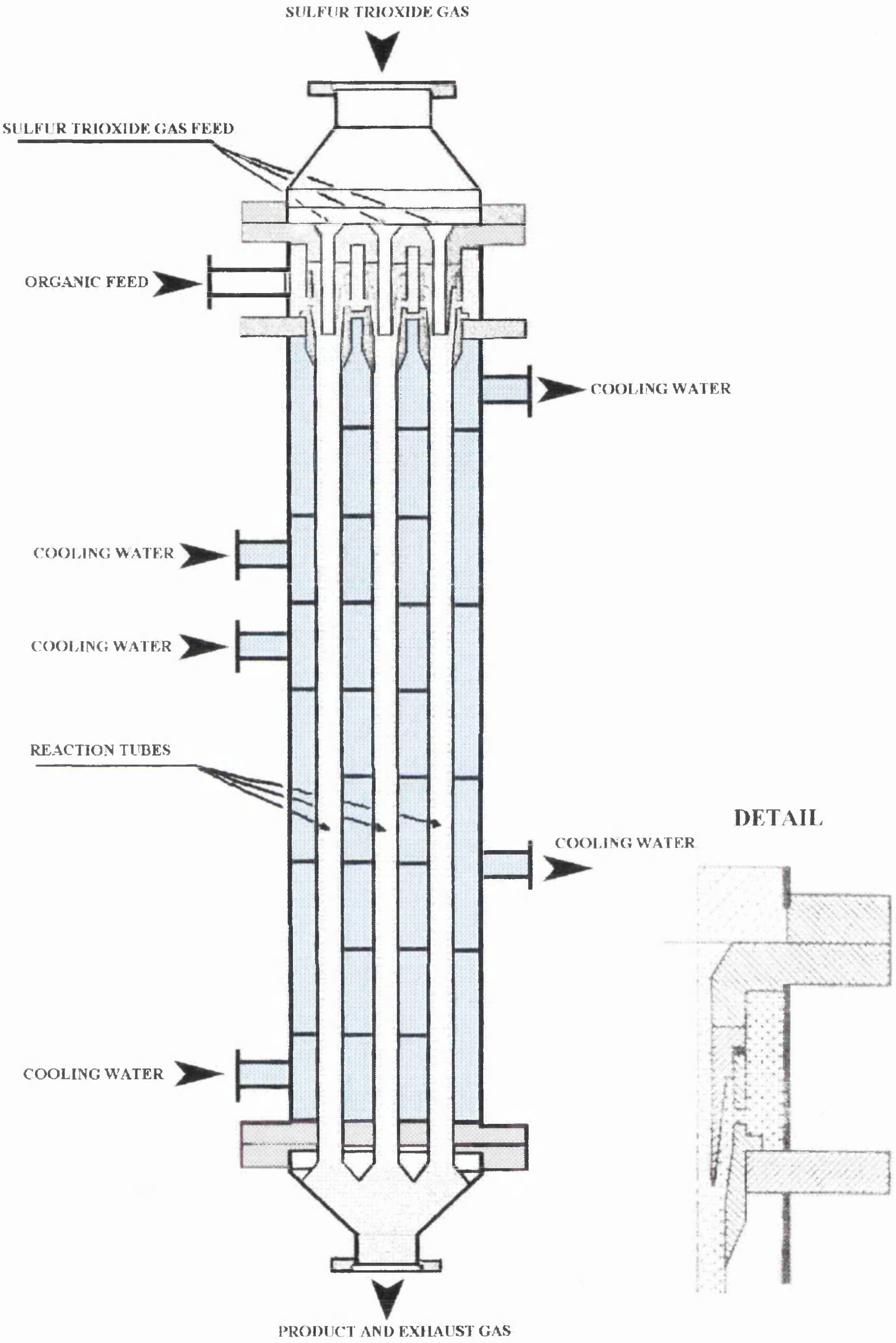

SULFUR TRIOXIDE GAS
SULFUR TRIOXIDE GAS FEED
ORGANIC FEED
COOLING WATER
COOLING WATER
COOLING WATER
REACTION TUBES
DETAIL
COOLING WATER
COOLING WATER
PRODUCT AND EXHAUST GAS

Figure 3

After the reactor, the SO_3 exhaust gas is separated from the acid product. The exhaust gas is then cleaned before emission to the atmosphere. The remaining organic matter and SO_3/H_2SO_4 droplets are removed using an electrostatic separator (ESP).

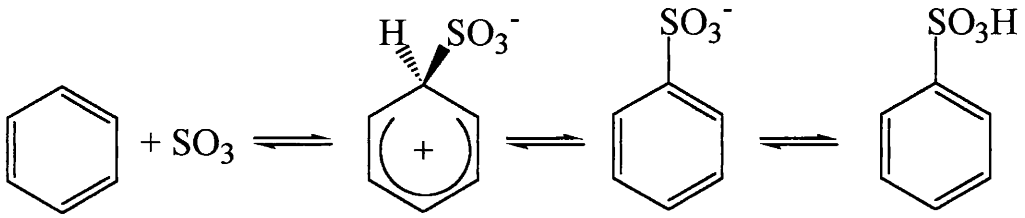
Depending on the organic feedstock used in the reaction, before neutralisation further reaction steps may be needed. In the case of LAB an 'ageing' step is required to convert intermediates formed in the sulfonation process into the desired sulfonic acids.[4] A further hydrolysis step is also required to convert the unwanted sulfonic anhydride side product into the sulfonic acid. This requires the addition of a small amount of water (approximately 1%). The neutralisation step is finally carried out using any one of a range of alkaline chemicals including sodium hydroxide, ammonia and sodium carbonate.

Although sulfonations of different feedstocks in industry are carried out predominantly using SO_3/air, there are still problems that need to be overcome relating to these reactions. These problems may seem relatively trivial, however when carried out on such a large scale they gain in significance. Most of the problems are associated with side reactions, leading to the formation of undesired products. These will be investigated on a molecular scale by considering the reaction mechanisms.

1.3 Aromatic Sulfonation

Sulfonation is an electrophilic substitution reaction, in which a "sulfo" group replaces a hydrogen atom bonded to a carbon centre. In the case of aromatic sulfonation the hydrogen atom that is substituted is bonded to one of the carbon atoms in the aromatic ring.[5]

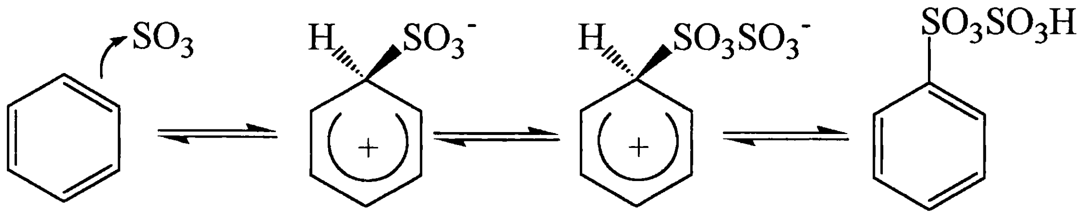
A range of reagents can be used as a source of the sulfo-group in sulfonation reactions. Many of these reagents including sulfuric acid, oleum and chlorosulfonic acid react in protic media with the reaction mechanism well defined and understood. SO_3 sulfonations in aprotic conditions are less well understood, and the reaction mechanism is more complicated than early predictions (Scheme 1).



Scheme 1

Evidence of this can be seen in the formation of side products. These include sulfonic anhydrides and di-aryl sulfones.

In all sulfonations it is believed that the sulfonating species is SO_3, whether it is combined with a nucleophile, part of a complex, or simply an individual entity.[6] SO_3 is now believed to exist as a monomer in the gaseous form, contrary to earlier suggestions. Early aromatic sulfonation studies found the reaction to be first order with respect to the aromatic substrate and second order with respect to sulfur trioxide. It was postulated that this could be due to the existence of sulfur trioxide as a dimer.[7,8,9] Another suggestion was that the sulfur trioxide was adding in two successive steps to form a pyrosulfonic acid intermediate (Scheme 2).



Scheme 2

Evidence from the Raman spectrum of SO_3 gas suggests that sulfur trioxide exists as a monomer. There is a possibility that some will be present as the cyclic trimer, but not as the dimer.[10] The evidence pointing towards a pyrosulfonic acid intermediate was further supported by Rueggeberg who thought it provided a valid explanation for the observed phenomena in the sulfonation of benzene with sulfur trioxide in sulfur trioxide solvent.[11] It was found that with the addition of a small quantity of acetic acid to the reaction mixture, the sulfone product yield decreased. This was seen as further evidence in favour of the mechanism that proceeds via the pyrosulfonic acid.

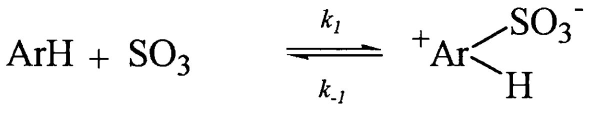
Christensen supported the argument in favour of a pyrosulfonic acid intermediate with work on the sulfonation of halobenzenes.[12] He found that the ratio of SO_3 consumed to ArH converted was equal to 0.5. He proposed that the formation of the pyrosulfonic acid accounted for these observations.

1.3.1 Primary sulfonation

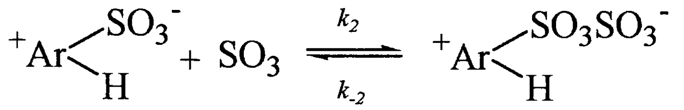
It is now believed that sulfonation involves a priming step, forming the initial sulfonic acid or sulfonic acid Wheland intermediate followed by the formation of a pyrosulfonic acid. This is then involved in the secondary sulfonation step forming the final sulfonic acid product along with the side products including sulfonic anhydrides and diaryl sulfones.

Cerfontain *et al.*[13, 14] used competition experiments to investigate the possibility of a primary kinetic isotope effect in the sulfonation of benzene with SO_3. In *inter*molecular competition reactions between C_6H_6 and C_6D_6 non-significant kinetic isotope effects were observed. These results included reactions carried out in the absence of solvent[13], in nitromethane and nitrobenzene.[14] *Intra*molecular competitive sulfonations using [1,3,5-$^2H_3$] benzene as the aromatic substrate, to form a mixture of $C_6H_3D_2SO_3K$ and $C_6H_2D_3SO_3K$ allowed a measure of the kinetic isotope effect that was not affected by outside factors, such as mixing and diffusion control. Again the kinetic isotope effect was found to be non-significant.

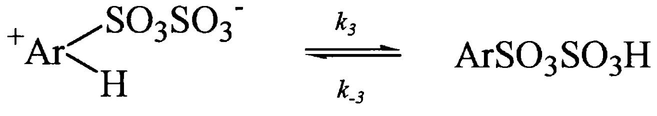
Cerfontain considered several series of reactions in complexing solvents, carried out by his own group and those of Hinshelwood and Christensen. It was found that the sulfonation of chlorobenzene, *p*-dichlorobenzene and iodobenzene in nitromethane were all first order with respect to the aromatic substrate and second order with respect to SO_3.[12, 15] Similar observations were made for reactions involving the sulfonation of chlorobenzene, benzene, bromobenzene and 4-nitrotoluene in nitrobenzene.[7, 8] In these reactions it appears that $k_{-1}.\ (k_{-2}+k_3) >> k_2.k_3[SO_3]$.



$$\mathrm{ArH} + \mathrm{SO_3} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^{+}\mathrm{Ar}{<}^{\mathrm{SO_3^-}}_{\mathrm{H}} \qquad (1)$$



$${}^{+}\mathrm{Ar}{<}^{\mathrm{SO_3^-}}_{\mathrm{H}} + \mathrm{SO_3} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} {}^{+}\mathrm{Ar}{<}^{\mathrm{SO_3SO_3^-}}_{\mathrm{H}} \qquad (2)$$



$${}^{+}\mathrm{Ar}{<}^{\mathrm{SO_3SO_3^-}}_{\mathrm{H}} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{ArSO_3SO_3H} \qquad (3)$$

Using the kinetic isotope effect data and the orders of reaction calculated from these reactions, Cerfontain proposed that the primary sulfonation and formation of the pyrosulfonic acid could be described as a three step process (Eqn.1-3).[15] This involves the formation of the σ-complex via the electrophilic attack on the aromatic ring by the electron deficient sulfur of the SO_3 molecule. The second step then involves the addition of a second SO_3 unit to the sulfonium anion of the σ-complex (Eqn.2), with the final step being the proton abstraction to form the neutral pyrosulfonic acid (Eqn.3). The fact that the kinetic isotope effects were found to be non-significant suggests that the rate determining step is not the third step of the reaction sequence, but more likely to be the second step (Eqn.2), in reactions in complexing solvents.

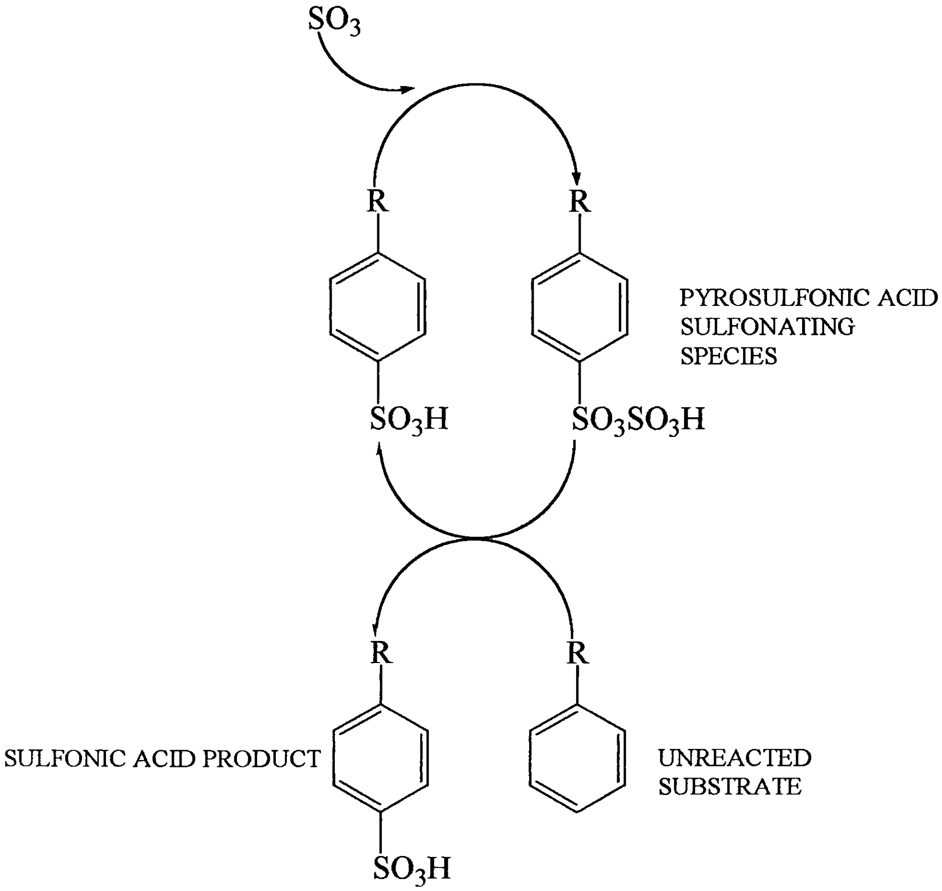
The sulfonation of *p*-dichlorobenzene in $CFCl_3$ lead to conversion of the substrate corresponding to only 50% of the initial amount of SO_3 added to the reaction.[15] The reaction in $CFCl_3$ is found to be first order with respect to both substrate and SO_3, implying $k_2.k_3[SO_3] >> k_{-1}.(k_{-2}+k_3)$, with the first step now being considered rate determining (Eqn.1). This contrasts with the case of reactions in complexing solvents.

It can be shown that irrespective of the source of sulfonating species, by application of steady state treatment of the two σ-complexes the following rate equation can be arrived at (Eqn.4).

$$\text{Rate}\,(ArS_2O_6H) = \frac{k_1.k_2.k_3}{k_{-1}.(k_{-2}+k_3) + k_2.k_3.[SO_3]}.[ArH].[SO_3]^2 \qquad (4)$$

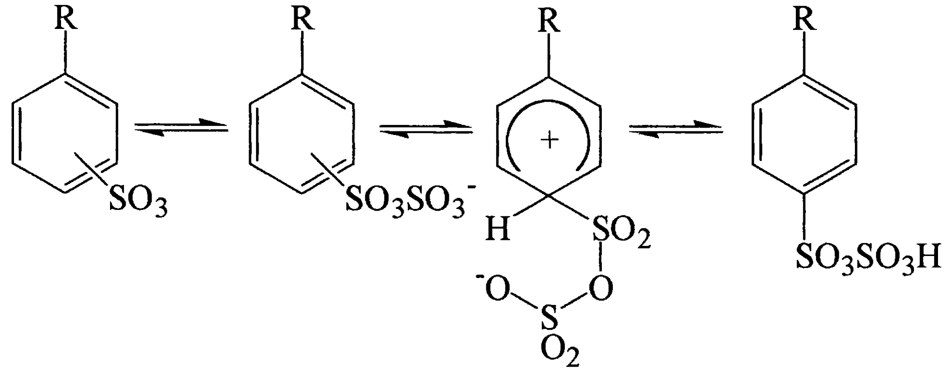
Roberts and Morley carried out MO calculations on the sulfonation of toluene, used as a model to simulate LAB, and found good agreement with the experimental work on the sulfonation of chlorobenzenes in non-complexing solvents.[16] They predicted that the first step would be rate determining (Eqn.1). In the same publication *ab initio* MO calculations were used to calculate reaction enthalpies for the reaction steps in the sulfonation process, and subsequently activation energies and half-lives were calculated for sulfonation. The calculated values in this work did not correspond to the values observed in FFRs for the industrial sulfonation of LAB. The half-life observed in the industrial reactors is less than 30 seconds, whereas the half-life calculated for toluene is approximately 3.5 years. This difference is surprising given the good agreement for other calculated values within the publication compared to experimental values. An example of this can be seen with the bond lengths calculated (-33.5 kcal mol^{-1}) and experimentally observed (-33.1 kcal mol^{-1}). Due to the fact that LAB is less reactive towards sulfonation than toluene, it is unlikely that the estimations of the activation energies are inaccurate enough to account for the large differences in half-life. [17, 18]

The explanation offered by Roberts and Morley is that the Wheland intermediate (σ-complex) does not play a major role in the overall reaction pathway. An alternative reaction pathway was proposed in which the Wheland intermediate involved in the main is that of the pyrosulfonate (Scheme 3).[16]



Scheme 3

Scheme 4 shows that an initial reaction takes place to form the first equivalent of the sulfonic acid. This is usually referred to as the *priming sequence*. This could take place via a π-complex originally proposed by Gold and Satchell, followed by the addition of a second molecule of SO_3 to form a pyro-π-complex (Scheme 3).[19] The alternate route is via the more conventional σ-bonded intermediate as shown (Scheme 1).[16]



Scheme 4

If the reaction pathway involving the formation of the π-complex is considered, it avoids the formation of a Wheland intermediate after the addition of a single equivalent of SO_3 to the aryl substrate. Enthalpy calculations for this proposed route lead to a predicted half-life of 5.5 seconds at 50°C. It should be noted that if the reaction to the pyrosulfonic acid proceeds via the π-pyrosulfonate Wheland intermediate, a six-membered transition state can be achieved with the oxygen anion and aromatic ring proton bond length of 1.67 Å being typical for a hydrogen bond (Figure 4).[16]

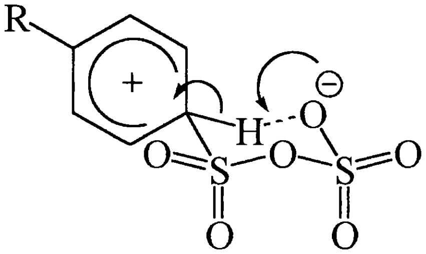


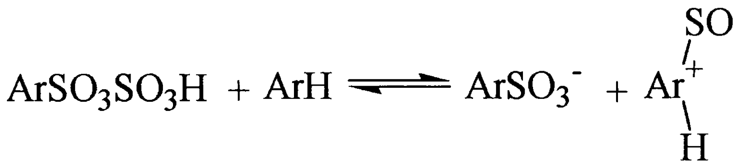
Figure 4

1.3.2 Secondary sulfonation

Following the formation of the pyrosulfonic acid, now agreed to be the main sulfonating species, a series of secondary sulfonations can then take place resulting in the formation of the final products including sulfonic acids, sulfonic anhydrides and sulfones.

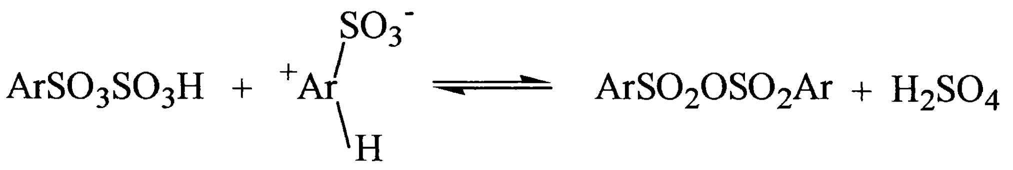
The secondary sulfonation could be as simple as the loss of SO_3 from the pyrosulfonic acid, leaving the sulfonic acid as the product and still obeying the second order kinetics observed for the SO_3. However it has previously been proposed that the pyrosulfonic acid could act as the sulfonating agent.[15]

Cerfontain *et al.* carried out a series of experiments looking into the product isomer ratio in sulfonation experiments, using toluene as the aryl substrate and sulfonating agents including sulfur trioxide, oleum and methanepyrosulfonic acid. In the reactions with toluene it was found that the percentage of the *ortho*-toluenesulfonic acid was higher when the reaction was analysed in the early stages, with the percentage decreasing in the later stages. Cerfontain attributed this observation to the fact that the sulfonation in the early stages of the reaction was performed by the sulfur trioxide as discussed earlier (Eqn.1) rather than by the toluenepyrosulfonic acid (Eqn.5).[20]



$$\mathrm{ArSO_3SO_3H} + \mathrm{ArH} \rightleftharpoons \mathrm{ArSO_3^-} + \overset{\mathrm{SO_3H}}{\underset{\mathrm{H}}{\mathrm{Ar}^+}} \qquad (5)$$

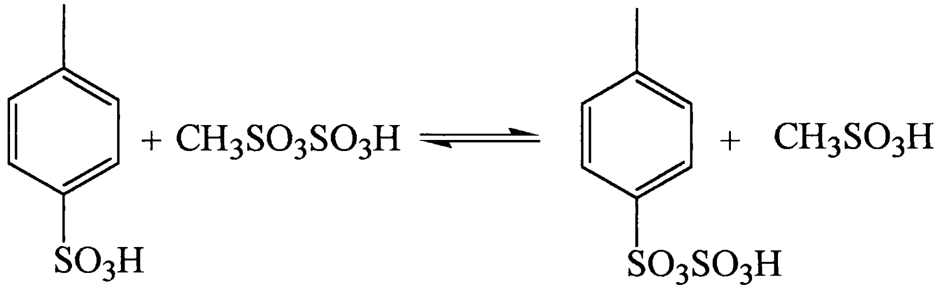
Cerfontain compared the results of the reactions with toluene to some that were carried out using *p*-chlorobenzene in $CFCl_3$. The final product for the reactions of *p*-chlorobenzene at low substrate concentrations is not the *p*-chlorobenzenesulfonic acid as expected. The major product was found to be the *p*-chlorobenzenesulfonic anhydride (Eqn.6).



$$\mathrm{ArSO_3SO_3H} + {}^{+}\mathrm{Ar}\overset{\mathrm{SO_3^-}}{\underset{\mathrm{H}}{}} \rightleftharpoons \mathrm{ArSO_2OSO_2Ar} + \mathrm{H_2SO_4} \qquad (6)$$

This is due to the fact that since *p*-chlorobenzene is less reactive than toluene towards electrophilic substitution, the pyrosulfonic acid will react preferentially with the sulfonic acid rather than the substrate (Eqn.6). This is the opposite of the case involving the more reactive toluene (Eqn.5). Cerfontain suggested that in the reaction with toluene, after approximately 5% conversion of substrate to sulfonic acid and subsequently the pyrosulfonic acid, the *p*-toluenepyrosulfonic acid becomes the major sulfonating species. Addition of further SO_3 to the reaction converts *p*-toluenesulfonic acid to *p*-toluenepyrosulfonic acid, subsequently sulfonating any unreacted starting material.[20]

The reaction in methanesulfonic acid solution (consisting of $CH_3SO_3SO_3H$, CH_3SO_3H, $(CH_3SO_2)_2O$ and H_2SO_4 in the ratio of 18.1:19.0:14.7:14.7 as described by Robinson and Silberberg [21]) gave results which were only very slightly influenced by the reaction duration and the percentage completion (or toluene conversion). It was observed that the percentage of *ortho* product for the sulfonation of toluene in methanesulfonic acid at high percentage conversion (0.11±0.01) was the same as that for the reaction of neat toluene with sulfur trioxide (0.11±0.01). It was suggested that this was further evidence for the fact that the pyrosulfonic acid generated *in situ* acts as a reactive secondary sulfonating species. It is believed that in the methanesulfonic acid solution the methanepyrosulfonic acid is the secondary sulfonating species, whereas at high substrate conversion the methanepyrosulfonic acid reacts with the toluenesulfonic acid to form the toluenepyrosulfonic acid (Eqn.7).[20]



(7)

If the mechanism for the pyrosulfonic acid being formed *in situ* is to be considered, the side reactions associated with its reaction need to be considered. These include the formation of sulfonic anhydrides and diaryl sulfones.[4]

1.4 Sulfonation side reactions

Despite the fact that sulfonation of LAB with sulfur trioxide is a very rapid reaction, that can for practical purposes can be considered diffusion controlled, the reaction does not reach completion in the FFR. The reaction requires a further ageing step lasting for about 30-40 min at 45-55°C.

Typically the LAS yield following reaction in the FFR is approximately 92%, which increases to approximately 98% as a result of the extra ageing step. The explanation offered by Roberts for this phenomena is that a side reaction is competing with the primary and secondary sulfonation reactions forming sulfonic anhydrides (Eqn.8).[4]

$$2ArH + 3SO_3 \longrightarrow ArSO_2OSO_2Ar + H_2SO_4 \qquad (8)$$

This agrees with the earlier observations of Cerfontain *et al.* who worked on a laboratory scale.[15] Roberts suggested that the reason behind the increase in percentage conversion during the ageing step was due to the fact that in combination, the LAS anhydride and the sulfuric acid act as a slow sulfonating agent converting the residual LAB to more LAS (Eqn.9).

$$\mathrm{ArH} + \mathrm{ArSO_2OSO_2Ar} + \mathrm{H_2SO_4} \longrightarrow 3\mathrm{ArSO_3H} \qquad (9)$$

Another side reaction that takes place is the formation of diaryl sulfones and sulfuric acid (Eqn.10). It appears that sulfone formation is not reversible, and it is this reaction that limits the overall conversion to LAB to LAS to less than 100%.

$$2\mathrm{ArH} + 2\mathrm{SO_3} \longrightarrow \mathrm{ArSO_2Ar} + \mathrm{H_2SO_4} \qquad (10)$$

The reaction forming diaryl sulfones is also responsible for producing a small amount of sulfuric acid, which at the moment is unavoidable. The sulfone levels in the final reaction product mixture are usually less than 1%, and are dependent on the ratio of sulfur trioxide to LAB supplied to the reactor.[4]

1.4.1 Mechanism of sulfonic anhydride formation

The mechanism for aromatic sulfonic anhydride formation was originally proposed by Christensen whilst working on the sulfonation of iodobenzene. He found that when working in a Lewis base solvent at high $[\mathrm{SO_3}]/[\mathrm{C_6H_5I}]$ ratios *p*-iodobenzenesulfonic anhydride precipitated out of solution as the main product. It was found that when the reactions were carried out at lower $[SO_3]/[C_6H_5I]$ ratios, the sulfonic anhydride formation was retarded. This appears to be due to a reaction (Eqn.11) similar to that involved in the ageing process (Eqn.9). It was predicted that the precipitated sulfonic anhydride was complexed to an equivalent of sulfuric acid, and this was further confirmed by the increased solubility of *p*-iodobenzenesulfonic anhydride that was observed with the addition of 0.3-0.6 M sulfuric acid to the nitromethane solution.[12]

$$(RSO_2)_2O.H_2SO_4 + RH \longrightarrow 3\,RSO_3H \qquad (11)$$

Roberts has more recently suggested that the formation of sulfonic anhydrides is due to the reaction between a sulfonic acid and a pyrosulfonic acid (Eqn.12).[4]

$$ArSO_3H + ArSO_3SO_3H \longrightarrow ArSO_2OSO_2Ar + H_2SO_4 \qquad (12)$$

This is a feasible pathway, and appears more likely than earlier suggestions by Cerfontain *et al.* that were reliant on two molecules of pyrosulfonic acid reacting together (Eqn.13).[15] This is possible, however the evidence presented thus far suggests that pyrosulfonic acids are very reactive and are not a long-lived species. This casts doubt as to whether the pyrosulfonic acids are able to build-up to sufficient concentrations for this type of reaction to take place on a large scale.

$$2\,RSO_3SO_3H \longrightarrow (RSO_2)_2O + H_2SO_4 + SO_3 \qquad (13)$$

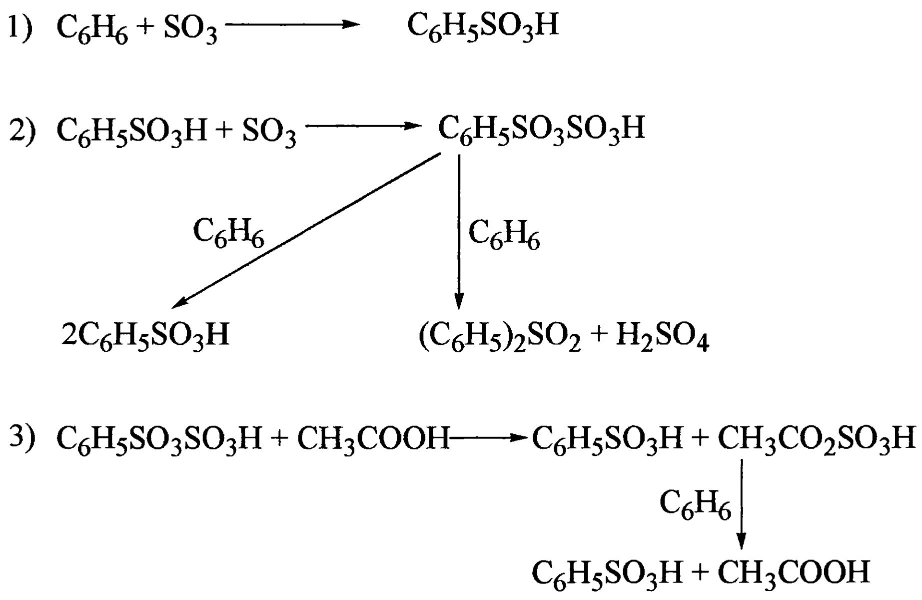
Cerfontain also found that the reaction of *p*-dichlorobenzene with sulfur trioxide gave a precipitate, analysis of which showed it to be a 1:1 complex of *p*-dichlorobenzenesulfonic anhydride with disulfuric acid (Eqn.14). It was also concluded in this paper that the 2,5-dichlorobenzenesulfonic acid was not formed via the sulfonic anhydride as the anhydride was found to be stable at room temperature in the presence of 37% sulfuric acid.[15]

$$2Cl_2C_6H_4 + 4SO_3 \longrightarrow (Cl_2C_6H_3SO_2)_2O{\cdot}H_2S_2O_7 \qquad (14)$$

1.4.2 Mechanism of sulfone formation

Sulfones are formed as relatively minor by-products in the aromatic sulfonation process, however due to their nature they are of interest. The sulfones formed in the sulfonation of LAB are insoluble waste product of limited use and appear to be the limiting factor in preventing a quantitative yield of LAS being produced.

Rueggeberg originally suggested that sulfones were formed in aromatic sulfonation reactions with benzene via a pyrosulfonic acid intermediate. This explanation accounts for the observation that the amount of sulfone formed in some aromatic sulfonation reactions was reduced on addition of small amounts of carboxylic acid to the reaction mixture (Scheme 5).[11]

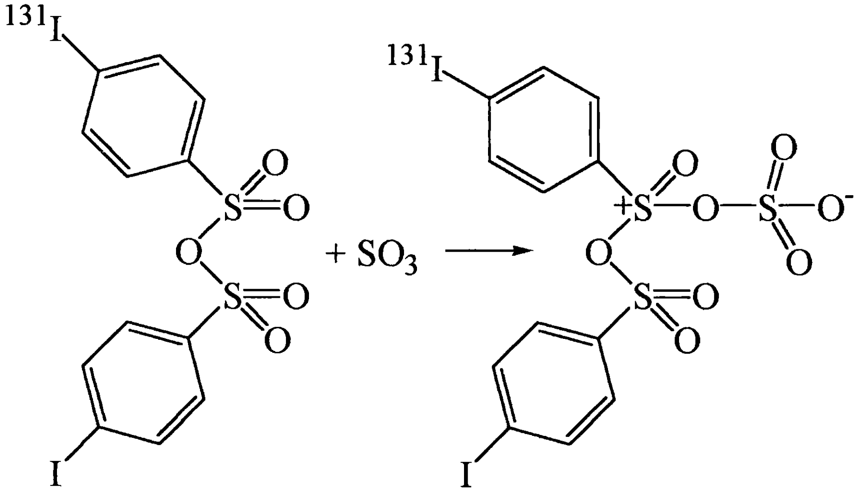


Scheme 5

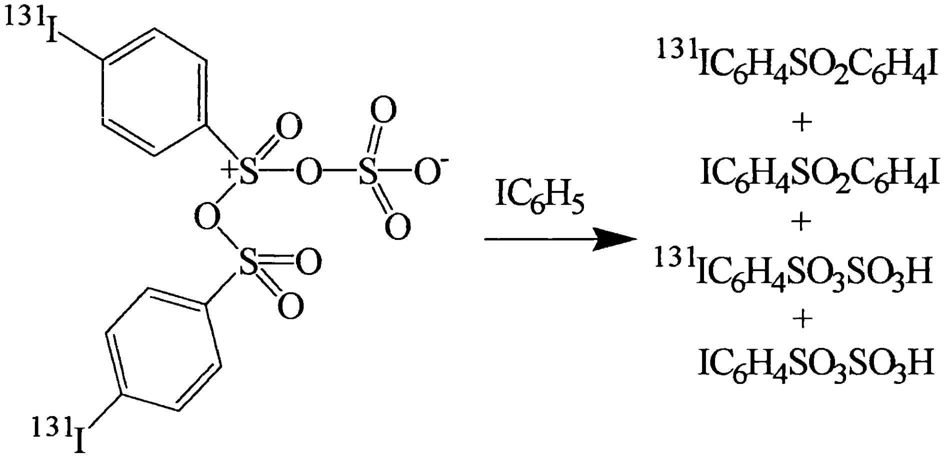
It was the formation of acetylsulfuric acid during the sulfonation of benzene in the presence of acetic acid (Step 3, Scheme 5), that led Rueggeberg to the conclusion that the pyrosulfonic intermediate was involved in the formation of diaryl sulfone (Step 2, Scheme 5). The acetylsulfuric acid that is formed can itself act as a sulfonating agent, and can go on to form further sulfonic acid. The acetylsulfonic acid however cannot go on to form the sulfonic anhydride.

Christensen carried out a limited series of reactions that supported the belief that the sulfone is produced via a pyrosulfonic acid intermediate. The series of reactions included the reaction of two equivalents of sulfonic acid with a single equivalent of SO_3, as well as the reactions of iodobenzene with sulfonic anhydride, and sulfur trioxide with sulfonic anhydride. In this series of reactions no sulfone was formed. It is concluded that in order for the sulfone formation to take place then all three components, the SO_3, sulfonic anhydride and the aryl substrate must be present. In these reactions it should be noted that of the ^{131}I-labelled iodobenzenesulfonic anhydride used, only approximately 5% of the sulfone recovered contained the isotopically labelled iodine.[12]

Christensen proposed that two different routes to the sulfone were in competition, both with the same initial step (Eqn.15). The second step of the reaction sequence had been expected to produce the sulfone product (Eqn.16). Christensen realised that if this had been the only route to the sulfone then the proportion of labelled product would be much higher than the observed 5%. The reason for the observations is nt fully understood, and indeed doubts over the accuracy of the work exist.



(15)



(16)

The first stage of this reaction sequence is the formation of a complex between the sulfonic anhydride and an equivalent of sulfur trioxide (Eqn.15). In this step the sulfur trioxide is acting as a Lewis acid, in a similar manner to that which is shown by aluminium chloride in Friedel-Crafts sulfonylation reactions (See Chapter Two).[12] Field [22] studied the aluminum chloride catalysed sulfonylation reaction between benzenesulfonic anhydride and benzene (Eqn.17). When optimised the reaction achieved a 99% yield, which supports Christensen's view that the sulfur trioxide could be acting as a Lewis acid catalyst.[12]

$$(C_6H_5SO_2)_2O + C_6H_6 \xrightarrow{AlCl_3} (C_6H_5)_2SO_2 + C_6H_5SO_3H.AlCl_3 \quad (17)$$

It is in the second step of the reaction where there is a difference between the aluminium chloride and the sulfur trioxide catalysed sulfonylation reactions. In the reaction catalysed by aluminum chloride it is only the sulfonium cation produced after the complex is formed that goes on to form the diaryl sulfones. When sulfur trioxide acts as the catalyst it is possible for both the cationic portion (Eqn.16) and the anionic portion (Eqn.18) to proceed to form diaryl sulfones. This is how both the ^{131}I-labelled iodobenzene and the standard iodobenzene both appear in sulfone products. The reaction with the anion initially forms the pyrosulfonic acid, which then goes on to form the sulfone product. If the sulfone was produced from only these two reactions then the distribution of the isotopically labelled iodine would be much more even than the 95:5 ratio that Christensen observed.

From the data available to date it would appear that the high sulfonating activity of sulfur trioxide far exceeds its activity as a Lewis acid. It has been proposed that the -SO_3 sulfonates the sulfonic acid to form the pyrosulfonic acid (Eqn. 19), which can then go on to form the diaryl sulfone (Eqn.18).

$$RSO_3SO_3H + RH \longrightarrow R_2SO_2 + H_2SO_4 \quad (18)$$

$$RSO_3H + SO_3 \longrightarrow RSO_3SO_3H \quad (19)$$

It is apparent that although the case using iodobenzene as the substrate is relatively well understood, in the overall sulfonation of LAB the formation of the sulfonic anhydride and diaryl sulfone are still not fully understood.

It is clear that there is scope for further research into aromatic sulfonation and sulfonylation. A better understanding of the side reactions involved in the sulfonation process will lead to improved efficiency and profitability, two areas of great concern to the chemical industry.

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Chapter Two

Friedel-Crafts sulfonylation reactions

2.1 Friedel-Crafts sulfonylation reactions

The reactions of sulfonic acid derivatives have been well documented over the years, with Friedel-Crafts type sulfonylation reactions receiving particular attention due to their wide range of applications in synthetic chemistry.[1] The Friedel-Crafts type sulfonylation reactions are an extension of the original electrophilic substitution reactions first reported in 1877 by Charles Friedel and James Crafts.[2] In the original work it was found that benzene rings could be alkylated by an alkyl halide in the presence of aluminum chloride (Eqn.1). This work was extended to include acylation, which is an important direct synthetic route to aryl ketones (Eqn.2).

$$\mathrm{ArH + RCl \xrightarrow{AlCl_3} ArR + HCl} \qquad (1)$$

$$\mathrm{ArH + RCOCl \xrightarrow{AlCl_3} ArCOR + HCl} \qquad (2)$$

Aromatic sulfonylation reactions are analogous to acylation reactions, and have been studied from both synthetic and kinetic points of view.[1(b)] A range of different sulfonylating agents can be employed in Friedel-Crafts type sulfonylation reactions, including sulfonyl halides (Eqn.3), sulfur monochloride (Eqn.4), sulfur dichloride (Eqn.5), thionyl chloride (Eqn.6) and sulfuryl chloride (Eqn.7).

$$RSO_2Cl + ArH \xrightarrow[\text{Fe powder}]{AlCl_3 \text{ or}} ArSO_2R + HCl \qquad (3)$$

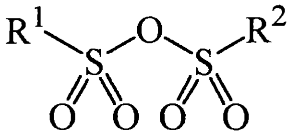
$$2ArH + S_2Cl_2 \xrightarrow[\text{Fe powder}]{AlCl_3 \text{ or}} ArSAr + 2HCl + S \qquad (4)$$

$$2ArH + SCl_2 \xrightarrow[\text{Fe powder}]{AlCl_3 \text{ or}} ArSAr + 2HCl \qquad (5)$$

$$2ArH + SOCl_2 \xrightarrow[\text{Fe powder}]{AlCl_3 \text{ or}} ArSOAr + 2HCl \qquad (6)$$

$$2ArH + SO_2Cl_2 \xrightarrow[\text{Fe powder}]{AlCl_3 \text{ or}} ArSO_2Ar + 2HCl \qquad (7)$$

Sulfonic anhydrides (Figure 1) can also be used as sulfonylating agents (Eqn.8) and show similar behaviour to sulfonyl chlorides, however previous similar studies relevant to this work have concentrated on the reactions of sulfonyl chlorides in the main.



R^1 = Alkyl, aryl

R^2 = Alkyl, aryl

Figure 1

$$RSO_2OSO_2R + ArH \xrightarrow{AlCl_3} RSO_2Ar + RSO_3H \qquad (8)$$

Friedel-Crafts acylation reactions can be catalysed by Lewis[2] and protic acids[3], zeolites[4] and other surface catalysts such as graphite[5]. Friedel Crafts sulfonylation reactions have also been catalysed by both Lewis[4] and protic acid[6] catalysts and zeolites[7]. In this introduction to sulfonylation, reactions involving sulfonyl chlorides and sulfonic anhydrides will be considered due to the similar reaction pathways involved.

2.2 Introduction to Lewis acid catalysis of sulfonylation reactions

Lewis acid catalysts for sulfonylation reactions have been studied extensively since the early work of Friedel and Crafts.[2] The early work concentrated on the reaction of sulfonyl halides with aromatic substrates in the presence of aluminum chloride. Other Lewis acid catalysts have been studied, however many of the mechanistic hypotheses are based on work originally carried out using aluminum chloride.

Lewis acids catalyse reactions by accepting an electron pair from a donor. In order for this to be possible, a Lewis acid by definition must have a vacant low energy orbital it can use for bonding. The range of Lewis acids is wider than that of protic acids. They include not only H^+, but also other positively charged ions such as Mg^{2+}. In a similar way compounds such as $AlCl_3$ and BF_3 have unfilled valence shells that can accept electrons, which by definition must be donated by a Lewis base.

In sulfonylation reactions Lewis acids catalyse the reactions by helping to form an electrophilic centre where reaction can then take place. The different catalysts will be considered in more detail below.

2.2.1 Introduction to $AlCl_3$ catalysis of sulfonylation reactions

In early sulfonylation studies Olivier investigated reactions carried out in an excess of various aromatic compounds as solvent with aluminum chloride as catalyst.[8] These included benzene, toluene, chlorobenzene, bromobenzene, and nitrobenzene. The work showed that the sulfone yield from the sulfonyl chloride was quantitative. These results led to a kinetic investigation of the reactions of *p*-bromobenzene sulfonyl chloride with benzene.[8] In this study it was observed that the rate of reaction was proportional to the amount of catalyst used, as long as no excess catalyst was used. A small excess of catalyst was shown to produce a large increase in the rate of reaction. Olivier found that in the absence of catalyst no reaction took place. The following order of reactivity of various aromatic benzene derivatives was observed: toluene > benzene > chlorobenzene > bromobenzene > nitrobenzene. The reaction involving nitrobenzene was found to give no sulfone product, which was attributed to the fact that the nitrobenzene was found to form a stable crystalline addition complex with aluminum chloride.

Olivier also investigated substituent effects on the rates of reaction of *para*-substituted benzenesulfonyl chlorides with excess benzene.[9] The catalyst used was again aluminum chloride. It was found that when electron-donating groups are present in the *para*-position the rates of reaction appear to be accelerated and when electron-withdrawing groups are present the rate of reaction decreased. The study found that *p*-methyl was rate enhancing compared to hydrogen, whereas the *p*-nitro group was found to show the strongest rate decreasing effect. The overall order of rate of reaction was *p*-methyl > hydrogen > *p*-iodo > *p*-bromo > *p*-chloro > *p*-nitro.[9] Olivier also looked at sulfonylation reactions using mixtures of different aromatic sulfonyl chlorides.[10]

Olivier also went on to study the reactions of a range of aromatic compounds with an excess of benzenesulfonyl chloride using aluminum chloride as catalyst.[11] He demonstrated that when one mole of aluminum chloride was used only one mole of the sulfonyl chloride reacted with the substrate. It was concluded that the aluminum chloride was acting as a reagent as well as a catalyst.

Brown *et al.* carried out the next major aromatic sulfonylation study in the 1950s.[12, 13, 14] Following work carried out on benzoylation reactions[15], Brown noticed that there was a marked contrast between their results and the observations made by Olivier on aromatic sulfonylation reactions.[8, 9, 10, 11] Brown believed that the benzoylation reactions and aromatic sulfonylation reactions were analogous and that the differences in their behaviour were worth investigating further. Jensen and Brown noticed that in the early studies of Olivier there was a lot of variation in the rate constants depending on the initial aluminum chloride concentration. Olivier even experienced rate constants varying in individual experiments.

Brown and Jensen believed that the use of an unreactive polar solvent such as nitrobenzene would help to avoid the difficulties experienced by Olivier.[13] Brown and Jensen therefore carried out benzoylation[16] and benzenesulfonylation[12] reactions in nitrobenzene. The observed reaction kinetics proved to be far more complicated than they had anticipated. In the case of the benzoylation reactions it was concluded that the complications were the result of peculiarities of the aluminum chloride-nitrobenzene solution, and not due to the Friedel-Crafts reactions themselves. A similar situation appears to exist in the case of the sulfonylation reaction. Arenesulfonic acids are far stronger than the corresponding benzoic acids, and therefore arenesulfonyl chlorides are less basic than benzoyl chlorides. It was deduced that when an arenesulfonyl chlorides and aluminum chloride are present in solution in nitrobenzene, the metal halide is predominantly associated with the nitrobenzene. As a result of these considerations Jensen and Brown proposed the following mechanism (Eqns.9-11).[13]

$$RSO_2Cl + AlCl_3 .\ O_2NC_6H_5 \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} RSO_2Cl.\ AlCl_3 + C_6H_5NO_2 \quad (9)$$

$$RSO_2Cl.\ AlCl_3 \underset{k'_{-2}}{\overset{k'_2}{\rightleftharpoons}} RSO_2^+ + AlCl_4^- \quad (10)$$

$$ArH + RSO_2^+ + AlCl_4^- \xrightarrow{k'_3} ArSO_2R.\ AlCl_3 + HCl \quad (11)$$

The mechanism can be summarised as follows: when highly reactive aromatics are involved in the reaction, the ionisation step is rate controlling (Eqn.10), and the rate of reaction is independent of the concentration and specific structure of the aromatic. This results in second order kinetics being observed (Eqn.12), with k_2 being equal to the product of k'_2 (for ionisation of the aluminum chloride-sulfonyl chloride complex) and the equilibrium constant for Equation 9.

$$\text{rate} = k_2[AlCl_3][ArSO_2Cl] \quad (12)$$

When less reactive aromatics are involved in the reaction then the third step of the sequence (Eqn.11), the reaction of the aromatic with the sulfonium cation, is rate determining. These reactions are third order (Eqn.13).

$$\text{rate} = k_3[\mathrm{AlCl_3}][\mathrm{ArH}][\mathrm{ArSO_2Cl}] \qquad (13)$$

The only shortfall in the work by Brown and Jensen was that the results outlined above provide no evidence for the nature of the aluminum chloride-sulfonyl chloride complex. The mechanism they outlined includes two forms of the complex (Eqn.10). In order to obtain a greater understanding of the reaction intermediates Jensen and Brown reinvestigated the kinetics of the reactions of toluene and benzene with excess benzenesulfonyl chloride. Olivier had earlier looked at these reactions and observed many complications, although he had established the overall reaction stoichiometry. It had been shown that one mole of aluminum chloride was utilised per mole of sulfone produced. The reaction involving toluene was shown to exhibit good second-order kinetics (Eqn.14).

$$\text{rate} = k_2[\mathrm{C_6H_5SO_2Cl.\ AlCl_3}][\mathrm{CH_3C_6H_5}] \qquad (14)$$

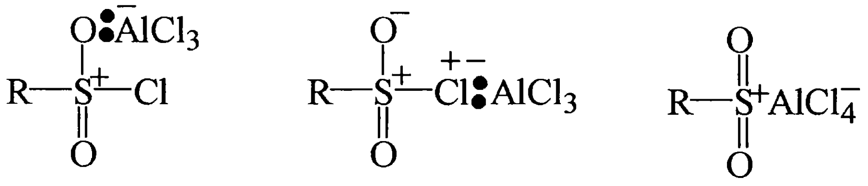
The toluene was believed to be reacting with either the undissociated ion pair ($C_6H_5SO_2^+AlCl_4^-$) or the non-ionised isomeric form of the addition compound ($C_6H_5SO_2Cl.AlCl_3$).

The benzenesulfonylation of chlorobenzene was found to be more complicated than had been expected, with the kinetics being three-halves-order (Eqn.15). The rate-determining step in the reaction appears to involve the reaction of the aromatic substrate with the dissociated benzenesulfonium cation.

$$\text{rate} = k_{3/2}[\mathrm{C_6H_5SO_2Cl.\ AlCl_3}]^{1/2}[\mathrm{C_6H_5Cl}] \qquad (15)$$

In the corresponding reaction with benzene the kinetics were observed to exhibit peculiarities, suggesting that the reaction could follow both of the two pathways simultaneously. A proportion of the benzene could react with the dissociated ions, and a proportion could react with the undissociated complex.

In his studies of sulfonylation using benzenesulfonyl chloride, Olivier found that benzenesulfonyl chloride and diphenyl sulfone formed complexes with aluminum chloride, however the exact structure of these complexes was not known. The degree of complexation was determined cryoscopically, with the weight of the addition complex being measured. In the rate equations the complex of the sulfonylating agent and aluminum chloride is represented as $C_6H_5SO_2Cl.AlCl_3$. The true representation could be one of three possibilities, as shown below (Figure 2). Of the three structures shown in Figure 2, structure (I) is more likely to exist in higher concentrations than structure (II) due to the fact that oxygen is more basic than chlorine towards aluminum chloride.



(I) (II) (III)

Figure 2

It should be noted that structure (III) could exist as either an associated ion pair or as separate ions.

Truce and Vriesen[17] reported the optimisation of the amount of aluminum chloride that is used to catalyse the methanesulfonylation of benzene. It was observed that in contrast to the arylsulfonylations reported by Olivier, an excess of aluminum chloride did not have a detrimental effect on the reaction yield. It was believed that this is due to the stabilising effect of the different resonance structures, as shown in Figure 3.

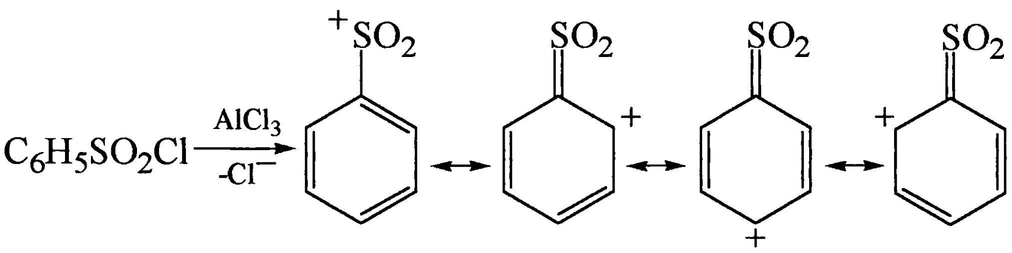


Figure 3

The work that has been covered so far concentrates on catalysis by aluminum chloride, and although a lot of the early sulfonylation studies did utilise aluminum chloride other Lewis acid catalysts have also been used.

2.2.2 Other Lewis acid catalysts in sulfonylation reactions

As well as carrying out work using aluminum chloride, Truce and Vriesen also conducted a study on the effectiveness of a range of Lewis acid catalysts in the sulfonylation of benzene with methanesulfonyl chloride.[17] Although a number of reactions were carried out using different amounts of catalyst, a comparison was made of the reactions utilising one equivalent of catalyst with respect to the sulfonyl chloride. Reactions utilising $AlBr_3$ and BF_3 were found to give no reaction, whilst other catalysts gave varying results as shown below (See Table 1).

Table 1. Methanesulfonylation of benzene with various Lewis acid catalysts	
Lewis Acid	Yield of methyl phenyl sulfone after 30 hours reaction (%)
$AlCl_3$	80
$FeCl_3$	70
$SbCl_5$	30
$AlBr_3$	-
BF_3	-

Jensen carried out work comparing the relative activities of different Lewis acid catalysts.[18] It was observed that $GaCl_3$ was more active than $AlCl_3$, which was in turn more active than $SnCl_4$. The ratios of rates were approximately 250:1:1/250. The relative activities have been attributed to more than one contributing factor. They can be partially assigned to the relative acid strengths of the catalysts. Another factor is that the order strongly depends on the relative basicity of oxygen and chlorine to $GaCl_3$ and $AlCl_3$. *i.e.*, the oxygen and chlorine atoms of the sulfonyl halide involved. This accounts for the unusual order of reactivity where $GaCl_3$ is more reactive than $AlCl_3$.[18]

The reaction between naphthalene and benzenesulfonyl chloride has been reported to only proceed at high temperatures, although it has been successfully catalysed by a number of different Lewis acid catalysts.[19] When the reaction is carried out in nitrobenzene, using $AlCl_3$, $SnCl_4$, or $FeCl_3$ as catalyst, the principle isomer obtained is β-naphthyl phenyl sulfone as shown in Table 2. This is in stark contrast to the reaction carried out in ethylene dichloride and catalysed by $AlCl_3$, in which the major product is the α substituted isomer (α:β = 80:20).

Table 2. % Sulfone Yield in the sulfonylation of naphthalene with benzenesulfonyl chloride in nitrobenzene

Catalyst	Temp. (°C)	% Yield of Sulfone	α:β
$AlCl_3$	140-160	86	7:93
$SnCl_4$	140-160	56	10:90
$FeCl_3$	140-160	73	17:83

The use of $ZnCl_2$ as a catalyst in preparation of phenyl naphthyl sulfones has also been reported, with excellent yields.[20]

2.3 Introduction to protic acid catalysis of sulfonylation reactions

Although Friedel-Crafts type sulfonylation reactions are usually catalysed by Lewis acids, a limited amount of work has been carried out using protic acids as catalysts. Effenberger and Huthmacher carried out a number of Friedel-Crafts type sulfonylation reactions catalysed by protic acids. [21] Both trifluoromethane sulfonic acid and phosphoric acid were used in reactions involving a number of aromatic sulfonyl chlorides. The arenes used in the reactions were restricted to benzene and *p*-xylene. In attempted reactions with both benzene and *p*-xylene, *p*-chlorobenzenesulfonyl chloride did not react when catalysed by trifluoromethane sulfonic acid. When 85% phosphoric acid was used as the catalyst, the reactions were more successful: Benzene giving a 31% yield and *p*-xylene giving a 70% yield of the corresponding diaryl sulfones. The reactions were then compared to similar reactions catalysed by the Lewis acids $AlCl_3$ and $FeCl_3$. Both sets of reactions catalysed by protic acids compared favourably with those catalysed by $AlCl_3$. When compared to the reactions catalysed by $FeCl_3$ the reaction with benzene was not as successful, although in the reaction of *p*-xylene the results were very close. [21]

In the same study benzenesulfonyl chloride was reacted with both benzene and *p*-xylene using the same range of catalysts. Although benzenesulfonyl chloride was shown to react with both arenes when catalysed by trifluoromethanesulfonic acid, the yields were not as high as when Lewis acid catalysts were used. The reactions of benzenesulfonyl chloride catalysed by phosphoric acid gave very low yields and the reaction between *p*-toluenesulfonyl chloride and both arenes, when catalysed by phosphoric acid, gave very low yields. However when trifluoromethanesulfonic acid was used as the catalyst, the corresponding sulfones were obtained in good yields (77-95%). The sulfonylation reactions carried out in this study by Effenberger were performed at 120°C over a period of 8 hours. [21]

Ono *et al.* successfully used trifluoromethanesulfonic acid to catalyse Friedel-Crafts reactions between methanesulfonic acid and deactivated benzene derivatives. [22] This work was carried out after it had been discovered that using traditional Lewis acid catalysts, an unsatisfactory complex reaction mixture was obtained. It was suggested that the reason for the improved yields of the desired methyl aryl sulfones, was partly due to the elimination of competing electrophilic reactions. It was found that in the reaction between methanesulfonyl chloride and 1,3-dichlorobenzene catalysed by $AlCl_3$ approximately 40% of the reaction yield was 1,2,5-trichlorobenzene. This was produced by a competing electrophilic chlorination reaction, with the non-ionic complex being the source of the chlorine atom (See Figure 4, Mechanism α).

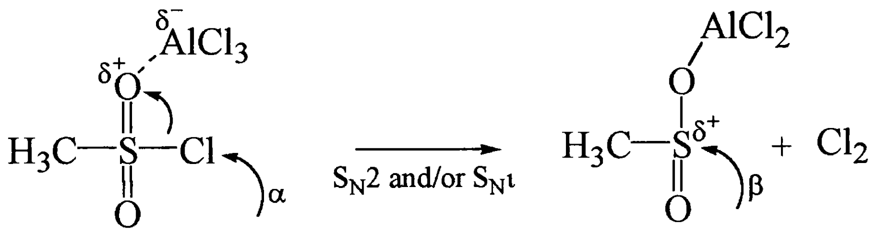


Figure 4

By avoiding the use of $AlCl_3$, the chlorination reaction was eliminated completely. [22] In the reactions, the methanesulfonic anhydride was formed *in situ*, from methanesulfonic acid and thionyl chloride, as described originally by Meyer.[23] The trifluoromethanesulfonic acid catalyst was added to the reaction following the formation of the anhydride. The quantity of catalyst used was 5% with respect to the methanesulfonic acid starting material.

The use of sulfonic acids as starting materials in sulfonylation reactions, catalysed by protic acids to form sulfones has been well documented.[24, 25, 26, 27, 28] Some of these reactions are Friedel-Crafts type reactions, however when the reaction involves the elimination of water the reactions are more commonly considered as condensation or dehydration reactions. These reactions will be covered in Chapter 3 in the discussion of synthesis of diaryl sulfones.

Solid protic acids and solid supported protic acids have been used to catalyse Friedel-Crafts type sulfonylation of aromatic substrates. In an investigation into cation exchanged zeolite β catalysis of the methanesulfonylation of arenes, Smith *et al.* initially compared a range of proton form zeolites as catalysts. It was found that the zeolite β offered the best *para*-selectivity (*o:m:p* = 37:11:53) and a good yield (79%).[7]

It can be see from the literature that a great deal of work has been carried out researching the reactions of aryl sulfonyl chlorides and also methanesulfonic anhydride, however the Friedel-Crafts type sulfonylation reactions involving the arylsulfonic anhydrides have not been investigated in such depth. In order to carry out such a study more knowledge of the reaction and the products was required.

2.4 Identification of sulfonylation products and reaction components

Before any analytical studies could be carried out on aromatic sulfonylation reactions, the reaction products had to be identified. Initial attempts were made to separate the reaction products using thin layer chromatography (TLC). In the reaction of *p*-toluenesulfonic anhydride with an excess of toluene, an initial sample, taken at t = 0 showed that no di-*p*-tolyl sulfone was present by co-elution. A sample then taken after 1 hour showed that a small trace of di-*p*-tolyl sulfone was present. Co-elution also demonstrated the presence of *p*-toluenesulfonic acid.

2.5 Analytical methodology for aromatic sulfonylation reactions

Once it was known that the sulfone was being formed, it was decided to develop a high performance liquid chromatography system to analyse the reaction. After several attempts to find a good analytical method, reverse phase chromatography was identified as the optimum technique to use to analyse the whole of the reaction mixture. This was achieved using an eluent composition of 70% methanol, 30% H_2O. The amount of sulfone present in the reaction mixture at any given time was measured using HPLC and an internal standard. An internal standard was required that could be added to the reaction mixture at the start of each reaction, without interfering in any way with it's progress. An inert or deactivated compound was therefore required, preferably of similar structure to some of the components in the reaction mixture. The choice of an appropriate internal standard also took into consideration the need for a strong chromophore, giving strong sharp peaks by UV absorption detection. Several different compounds were tested, for both strength of response and retention time. It was found that *o*-nitrotoluene displayed all the required characteristics, and did not elute at the same time as any of the products from the sulfonylation reactions that were to be studied (Figure 5).

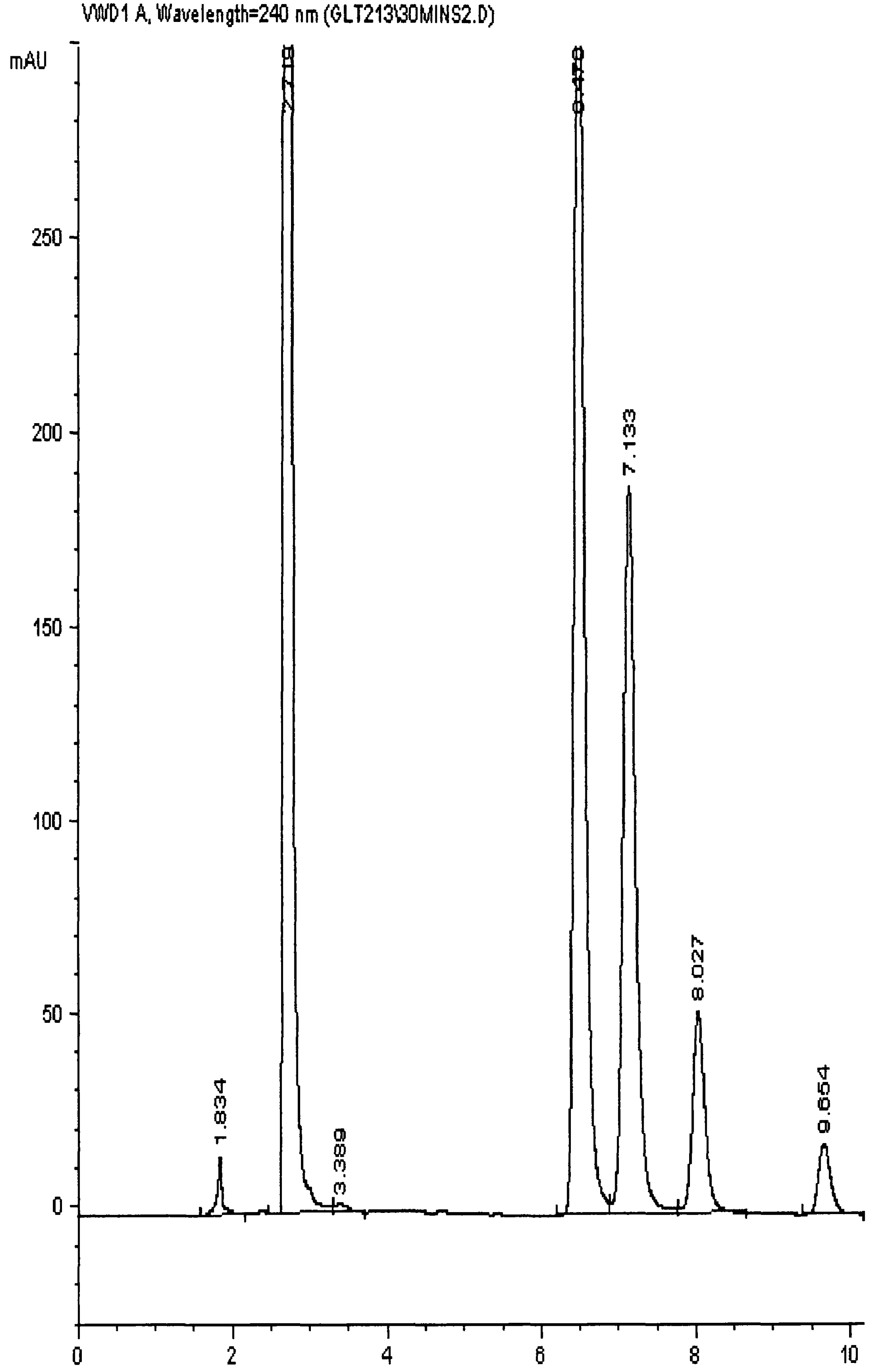

VWD1 A, Wavelength=240 nm (GLT213\30MINS2.D)
mAU
250
200
150
100
50
0
1.834
2.718
3.389
7.133
8.027
9.654
0
2
4
6
8
10

Figure 5

Attempts were made to react *o*-nitrotoluene with *p*-toluenesulfonic anhydride, using a number of different catalysts. Both Lewis and protic acid catalysts were used in an attempt to initiate a reaction with no success. This provided the confirmation that was required that *o*-nitrotoluene would be a suitable internal standard to use in sulfonylation reactions. Once an internal standard had been selected, a response factor for di-*p*-tolyl sulfone had to be calculated. The response factor is a detector response / unit concentration measurement, specific to a given compound. The response factor was then calculated for each of the products to be analysed using pure samples in order to obtain a calibration plot (Appendix 1).

The peaks due to the major components (Figure 5) were all initially identified by co-injection, and then later confirmed by Liquid Chromatography Mass Spectrometry (LCMS) as shown (See Figure 6).

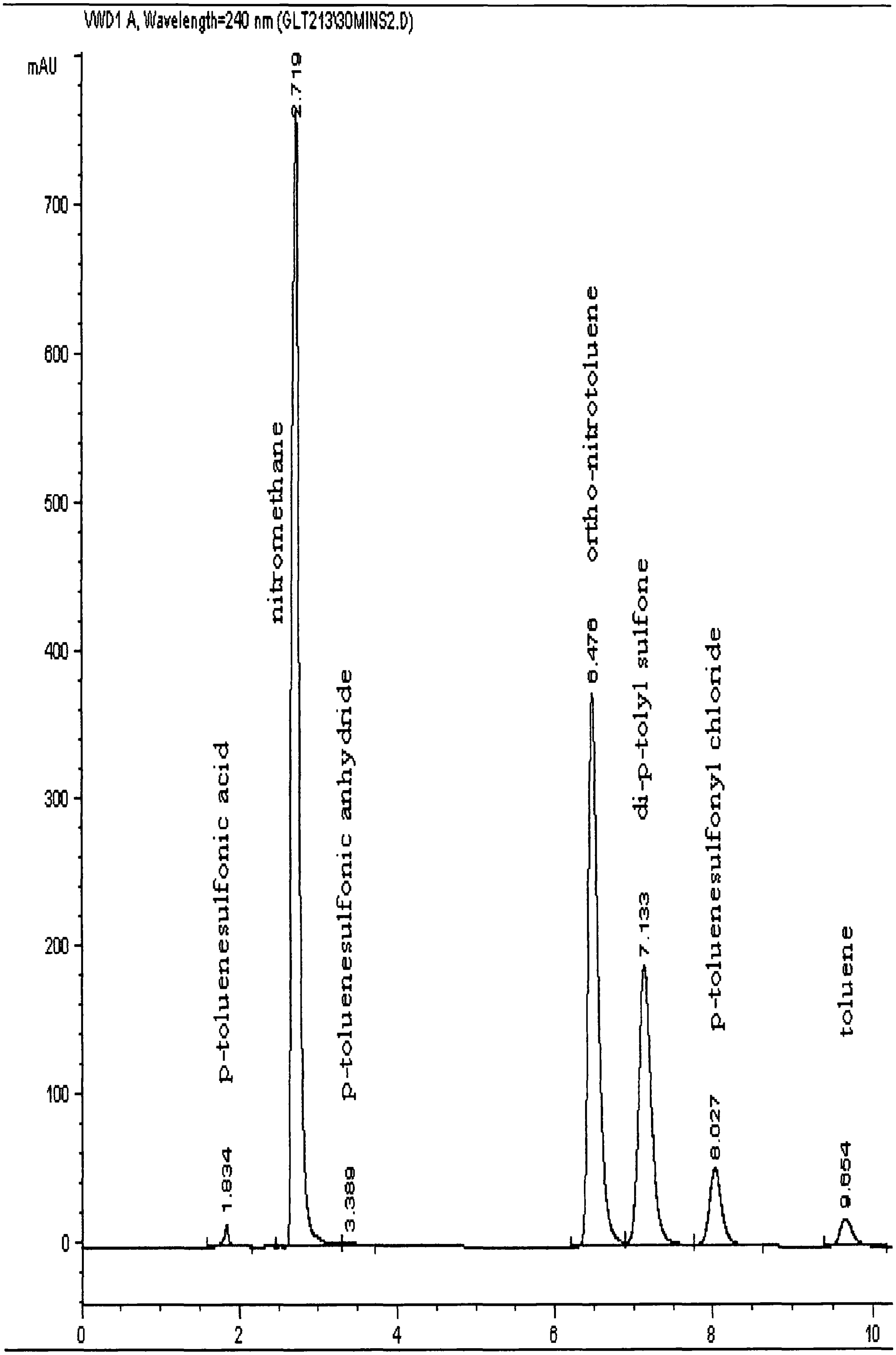

VWD1 A, Wavelength=240 nm (GLT213\30MINS2.D)
mAU
700
600
500
400
300
200
100
0
0
2
4
6
8
10
p-toluenesulfonic acid
1.834
nitromethane
2.719
p-toluenesulfonic anhydride
3.389
ortho-nitrotoluene
6.476
di-p-tolyl sulfone
7.133
p-toluenesulfonyl chloride
8.027
toluene
9.654

Figure 6

An initial study was carried out to test the reproducibility of the HPLC sampling technique. In homogenous reactions it was predicted that the dispersion of the components in the reaction mixture would be even at any given time. This was tested by taking several samples, all at the same time from a sulfonylation reaction believed to have reached completion. The results from this are shown below (See Table 3).

Table 3. Tests results from reproducibility study of HPLC analytical technique

Time (min)	% Sulfone Yield		
	Sample A	Sample B	Mean
90	82.62	82.48	82.55
130	82.35	82.71	82.53

It can be seen from the results in Table 3 that the technique is precise and reproducible. It was felt that this method of analysis would be well suited to the sulfonylation work being undertaken.

2.6 Autocatalytic reaction of *p*-toluenesulfonic anhydride with toluene

We first studied the reaction in toluene at reflux with no added catalyst. This reaction is based on a reaction carried out by Field.[29] The reaction was carried out at 150^0C using a large excess of toluene. The reaction was followed by HPLC, sampling every 10mins in the early stages of the reaction. In the later stages the reaction was sampled every 20mins.

When the yield of di-*p*-tolyl sulfone (%) was plotted against time (min), a sigmoid curve is seen (Figure 7). This reaction was shown to be autocatalytic and a rate constant was evaluated using a curve fitting procedure. The rate constant was found to be 2.02 $mol^{-1}dm^{3}min^{-1}$.

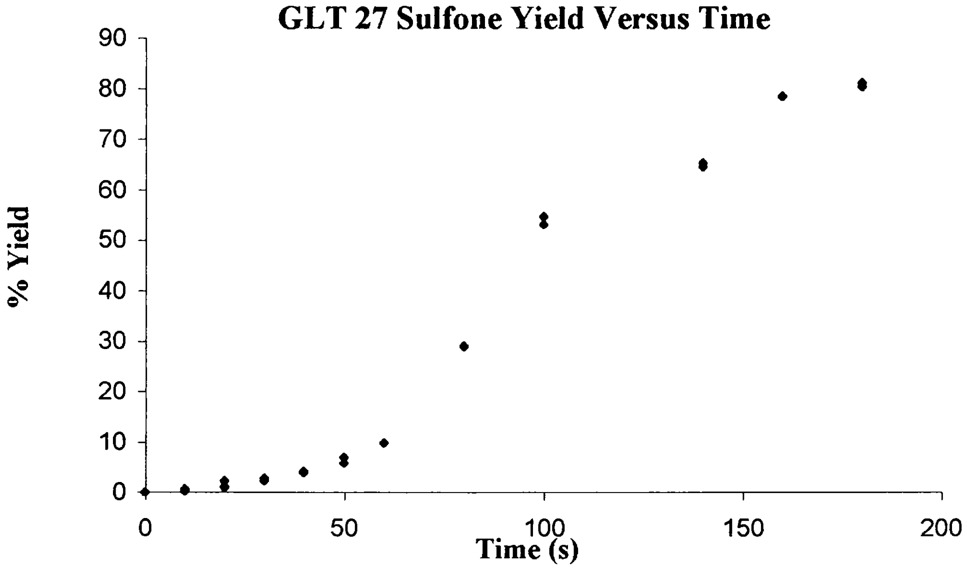


Figure 7

The order of the reaction was worked out using Jantel Scientific Table Curve 2D. Table Curve 2D is an automated computer package that has a built in memory of 3456 linear and non-linear equations. The 3456 equations can be broken down into subsets, including a subset of 58 different kinetic equations. The data is entered into the program in an X-Y table format. Table Curve then uses one of the curve fitting preferences to estimate the appropriate equation. The different fitting preferences available for non-linear curves include least mean squares, maximum number of iterations, the convergence precision and intercept options. As well as the 58 built in kinetic equations, a number of user-defined equations may also be added to the memory of the program, for any given automated fit. The data processing then orders the valid equations by the selected goodness of fit criteria.

In order to estimate the order of reaction for the uncatalysed reaction between toluene and *p*-toluenesulfonic anhydride, the preferred method used for estimating the rate equation was the r^2 method. Using the memory of 58 kinetic equations, a good match was not found.

Further research was carried out considering other reactions that had been previously studied that displayed similar characteristics. Examples of such kinetics are found in the acid-catalysed hydrolyses of various esters and similar compounds. Many biochemical processes also display the same behaviour, including the conversion of trypsinogen into trypsin. These reactions are second order autocatalytic reactions.

If the stoichiometric equation is A = B + …, and the rate expression:

$$-dA/dt = kAB$$

If A is the concentration of *p*-toluenesulfonic anhydride, A_0 the initial concentration of *p*-toluenesulfonic anhydride, B the concentration of *p*-toluenesulfonic acid and B_0 the initial concentration of *p*-toluenesulfonic acid it follows that in this type of reaction $A_0 - A = B - B_0$, therefore $B = A_0 + B_0 - A$. Integration by partial fractions (Appendix 2) yields

$$\frac{1}{A_0 + B_0} . \ln . \frac{A_0 B}{B_0 A} = kt$$

If rearranged to solve for B as a function of t, this yields

$$kt\,(A_0 + B_0) = \ln \frac{A_0B}{B_0A}$$

$$e^{kt\,(A_0 + B_0)} = \frac{A_0B}{B_0A}$$

$$e^{-kt\,(A_0 + B_0)} = \frac{B_0\,(A_0 + B_0 - B)}{A_0B}$$

$$\frac{A_0}{B_0} \,.\, e^{-kt\,(A_0 + B_0)} = \frac{A_0 + B_0}{B} \;\; -1$$

$$1 + \frac{A_0}{B_0} \,.\, e^{-kt\,(A_0 + B_0)} = \frac{A_0 + B_0}{B}$$

$$B = \frac{A_0 + B_0}{1 + (A_0 / B_0).e^{-k(A_0 + B_0)t}}$$

This gives the sigmoid curve typical of autocatalytic reactions. Having rearranged the reaction equation for B as a function of *t*, it was entered as a User Defined Function into Table Curve 2D (Appendix 3). Having entered the equation a very good fit was found. The data from the different fitting preferences is shown below (Table 4), and it can be seen that the r^2 value is very good match to the theoretical values.

Table 4. Second order autocatalytic reaction goodness of fit data	
Goodness of fit indicator	Value
r^2	0.9994506
DOF Adjusted r^2	0.9993721
Fit Standard Error	0.0002754
F-Statistic	2.001e+04

From the information obtained on the autocatalytic reaction it can be deduced that if the starting material did not contain a small trace of acid catalyst, then the reaction would not proceed at all.

Below is shown the kinetic plot of the uncatalysed reaction between toluene and *p*-toluenesulfonic anhydride (Figure 8). The black curve is the theoretical reaction profile curve, with the 99% confidence limits shown in red.

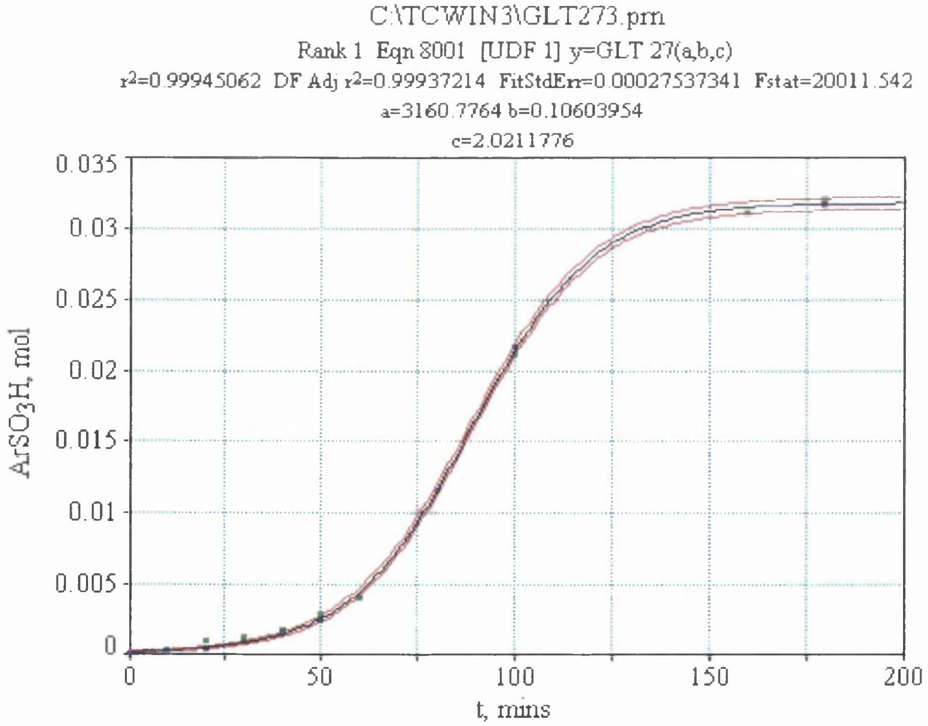


Figure 8

2.7 $AlCl_3$ catalysed reactions of *p*-toluenesulfonic anhydride with excess toluene

The reaction between *p*-toluenesulfonic anhydride and excess toluene was investigated in the presence of aluminum chloride catalyst. The reaction was originally studied by Field, who found that an almost quantitative yield could be achieved based on the amount of anhydride starting material.[29] Field compared his own work using various sulfonic anhydrides to the previous work of Beckurts and Otto who had studied the Friedel-Crafts reaction of aromatic sulfonyl chlorides with aromatic hydrocarbons. The Friedel-Crafts reaction of benzenesulfonyl chloride with benzene and 1 mole equivalent of aluminum chloride was reported to give diphenyl sulfone in 82% yield.[30] The same reaction when repeated by Field was found to give only a 70% yield of sulfone, however the product was believed to be of greater purity.[29] When benzenesulfonic anhydride was used in the sulfonylation reaction, then a 99% yield of diphenyl sulfone was recorded.

In this study we conducted analogous work using *p*-toluenesulfonic anhydride. Beckurts and Otto reported the reaction of toluene with *p*-toluenesulfonyl chloride to form di-*p*-tolyl sulfone in 87% yield when catalysed with aluminum chloride.[30]

The reaction between *p*-toluenesulfonic anhydride and toluene catalysed by aluminum chloride was carried out in this study. The reactions were carried out at room temperature using varying amounts of aluminum chloride catalyst. The maximum yield of di-*p*-tolyl sulfone achieved in the reactions was 83%. This was achieved when just over 2 mole equivalents of catalyst were used to catalyse the reaction. The final yield of di-*p*-tolyl sulfone achieved in each case is shown below (See Table 5).

Table 5. Reaction of *p*-toluenesulfonic anhydride with toluene in the presence of varying quantities of $AlCl_3$ (292K).

Mol. Eq. of $AlCl_3$	Sulfone Yield (%)
0.10	4
0.51	40
1.0	53
2.2	83
3	83

The reactions were found to be very rapid, complete in approximately 2 minutes. The reaction profiles can be seen below in Figure 9 and Figure 10. Figure 9 shows a typical individual reaction profile. It can be seen that the reaction is very rapid and that the sulfone product is stable over time. Figure 10 shows a comparison between the different quantities of $AlCl_3$ used as a catalyst for the series of reactions. All the reactions are rapid, with only the final yield apparently affected by the amount of catalyst used.

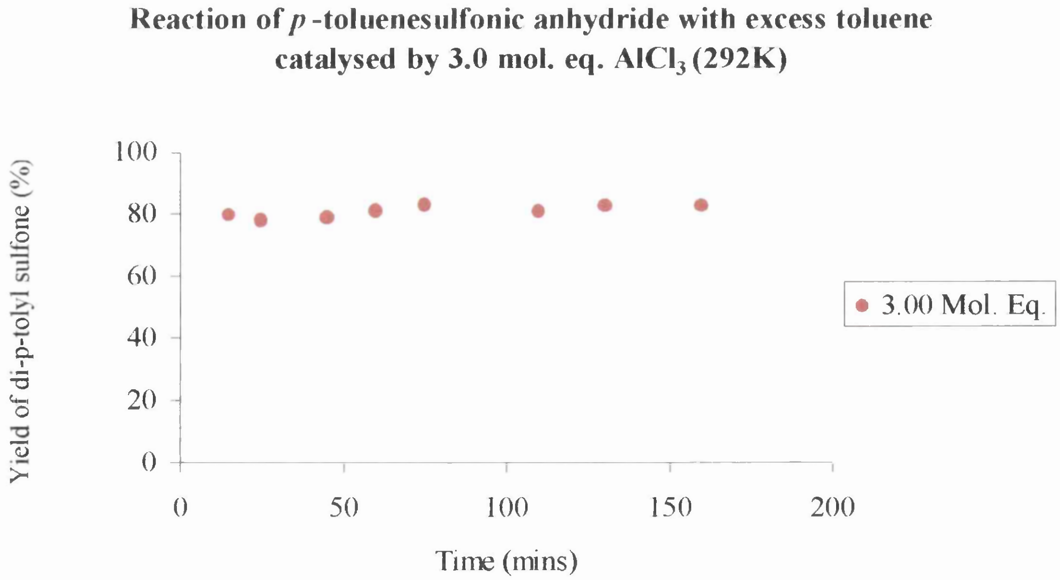
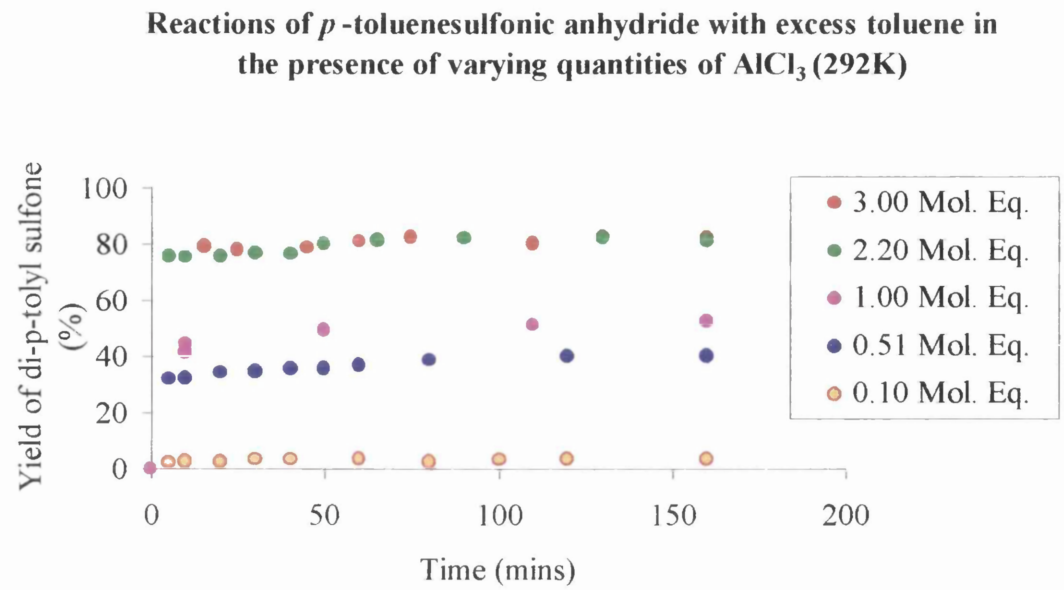


Figure 9



Reactions of *p*-toluenesulfonic anhydride with excess toluene in the presence of varying quantities of $AlCl_3$ (292K)

Figure 10

Although a maximum sulfone yield of only 83% was measured, no residual sulfonic anhydride was detected. It is believed that the residual sulfonic anhydride is consumed in a competing reaction such as the hydrolysis to form the sulfonic acid (Equation 16).

$$(CH_3C_6H_4SO_2)_2O + H_2O \longrightarrow 2\,CH_3C_6H_4SO_3H \qquad (16)$$

In an attempt to improve the yield of di-*p*-tolyl sulfone, similar reactions were carried out using nitromethane as solvent.

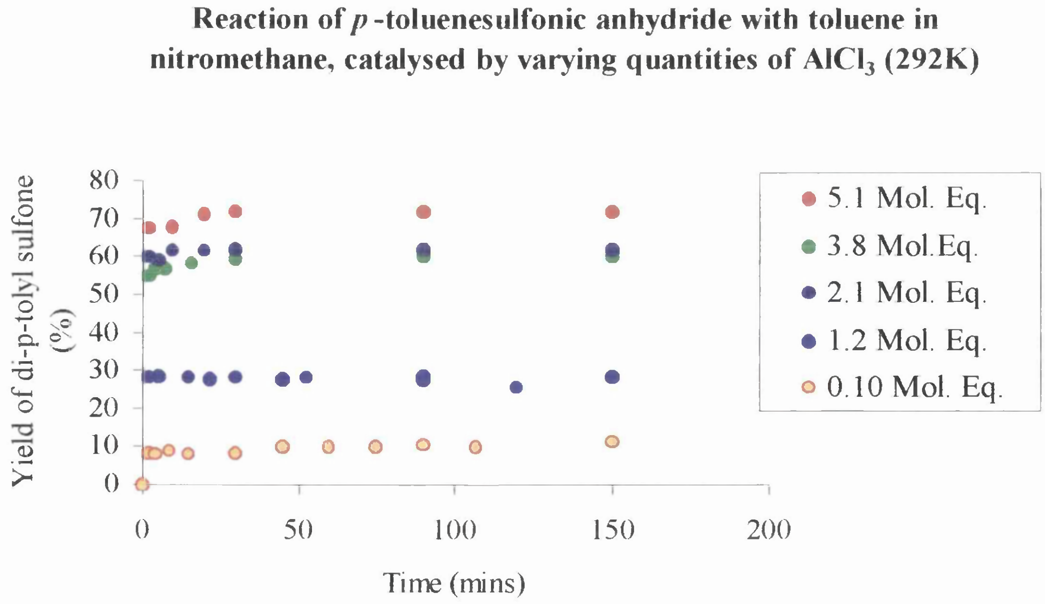
2.8 $AlCl_3$ catalysed reactions of *p*-toluenesulfonic anhydride with toluene in nitromethane

The reaction of the sulfonic anhydride with excess toluene in nitromethane was investigated. All the reactions were carried out at room temperature unless otherwise stated. The reactions were conducted in an inert atmosphere of dry nitrogen and followed for up to 3 hours, by taking aliquots and quenching using ethanol. The resulting samples were then analysed by reverse phase HPLC.

The reactions carried out in nitromethane (Figure 11) behaved in a similar manner to those previously carried out in toluene (Figure 10). The reactions were rapid, although the maximum yield of sulfone obtained was only 72%.

In an attempt to increase the yield of sulfone, the aluminum chloride used in the reaction was resublimed and used without being exposed to air. This would remove any aluminum oxide present in the chloride, increasing the level of purity, and thus efficiency as a catalyst. In the early reactions the aluminum chloride used was taken from a new supply of 99% purity from Lancaster. The resublimation was carried out using a drying pistol, and gave a product with a deep yellow colour. However, the use of freshly sublimed $AlCl_3$ did not increase the yield of sulfone significantly (75%).

As in the previous series of experiments, the maximum yield of sulfone was achieved when 2 equivalents of $AlCl_3$ were employed.



Reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane, catalysed by varying quantities of $AlCl_3$ (292K)

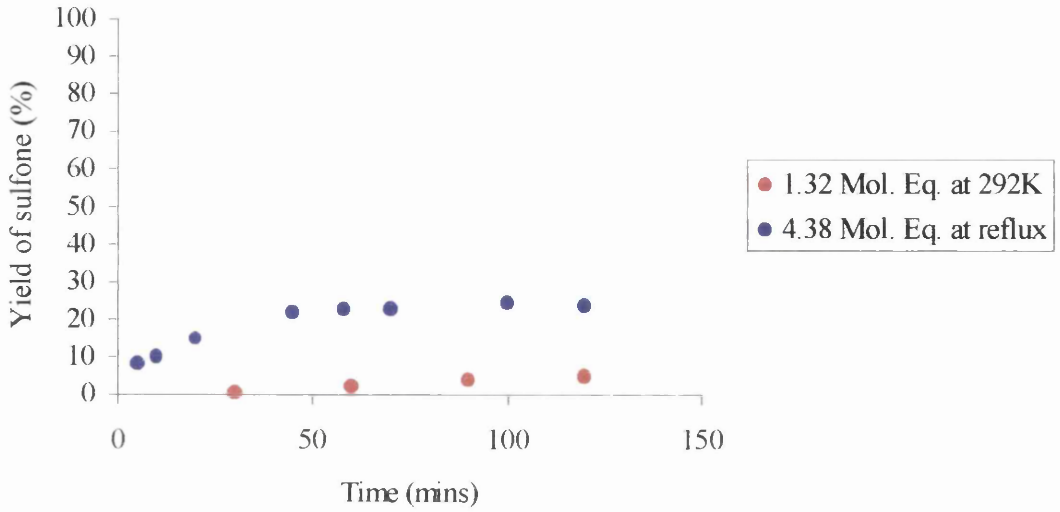
Figure 11

2.9 Other Lewis acid catalysed reactions *p*-toluenesulfonic anhydride with toluene in nitromethane

For comparison purposes a series of reactions using other catalysts were carried out. The first series of catalysts investigated were other Lewis acid catalysts. All of these reactions were carried out using excess toluene, in nitromethane, at room temperature, unless otherwise stated. As with the reactions involving $AlCl_3$, the reactions were conducted in an inert nitrogen atmosphere and were followed for up to three hours by taking aliquots and quenching them with ethanol. The resulting samples were then analysed by reverse phase HPLC using a C_{18} ODS II column with 70:30 methanol/water as eluent, and using *o*-nitrotoluene as internal standard.

The first of the Lewis acid catalysts investigated was $ZnCl_2$. Initially the reaction was carried out at room temperature using 1.38 mole equivalents of freshly fused $ZnCl_2$ with respect to the anhydride starting material. In contrast to the earlier literature the performance of the $ZnCl_2$ catalyst was poor, possibly due to the fact that $ZnCl_2$ only partially dissolved during the reaction. Figure 12 shows that the reaction was not as rapid as the reactions involving $AlCl_3$ and only a maximum sulfone yield of 29% was reached.

The reaction was repeated under reflux conditions using 4.38 mole equivalents of $ZnCl_2$. The reaction was followed over a period of 100 minutes, after which time the HPLC analysis showed that there was no anhydride remaining in the reaction mixture. The yield was again disappointing, reaching a stable maximum yield of 22% after 50 minutes.



Reaction between toluene and *p*-toluenesulfonic anydride in nitromethane, catalysed by different quantities of $ZnCl_2$

Figure 12

Other Lewis acid catalysts investigated included $SnCl_4$ and $TiCl_4$. Limited studies using $SnCl_4$ have been reported, but it was decided to carry out our own experiments for purposes of comparison.[18, 19]

The reactions were carried out under the same conditions as those in nitromethane using $AlCl_3$. The final yields of di-*p*-tolyl sulfone were not as high as with $AlCl_3$ and the reactions appear to display different characteristics. In the reactions with $AlCl_3$ the final yield of sulfone was dependent on the amount of catalyst used in each reaction. In the reactions catalysed by $SnCl_4$ (Figure 13) and $TiCl_4$ (Figure 14), the rate of reaction appears to depend on the amount of catalyst used, however the final yield in both cases is consistent (63% and 65% respectively) and does not depend on the amount of catalyst used (See Table 6).

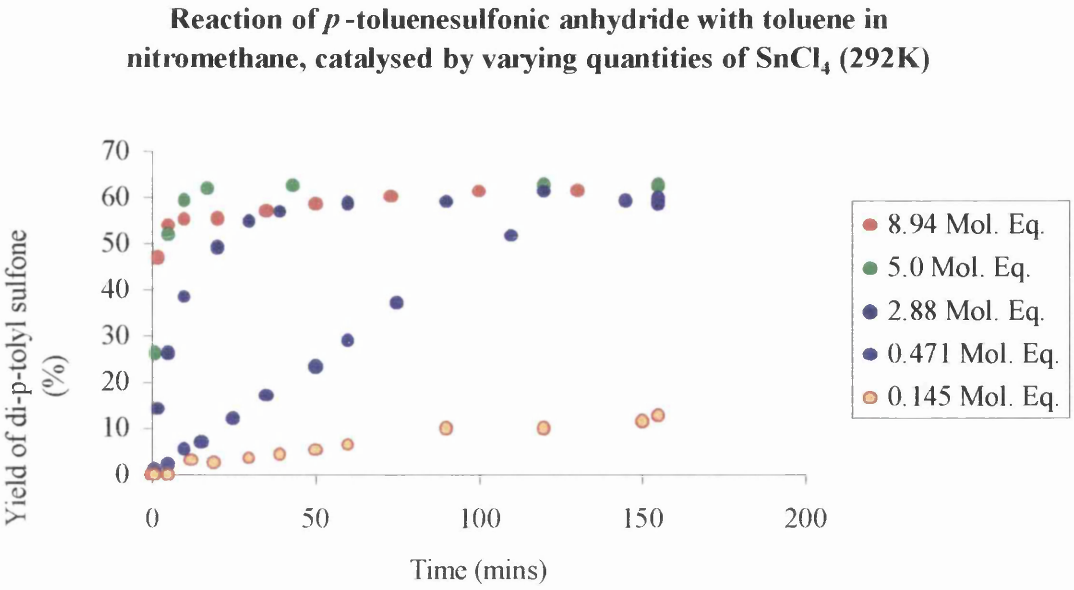


Figure 13

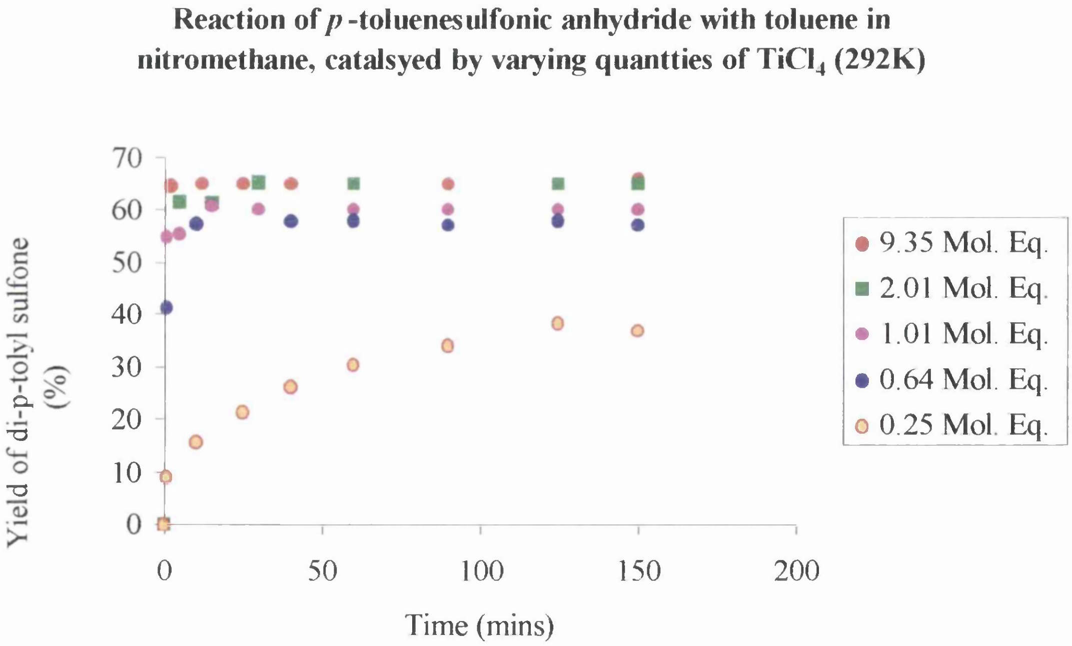


Figure 14

Despite all the precautions that were taken to carry out the experiments in an extremely dry environment, the fact that a quantitative yield of di-*p*-tolyl sulfone was not achieved suggests that a competing reaction is accounting for the remainder of the *p*-toluenesulfonic anhydride starting material. It is believed that this is the hydrolysis reaction forming *p*-toluenesulfonic acid. In order to remove any final trace of water in the reactions, an attempt was made to carry out the sulfonylation reaction in the presence of 4A° molecular sieves. The molecular sieves did not improve the yield of sulfone, and were found to break up in the reaction. The reaction yield appeared to fluctuate, however this may be due to inconsistent sampling due to the solid present in reaction. The final yield of sulfone may be low due to the fact that some product may be absorbed onto the surface of the molecular sieves, thus distorting the true figure, as shown below (See Table 6).

Table 6. Reaction of di-*p*-tolyl sulfonic anhydride with toluene in nitromethane, in the presence of varying quantities of $SnCl_4$ and $TiCl_4$ (292K)

Catalyst	Mol. Eq. catalyst	Mol. Eq. toluene	Yield (%)	Time to completion
$SnCl_4$	0.08	7.8	63	24 hours
$SnCl_4$	0.145	7.4	63	20 hours
$SnCl_4$	0.471	8.5	63	170 mins
$SnCl_4$	2.88	7.4	62	120 mins
$SnCl_4$	6.28	10.8	33*	200 mins
$SnCl_4$	8.94	6.6	63	100
$TiCl_4$	0.25	23.4	35	70
$TiCl_4$	0.64	20.4	58	< 10
$TiCl_4$	1.01	32.8	60	~10
$TiCl_4$	2.01	34.8	66	<1
$TiCl_4$	9.35	36.5	65	<1

* Reaction contained molecular sieves. The molecular sieves disintegrated, forming a suspension.

Titanium isopropoxide was also used as a catalyst in the reaction between toluene and *p*-toluenesulfonic anhydride. The reaction was carried out in nitromethane as the earlier studies had been, but the results were very disappointing. The maximum yield of sulfone obtained was 2.5%.

2.10 Reactions between toluene and *p*-toluenesulfonic anhydride in nitromethane with protic acid catalysts

The first protic acid catalyst that we considered was *p*-toluenesulfonic acid. This was based on the fact that the uncatalysed reaction was found to be autocatalytic, presumably catalysed by *p*-toluenesulfonic acid. The reaction was initially carried out in excess toluene, as the autocatalytic reaction had been. Despite the fact that the autocatalytic reaction appears to be successfully catalysed by the *p*-toluenesulfonic acid produced as a by-product in the sulfonylation reaction, the use of externally introduced *p*-toluenesulfonic acid as a catalyst, was not successful. This was due to the heterogenous nature of the reaction mixture, with the *p*-toluenesulfonic acid being largely insoluble in toluene. Similarly concentrated sulfuric acid gave poor results due to the formation of large quantities of insoluble *p*-toluenesulfonic acid, produced by the sulfonation of the toluene by the sulfonic acid catalyst in a competing reaction.

Trifluoromethanesulfonic acid (triflic acid) was also used as a catalyst in the sulfonylation of toluene by *p*-toluenesulfonic anhydride. Triflic acid gave good yields of di-*p*-tolyl sulfone, and did so efficiently i.e. when only a small molar equivalence of catalyst was employed (Table 7).

Table 7. Reaction between toluene and *p*-toluenesulfonic anhydride in nitromethane, catalysed by triflic acid (292K).

Mol. Eq. of CF_3SO_3H	Mol. Eq. of toluene	Yield (%)
1.929	15.4	69
0.2	10.3	50
3.98	17.9	73

As with $SnCl_4$ and $TiCl_4$, the initial rate of reaction appears to be roughly proportional to the amount of catalyst used (Figure 15).

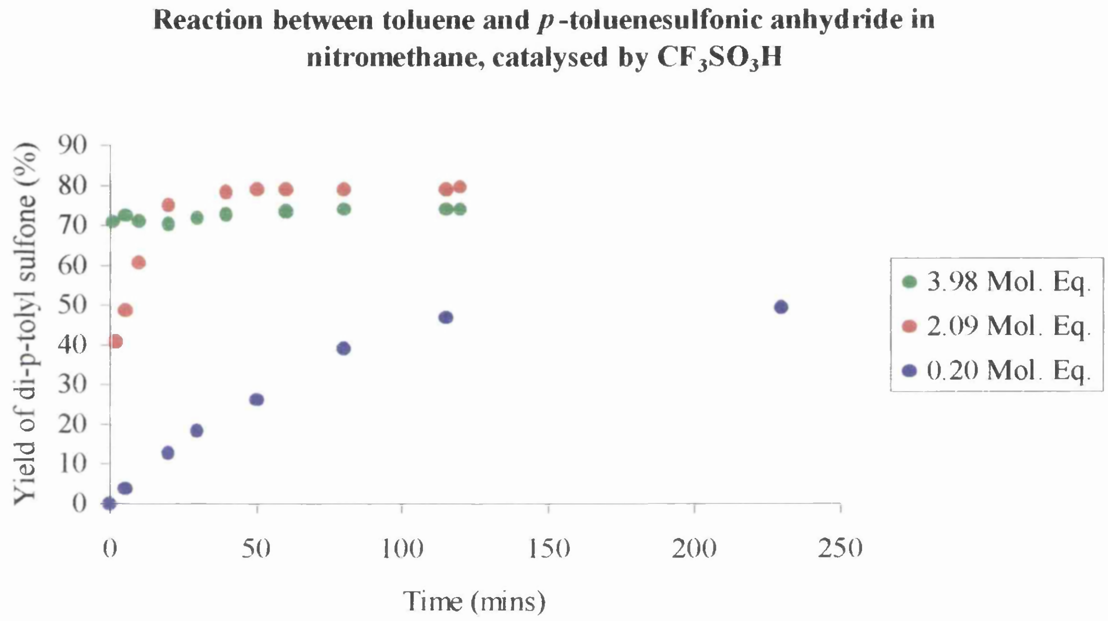


Figure 15

2.11 Graphite catalysed reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane

The reaction between toluene and *p*-toluenesulfonic anhydride catalysed by graphite powder was briefly investigated. This idea stemmed from the fact that Kodomari *et al.*

had used graphite as a catalyst in the acylation of aromatic substrates, reactions that can be considered analogous to Friedel-Crafts type sulfonylation reactions.[5] Between 1 and 4 equivalents of graphite were used. It was reported that when larger quantities were employed the yield was reduced due the appreciable absorption of the product and starting materials onto the surface of the catalyst.

In our study graphite was used both as a single equivalent, and as a large excess of approximately 100 mole equivalents with respect to the sulfonic anhydride starting material. The reaction itself was a little more difficult to analyse than most of the sulfonylation reactions due to the nature of the catalyst. The finely divided graphite powder had to be removed from the reaction mixture before analysis could be carried out. This required the reaction mixture to be quenched using ethanol, and filtered three times using a small syringe filter.

The reactions were attempted at both room temperature and reflux, with no significant reaction observed. The largest sulfone yield achieved was 1.6%. Even though the analytical method was rigorously tested and the starting material analysed for purity, such a small yield cannot be directly attributed to the graphite catalyst. The low yield is in contrast to the work carried out using carbonyl compounds where good yields in excess of 90% were achieved.

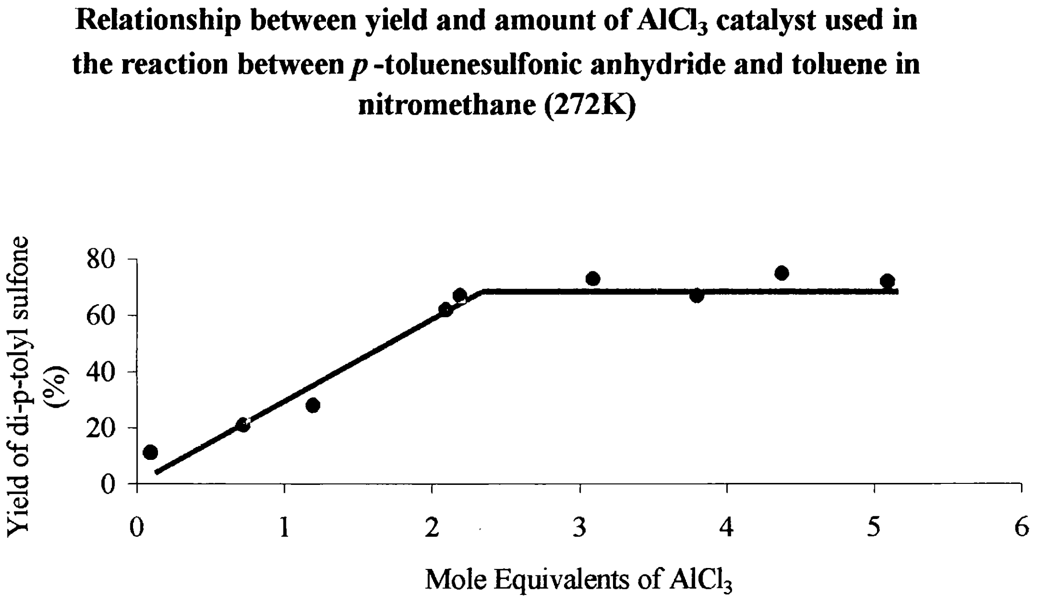
2.12 Summary and Perspectives

In the sulfonylation reactions that have been investigated in this initial study, some good yields of sulfone were achieved, however a truly quantitative yield has not been observed. The reactions appear to reach a steady state with no *p*-toluenesulfonic anhydride remaining, without seeing total conversion of anhydride to sulfone. It is believed that a competing reaction is removing anhydride from the reaction. This was investigated using HPLC analysis, and it was discovered that the unaccounted for anhydride was being hydrolysed to form *p*-toluenesulfonic acid. A mass balance was calculated in an attempt to account for all the starting material. The mass balance results are shown in Table 8. The results shown in Table 8 indicate that all the sulfonic anhydride starting material has been accounted for.

Table 8. Typical mass balance data for sulfonylation reactions between p-toluenesulfonic anhydride and toluene

% Conversion of *p*-toluenesulfonic anhydride starting material to:				Total % conversion
Di-*p*-tolyl sulfone	*p*-Toluenesulfonic acid	Ethyl-*p*-tolyl sulfonate	*p*-Toluenesulfonyl chloride	
73	25	0	0	98

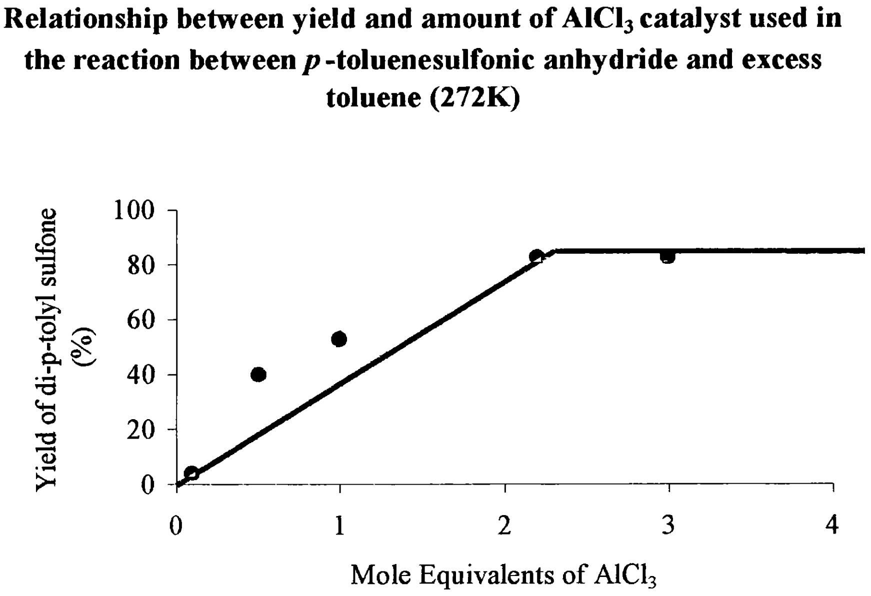
The different Lewis acid catalysts investigated appear to behave in two different ways. In the reactions involving $AlCl_3$, the yield of d-*p*-tolyl sulfone was approximately proportional to the amount of catalyst used. Figure 16 shows a plot of the yield of sulfone against the amount of catalyst used for the reactions carried out in nitromethane.



Relationship between yield and amount of $AlCl_3$ catalyst used in the reaction between *p*-toluenesulfonic anhydride and toluene in nitromethane (272K)

Figure 16

The reactions carried out in excess toluene behaved in a similar manner. In the reactions performed in excess toluene the maximum yield of sulfone achieved was 80% (Figure 17). The slightly lower maximum yield of sulfone achieved when the reactions were carried out in nitromethane (73%) as opposed to excess toluene (80%) is believed to be due to the degree of success achieved when drying the solvent.



Relationship between yield and amount of $AlCl_3$ catalyst used in the reaction between *p*-toluenesulfonic anhydride and excess toluene (272K)

Figure 17

The correlation is good with the reaction reaching a maximum yield of sulfone when a slight excess over 2 mole equivalents of catalyst is used. The yield of sulfone product does not appear to be reduced if a greater excess of catalyst is used. This is in contrast to the methanesulfonylation of benzene using methanesulfonyl chloride that Truce and Vriesen studied [17]. In their investigations it was found that the optimum yield of sulfone was achieved when a single mole equivalent of $AlCl_3$ was used.

An explanation for this is offered thus: Although the maximum yield of sulfone achieved in our studies was only 80% in excess toluene under the conditions used, quantitative yields of aromatic sulfones have been reported elsewhere under similar conditions. The implication is that when a quantitative yield of sulfone is achieved, 2 mole equivalents of catalyst are complexed to products or starting materials. Only a small amount of catalyst is actually responsible for catalysis of the reaction.

Considering the early work of Olivier, who studied the complexation of $AlCl_3$ with organosulfur compounds, this idea is well supported. Olivier showed that a strongly bonded 1:1 complex was formed between diphenyl sulfone and $AlCl_3$. It is fair to assume that di-*p*-tolyl sulfone would behave in the same manner, consuming 1 mole equivalent of the $AlCl_3$. The *p*-toluenesulfonic acid by-product is also believed to have a 1:1 interaction with $AlCl_3$ catalyst. In the reactions where all the sulfonic anhydride is not converted to sulfone, it is hydrolysed to form 2 equivalents of sulfonic acid. This then results in 2 equivalents of $AlCl_3$ complexing with 2 equivalents of acid, rather than 1 with the sulfone and 1 with the sulfonic acid. In both cases 2 mole equivalents of catalyst are complexed with products. This explains the difference between the optimum amount of catalyst when using sulfonic anhydrides as opposed to sulfonyl chlorides. When sulfonyl chlorides are used, no sulfonyl by-product is formed that can form a complex with $AlCl_3$.

In reactions catalysed by $SnCl_4$ and $TiCl_4$ and triflic acid, the yield of sulfone is roughly constant, although the initial rate of reaction varies as the amount of catalyst.

In these reactions it should be noted that the final yield of sulfone does not depend on the amount of catalyst used. This suggests that the catalyst does not form such a strong complex with the products as $AlCl_3$ does and hence, the catalyst is not taken out of circulation in the reaction and remains active for more than one cycle.

Graphite and titanium *iso*propoxide were found to be very poor catalysts for this reaction. The graphite was used in various quantities and at various temperatures, but to no avail.

Despite the fact that the reaction of toluene and *p*-toluenesulfonic anhydride is autocatalytic at reflux, *p*-toluenesulfonic acid proved to be an unsuccessful catalyst due to the heterogenous nature of the reaction mixture. Similarly concentrated sulfuric acid was not a satisfactory catalyst due to the formation of large quantities of insoluble *p*-toluenesulfonic acid.

Although the initial study has provided some interesting results, it has made apparent the need to carry out some more detailed studies on sulfonylation reactions involving aromatic sulfonic anhydrides.

Experimental

Typical procedures used for physical measurements

NMR was measured using a Bruker AV400 machine. The analyses were carried out using either $CDCl_3$ or d_6-DMSO solvent and trimethylsilane as the reference standard.

All melting points were measured using an Electrothermal 9100 melting point apparatus. All melting points were carried out in sealed glass capillary tubes. In order to exclude moisture from the measurement of sulfonic anhydride melting points, the anhydrides were transferred into the capillary tubes in a sealed glove box, under an atmosphere of dry nitrogen.

The mass spectrometry was carried out using a VG Micromass Quattro II triple quadrupole instrument. The work was carried out by the staff at the EPSRC National Mass Spectrometry Service Centre.

Typical procedure for the drying of toluene

Into a round-bottomed flask was placed toluene (1.5 l, 14 mol) and calcium hydride (5g, 0.12 mol). The mixture was stirred thoroughly under an inert atmosphere of dry nitrogen for a minimum period of 24 hours, and wherever possible was allowed to stir for 48 hours. The toluene was then distilled under dry nitrogen, and collected in a flame-dried round-bottomed flask under nitrogen. The toluene was stored over 4Å molecular sieves under dry nitrogen in the dark.

Typical procedure for the drying of nitromethane

The nitromethane was dried using the same technique as for toluene, however the molecular sieves were not used during the storage of the nitromethane due to the fact that they were observed to disintegrate over time. The nitromethane was also stored in the dark to prevent the formation of free radicals.

Typical procedure for the drying of aryl halides

The aryl halides were stirred over $CaCl_2$ in a similar manner, and then distilled under dry nitrogen. They were stored over 4Å molecular sieves, under an atmosphere of dry nitrogen and kept in the dark.

Typical procedure for the weighing of starting materials

It should be noted that in the following typical reaction procedures, the quantities used are given as approximate values e.g. (~ 0.3g, 2.2×10^{-3}mol). This indicates that approximately 0.3 grams of starting material was used, however in each experiment the exact quantity used was recorded. The exact quantity (measured to ± 0.003 g) was used in all calculations and measurements for each individual experiment.

HPLC Conditions

The samples were analysed using a Hewlett Packard HP1100 High Performance Liquid Chromatograph, fitted with a Hypersil ODS II column. The analytical runs were carried out isocratically, with the water used in the analysis doubly distilled. The samples taken from the reaction were quenched using ethanol. This not only quenched the reactions but also diluted the reactions so that the concentration was suitable for analysis by HPLC. The dilutions were carried out using approximately 10ml of ethanol for a reaction sample size of approximately 0.2ml. An approximate dilution was sufficient, as due to the presence of the internal standard in the reaction mixture the measurements are taken as relative measurements and therefore, the absolute concentrations are not required.

Apparatus:	HP1100	Detector:	UV / Vis
Column Length:	250 mm	Wavelength:	240 nm
External Diameter:	4.6 mm	Run time:	30 min.
Flow Rate:	1.0 ml/min.	Eluent Composition:	70% Methanol 30% Water

Areas of peaks corresponding to each of the reaction products were measured relative to the Internal Standard.

Quantitative calculation of reaction mixture content

The amount of each of the different reaction components present in the reaction mixture at a given time was determined from the areas of the peaks, the measured weight of the aliquot taken and the known weight of the of the internal standard added to the sample.

$$\text{Amount of comp. A} = \frac{\text{Comp. A peak area x Mass I.S. x Comp. A } \alpha^{*}}{\text{I. S. peak area}}$$

The component of most interest in this study was di-*p*-tolyl sulfone, one of the expected products from the sulfonylation reaction between *p*-toluenesulfonic anhydride and toluene. The percentage yield of sulfone at any given time was the information of the most use in this study. This was calculated in the following way:

$$\text{Moles of sulfone} = \frac{\text{Sulfone peak area x Moles I.S. x sulfone } \alpha^{*}}{\text{I. S. peak area}}$$

$$\text{\% Yield Sulfone} = \frac{\text{Moles of sulfone x 100}}{\text{Theoretical moles of sulfone}^{**}}$$

* Response Factor, α

** Based on the moles of sulfonic anhydride starting material.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with excess toluene, catalysed by $AlCl_3$

Into a flame-dried two-necked round-bottomed flask was placed toluene (~20ml, 0.18mol) and $AlCl_3$ ($\leq$0.5g, 3.8 x 10^{-3}mol). *Ortho*-nitrotoluene was added as an internal standard (~ 0.3g, 2.2 x 10^{-3}mol). The reaction was thoroughly stirred and whilst purging with dry nitrogen, *p*-toluenesulfonic anhydride (~0.3g, 9.2 x 10^{-4}mol) was added to the flask. The reaction was sampled using a syringe, and samples taken were quenched with ethanol (HPLC Grade) in preparation for analysis by HPLC, and sealed. The reaction was monitored for 3 hours with samples being taken at regular intervals, as determined by preliminary investigation. The samples were analysed by HPLC, and the sulfone yield calculated as described.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with excess toluene, catalysed by sublimed $AlCl_3$

Crude $AlCl_3$ was placed into a drying pistol followed by a glass wool plug. The drying pistol was fitted with a tap to allow attachment to a nitrogen line. The $AlCl_3$ was sublimed, collected and stored under nitrogen. The $AlCl_3$ ($\leq$0.5g, 3.8 x 10^{-3}mol) was transferred into a clean dry two-necked round-bottomed flask without exposure to air. To this was added toluene (~20ml, 0.18mol) and *ortho*-nitrotoluene was added as internal standard (~ 0.3g, 2.2 x 10^{-3}mol). The reaction was thoroughly stirred and whilst purging with dry nitrogen, *p*-toluenesulfonic anhydride (~0.3g, 9.2 x 10^{-4}mol) was added to the flask. The reaction was sampled using a syringe, and samples taken were quenched with ethanol (HPLC Grade) in preparation for analysis by HPLC and sealed. The reaction was monitored for 3 hours with samples taken at regular intervals, as determined by preliminary investigation. The samples were analysed by HPLC, and the sulfone yield calculated as described.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane, catalysed by $AlCl_3$

Into a flame-dried two-necked round-bottomed flask was placed toluene (~20ml, 0.18mol) and *p*-toluenesulfonic anhydride (~0.3g, 9.2 x 10^{-4}mol). *Ortho*-nitrotoluene was added as an internal standard (~ 0.3g, 2.2 x 10^{-3}mol). The reaction was thoroughly stirred, and whilst purging with dry nitrogen $AlCl_3$ (≤0.5g, 3.8 x 10^{-3}mol) was added to the flask. The reaction was sampled using a syringe, and samples taken were quenched with ethanol (HPLC Grade) in preparation for analysis by HPLC, and sealed. The reaction was monitored for 3 hours with samples taken at regular intervals, as determined by preliminary investigations. The samples were analysed by HPLC, and the sulfone yield calculated as described.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane, catalysed by $ZnCl_2$

Before the reaction was carried out, $ZnCl_2$ was freshly fused. This was carried out over a Bunsen burner, then cooled in an oven at 120°C. The $ZnCl_2$ was then crushed using a mortar and pestle. Following the preparation of the $ZnCl_2$ it was used immediately and the reaction was carried out as described for the reaction catalysed by $AlCl_3$ in nitromethane. The reactions were followed for 8 hours, due to the slow nature of the reaction.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane, catalysed by $SnCl_4$ (292K)

Into a flame-dried two-necked round-bottomed flask was placed toluene (~20ml, 0.18mol) and *p*-toluenesulfonic anhydride (~0.3g, 9.2×10^{-4}mol). *Ortho*-nitrotoluene was added as internal standard (~ 0.3g, 2.2×10^{-3}mol). The reaction was thoroughly stirred, and purged with dry nitrogen. The $SnCl_4$ was then added to the flask through a rubber septum using a syringe. The reaction was sampled using a syringe, and samples taken were quenched with ethanol (HPLC Grade) in preparation for analysis by HPLC, and sealed. The reaction was monitored for 3 hours with samples being taken at regular intervals, as determined by preliminary investigations. The samples were analysed by HPLC, and the sulfone yield calculated as described.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane, catalysed by $TiCl_4$ (292K)

The reactions catalysed by $TiCl_4$ were carried out in the same manner as those catalysed by $SnCl_4$.

Typical procedure for the reaction of *p*-toluenesulfonic anhydride with toluene in nitromethane, catalysed by $Ti(OCH(CH_3)_2)_4$ (292K)

The reactions catalysed by $Ti(OCH(CH_3)_2)_4$ were carried out in the same manner as those catalysed by $SnCl_4$.

Attempted sulfonylation of toluene with *p*-toluenesulfonic anhydride in the presence of graphite

Graphite powder was initially dried in an oven at 110°C for 24 hours to remove any moisture. Into a flame-dried two-necked round-bottomed flask was placed nitromethane, (19.1g, 0.18mol.), graphite powder (0.016g, 1.33mmol) and *p*-toluenesulfonic anhydride (0.31g, 9.5×10^{-4}mol). *Ortho*-nitrotoluene was added as an internal standard (0.622g, 4.67×10^{-3}mol). The reaction mixture was stirred thoroughly, and finally the toluene was introduced, (5.45g, 59.1×10^{-3}mol). At all times the reactions were carried out under a dry nitrogen atmosphere. Aliquots were taken regularly, and filtered after quenching with ethanol. Samples were analysed by reverse phase HPLC, using an ODS II C_{18} column. The reaction was allowed to continue for 3 hours, after which time the reaction chromatograms showed no remaining anhydride in solution. At room temperature no sulfone product was observed.

The reaction was repeated and heated to reflux, and again allowed to proceed for 3 hours. Again no sulfone product was observed.

Attempted sulfonylation of toluene with *p*-toluenesulfonic anhydride in the presence of excess graphite

Into a flame-dried two-necked round-bottomed flask was placed nitromethane solvent, (19.1g, 0.18mol.), dry graphite powder (1.5g, 0.12mol) and *p*-toluenesulfonic anhydride (0.31g, 9.5 x 10^{-4}mol) under a dry nitrogen atmosphere. *Ortho*-nitrotoluene was added as an internal standard (0.622g, 4.67 x 10^{-3}mol). The reaction was stirred thoroughly, and finally the toluene (5.45g, 59.1 x 10^{-3}mol) was introduced to start the reaction. Aliquots were taken regularly, and filtered after quenching with ethanol. Samples were analysed by reverse phase HPLC, using an ODS II C_{18} column. After 3 hours the reaction appeared to have reached completion, with no further di-*p*-tolyl sulfone formed. The sulfone yield was 0.5%.

A similar reaction was then carried out at reflux, with the reaction again monitored for 3 hours, after which time the di-*p*-tolyl sulfone yield (1.6%) appeared constant. The reaction was repeated again and a sulfone yield of 1% recorded.

Attempted reaction of *p*-toluenesulfonic anhydride with excess toluene, catalysed by *p*-toluenesulfonic acid

Into a flame-dried two-necked round-bottomed flask was placed toluene (~20ml, 0.18mol) and anhydrous *p*-toluenesulfonic acid (0.323g, 1.88 x 10^{-3}mol); *ortho*-nitrotoluene was added as an internal standard (~ 0.3g, 2.2 x 10^{-3}mol). The reaction was thoroughly stirred and whilst purging with dry nitrogen, *p*-toluenesulfonic anhydride (~0.3g, 9.2 x 10^{-4}mol) was added to the flask. At room temperature the reaction mixture was heterogenous. The reaction was heated to reflux which improved the homogeneity of the reaction, however some solid acid still remained undissolved.

The reaction was sampled regularly for 5 hours and quenched with ethanol as before, however HPLC analysis showed that no di-*p*-tolyl sulfone was formed in the reaction.

Attempted reaction of *p*-toluenesulfonic anhydride with excess toluene, catalysed by concentrated sulfuric acid

Into a flame-dried two-necked round-bottomed flask was placed toluene (~20ml, 0.18mol) and *p*-toluenesulfonic anhydride (~0.3g, 9.2×10^{-4}mol), and *ortho*-nitrotoluene was added as an internal standard (~ 0.3g, 2.2×10^{-3}mol). The reaction was thoroughly stirred and concentrated sulfuric acid was added as catalyst (1.84g, 18.8×10^{-3} mol). The reaction mixture was heated to reflux for a period of 1 hour, and samples were taken at regular intervals. Problems were encountered analysing the reaction due to crystallisation of the samples on cooling.

Appendix One

Calculation of response factor of di-*p*-tolyl sulfone

The response factor for di-*p*-tolyl sulfone was calculated using two standard solutions. One of the internal standard, *o*-nitrotoluene, and the other of di-*p*-tolyl sulfone. The details of the solutions are shown in Table 9.

Table 9. Details of standard solutions used to calculate factor for di-*p*-tolyl sulfone

Solution	Compound	F. W. (A.M.U.)	Quantity (g)	Volume (L)	Molarity (mol dm^{-3})
A	*o*-nitrotoluene	137.14	0.0397	0.25	1.16 x 10^{3}
B	di-*p*-tolyl sulfone	246.33	0.0621	0.25	1.01 x 10^{3}

Aliquots of varying sizes of each solution were accurately measured using a Finnpipette fixed volume mechanical pipette. These were then mixed thoroughly, and analysed by HPLC using the stated conditions. Measurements were repeated to give a set of results, from which a mean value of α could be obtained (Table 10).

Table 10. Co-injection data to calculate response factor for di-*p*-tolyl sulfone

Vol. A* (ml)	**Conc. A (mol dm^{-3})**	**Area A**	**Vol. B** (ml)**	**Conc. B (mol dm^{-3})**	**Area B**	**Response Factor B**
2	7.720×10^{-4}	735.2	1	3.361×10^{-4}	1605	0.199419
2	7.720×10^{-4}	761.8	1	3.361×10^{-4}	1646	0.201447
2	7.720×10^{-4}	701.6	1	3.361×10^{-4}	1520	0.200994
3	8.685×10^{-4}	801.7	1	2.521×10^{-4}	1218	0.191014
3	8.685×10^{-4}	797.7	1	2.521×10^{-4}	1206	0.19202
3	8.685×10^{-4}	798.8	1	2.521×10^{-4}	1206	0.192317
1	3.860×10^{-4}	370.7	2	6.723×10^{-4}	3541	0.182336
1	3.860×10^{-4}	371.7	2	6.723×10^{-4}	3592	0.180227
1	3.860×10^{-4}	367.1	2	6.723×10^{-4}	3529	0.18116
1	3.860×10^{-4}	360.3	2	6.723×10^{-4}	3445	0.18217
1	3.860×10^{-4}	360.5	2	6.723×10^{-4}	3465	0.181208
					Mean =	0.18943

* Standard solution of *o*-nitrotoluene

** Standard solution of di-*p*-tolyl sulfone

Appendix Two

Integration by partial fractions of rate equation for second order autocatalytic reaction

$$\mathrm{A} + \mathrm{B} = \mathrm{A}_0 + \mathrm{B}_0$$

$$\mathrm{B} = \mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A}$$

$$-\frac{d\mathrm{A}}{dt} = k\mathrm{AB} = k\mathrm{A}(\mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A})$$

$$\int_{\mathrm{A}_0}^{\mathrm{A}} \frac{d\mathrm{A}}{\mathrm{A}(\mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A})} = -\int_0^t k\mathrm{dt} = -kt$$

$$\frac{1}{\mathrm{A}(\mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A})} = \frac{\alpha}{\mathrm{A}} + \frac{\beta}{\mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A}}$$

By partial fractions we can see that

$$\int_{\mathrm{A}_0}^{\mathrm{A}} \left(\frac{1}{\mathrm{A}(\mathrm{A}_0 + \mathrm{B}_0)} + \frac{1}{(\mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A})(\mathrm{A}_0 + \mathrm{B}_0)}\right) dA = -kt$$

$$\int_{\mathrm{A}_0}^{\mathrm{A}} \frac{d\mathrm{A}}{\mathrm{A}} + \int_{\mathrm{A}_0}^{\mathrm{A}} \frac{d\mathrm{A}}{(\mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A})} = -kt(\mathrm{A}_0 + \mathrm{B}_0)$$

Change in variable, with limits from B_0 to B:

$$\mathrm{B} = \mathrm{A}_0 + \mathrm{B}_0 - \mathrm{A}$$

$d\mathrm{B} = -d\mathrm{A}$, therefore:

$$\int_{\mathrm{A}_0}^{\mathrm{A}} \frac{d\mathrm{A}}{\mathrm{A}} - \int_{\mathrm{B}_0}^{\mathrm{B}} \frac{d\mathrm{B}}{\mathrm{B}} = -kt(\mathrm{A}_0 + \mathrm{B}_0)$$

$$(\ln\mathrm{A} - \ln\mathrm{A}_0) - (\ln\mathrm{B} - \ln\mathrm{B}_0) = -kt(\mathrm{A}_0 + \mathrm{B}_0)$$

$$\ln\frac{AB_0}{A_0B} = -kt(A_0 + B_0)$$

$$\frac{1}{A_0 + B_0}\ln\frac{A_0B}{B_0A} = kt$$

Appendix Three

Table Curve 2D – User Defined Function

F1=#A/100000

F2=#B/1000

F3=(F1+F2)

F4=F1/F2

F5=-X*F3*(#C)

F6=F4*EXP(F5)

Y=F3/(1+F6)

Adjustable Parameter	Min	Start	Max
#A	0	389889	1E+25
#B	0	13.8676	1E+25
#C	-1E+25	0.01085	1E+25

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Chapter Three

Friedel Crafts Competition reactions on *p*-toluenesulfonic anhydride

3.1 Introduction

In the commercial synthesis of linear alkylbenzene sulfonic acids, the sulfonation reactions typically only achieve 98% conversion of LAB to sulfonic acids. Several by-products have been observed in the reactions including sulfonic anhydrides and sulfones. It is believed that the formation of sulfones in commercial sulfonation reactions may be due to the sulfonylation of LAB substrates by LAS anhydrides. It was therefore of interest to look at the relative rates of sulfonylation of a range of different aromatic substrates.

Relative rates of sulfonylation have previously been investigated using different aromatic substrates competing in reactions with different sulfonyl chlorides as the sulfonylating agent. Relative rates of sulfonylation with various sulfonylating agents have also been looked at. This work however contains very little data on aromatic sulfonic anhydrides. Typical studies in this field use halogenated aromatic substrates. As well as these we shall look at different LAB substrates that are of interest to Unilever.

Relative rate constants can be obtained by using different concentrations of individual substrates in a competitive reaction, where more than one component is allowed to compete under identical conditions for a common reactant (Figure 1).[1]

$$\mathrm{A} \xrightarrow{k_\mathrm{A}} \text{Product A}$$

$$\mathrm{B} \xrightarrow{k_\mathrm{B}} \text{Product B}$$

$$\mathrm{C} \xrightarrow{k_\mathrm{C}} \text{Product C}$$

Figure 1.

The reactions in competition must be of the same order, and if this is the case then the relative rate term, k_{rel} can be derived from the combination of integrated rate equations (Equation 1).

$$-dA/dt = k_A A$$

$$-dB/dt = k_B B$$

$$k_{rel} = k_A/k_B = (\ln A/A_0) / (\ln B/B_0) \qquad (1)$$

Relative rates are measured against a standard component which is attributed a nominal rate value ($k_B = 1$). Represented in Equation 1 are the initial and final concentrations of the standard, B_0 and B, and the initial and final concentrations of the substrate under investigation, A_0 and A.

In order to measure relative rates of reaction using competitive conditions, the initial rates can be considered. The rate of change in the concentration of A is equal to the concentration of A divided by the time, t_A. The same can be said of the change in the concentration of B. In cases where the time for the reactions of A and B is the same, then the relative rate can be measured in terms of the concentration alone, as shown below (Equation 2).

$$k_A = [A] / t_A$$

$$k_B = [B] / t_B$$

In cases where $t_A = t_B$ then:

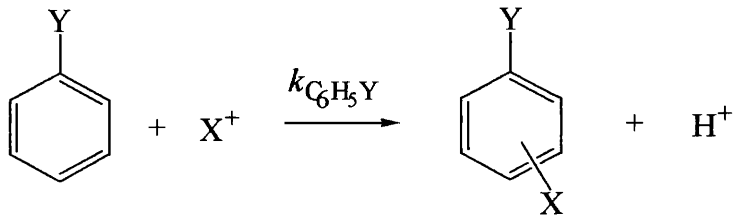
$$k_{rel} = k_A / k_B = [A] / [B] \qquad (2)$$

A convenient way to measure relative rates of reaction is to use competitive conditions, where two reactants are competing *in situ* for a single substrate. The analysis of the reaction mixture at a given time t, ensures that the reaction times for A and B are identical, thus providing a convenient method to study relative rates of reaction.

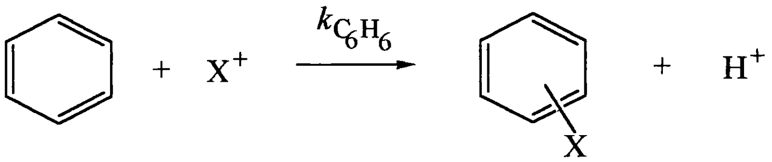
3.2 Partial rate factors

Brown and Stock looked at electrophilic substitution reactions in great detail, investigating competition reactions using toluene and benzene as the reaction substrates.[2] They observed that for a given reaction, the rate constant does not give a very complete picture of the reaction taking place. When a monosubstituted benzene derivative undergoes substitution of hydrogen, three possible positions of exchange exist: *ortho* (two equivalent positions), *meta* (two equivalent positions), and *para* (one). Thus in order to take into account the various positional isomers, further consideration should be given to the individual rate constants, and the following analysis was proposed.

If $k_{C_6H_5Y}$ is the observed rate constant for the reaction of the monosubstituted derivative:



then $k_{C_6H_5Y} = 2k_{o\text{-}Y} + 2k_{m\text{-}Y} + k_{p\text{-}Y}$. The corresponding reaction for benzene leads to $k_{C_6H_6} = 6k_H$, because the reagent has an equal probability of attacking each of the 6 carbon atoms of the ring.



The isomer distribution can be related to the individual rate constants for the monosubstituted reaction by:

$$\frac{\%\,ortho}{100} = \frac{2k_{o\text{-}Y}}{k_{C_6H_5Y}}$$

$$\frac{\%\,meta}{100} = \frac{2k_{m\text{-}Y}}{k_{C_6H_5Y}}$$

$$\frac{\%\,para}{100} = \frac{k_{p\text{-}Y}}{k_{C_6H_5Y}}$$

Partial rate factors are defined as the rates of substitution at each site individually, relative to benzene thus,

$$o_f^Y = \frac{k_{o\text{-}Y}}{k_H}$$

$$m_f^Y = \frac{k_{m\text{-}Y}}{k_H}$$

$$p_f^Y = \frac{k_{p\text{-}Y}}{k_H}$$

If we then combine the above relationships, we can obtain the following equations for the partial rate factors:

$$o_f^Y = \frac{3k_{C_6H_5Y}}{k_{C_6H_6}} \text{ x } \frac{\%\, ortho}{100}$$

$$m_f^Y = \frac{3k_{C_6H_5Y}}{k_{C_6H_6}} \text{ x } \frac{\%\, meta}{100}$$

$$p_f^Y = \frac{6k_{C_6H_5Y}}{k_{C_6H_6}} \text{ x } \frac{\%\, para}{100}$$

From the partial rate factors it is easy to assess the effect of the substituent Y on the reactivity of a given site. A partial rate factor greater than unity represents activation of a site by the substituent Y relative to hydrogen, and a factor less than unity represents deactivation.

3.3 Introduction to relative rates of sulfonylation

Although many groups have studied sulfonylation reactions over the years, most of the relative rate studies carried out have been concerned with the reactions of sulfonyl chlorides. Although not identical to the reactions involving the sulfonic anhydride, the reactions are of value to the current study, especially in planning the type of reactions to carry out, and the conditions under which to study them.

The first study carried out by Olivier used *p*-bromobenzenesulfonyl chloride as the sulfonylating agent.[3,4] Using non-competitive reaction conditions, Olivier found that different aryl substrates had the following order of reactivity: toluene > benzene > chlorobenzene > bromobenzene > nitrobenzene.

Olivier also carried out a series of sulfonylations using benzene (as active solvent) and aluminium chloride as catalyst. These were carried out under competitive conditions, with 0.1 equivalents of $AlCl_3$ with respect to the sulfonyl chloride starting material. An order of reactivity was observed for *para*-substituted benzenesulfonyl chlorides as follows: *p*-methyl > hydrogen > *p*-iodo > *p*-bromo > *p*-chloro > *p*-nitro. The order indicates that the presence of an electron-donating group in the *p*-substituted position is rate enhancing. Where electron-withdrawing groups are present in the position *para* to the sulfonyl chloride group the rate is decreased.

Olivier found in the study comparing the rates of reaction of the different *para*-substituted benzenesulfonyl chlorides, that the order of reactivity was generally the same as for the earlier study in which it was the aryl substrates that varied and not the sulfonyl chloride.[3,4] In the reactions using the differently substituted sulfonyl chlorides, the effect of substitution was less pronounced. In all the reactions the value of the rate constant was found to be dependant on the amount of catalyst used in the reaction. As a result Olivier quotes all rates as k_x, where x is the mole equivalent of catalyst used in the reaction. The results of the two studies are shown below (See Tables 1 and 2).

Table 1. Rates of reaction at 30 °C for the reaction between *p*-bromobenzenesulfonyl chloride and different aryl substrates, catalysed by AlCl$_3$

Reaction	*k*
p-BrC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_5$CH$_3$	$k_{0.1} = 0.00413$
p-BrC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_5$H	$k_{0.1} = 0.00111$
p-BrC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_5$Br	$k_{0.2} = 0.00102$
p-BrC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_5$Cl	$k_{0.2} = 0.00080$
p-BrC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_5$NO$_2$	$k_{0.2} = 0.00000$

Table 2. Rates of reaction at 30 °C for the reaction between different *p*-substituted benzenesulfonyl chlorides and benzene, catalysed by AlCl$_3$

Reaction	*k*
p-CH$_3$C$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_6$	$\mathrm{k}_{0.1} = 0.00646$
p-HC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_6$	$k_{0.1} = 0.00212$
p-IC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_6$	$k_{0.1} = 0.00140$
p-BrC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_6$	$k_{0.1} = 0.00111$
p-ClC$_6$H$_4$SO$_2$Cl.AlCl$_3$ + C$_6$H$_6$	$k_{0.1} = 0.00106$
p-NO$_2$C6H4SO2Cl.AlCl$_3$ + C$_6$H$_6$	$k_{0.1} = 0.000136$

Jensen and Brown studied benzenesulfonylation of toluene and benzene, in the presence of AlCl$_3$ as catalyst. [5, 6, 7, 8] They initially reconsidered the early results of Oliver and decided that sufficient data was not available to work out relative rates of reaction for the arylsulfonylation of toluene and benzene. As they had previously found that the reaction of toluene with benzenesulfonyl chloride-aluminium chloride in benzenesulfonyl chloride exhibited simple second order kinetics, they used this as a starting point to determine the toluene/benzene relative rates, as well as the isomer distribution for toluene under these conditions. [7]

Although slight peculiarities were observed in the benzenesulfonylation of benzene, it was possible to consider the reaction in benzene as a second order reaction, permitting its comparison with toluene. The peculiarities are due to the fact that the benzenesulfonylation of chlorobenzene exhibited three-halves order kinetics (Equation 3), whilst the benzenesulfonylation of toluene exhibited second order kinetics (Equation 4).

$$\text{Rate} = k_{3/2}\,[C_6H_5SO_2Cl.AlCl_3]^{1/2}[C_6H_5Cl] \qquad (3)$$

$$\text{Rate} = k_2\,[C_6H_5SO_2Cl.AlCl_3]\,[C_6H_5CH_3] \qquad (4)$$

The kinetics observed for benzene suggested that the reaction could follow two possible pathways, some of the benzene reacting with the separated ions and part reacting with the other reactive species, be they ion pairs or the unionised addition compound. This caused problems measuring the relative rate ratio for toluene and benzene as it is desirable for purposes of comparison that the two reaction pathways should be identical. Jensen and Brown found that they could virtually eliminate the pathway exhibiting three halves order kinetics for benzene, by altering the reaction conditions. By using a high concentration of $AlCl_3$, the ratio of dissociated ions to ion pairs (or addition compound) should be reduced. It was also found that the rate of formation of dissociated ions falls in a critical range, such that the process cannot compete with their removal by reactive aryl substrates. It was decided that the use of a high concentration of the less reactive species, would serve to remove the dissociated ions faster than they could be generated. Consequently it was concluded that the use of high concentrations of $AlCl_3$ and benzene should reduce the portion of the reaction proceeding via the dissociated ion pair to a negligible fraction of the total reaction. This would permit an estimation of relative reactivity from direct comparison of the relative rates.[8]

Unfortunately Jenson and Brown found that the reactivity of toluene is such that it was not possible to determine the rates at the same high concentration of hydrocarbon as in the reactions involving benzene. The problem was therefore overcome by extrapolating the k_2 values obtained with increasing concentration of hydrocarbon to 1.25M. This provided an estimated value of k_2 of 0.095. When used with the rate constant for the sulfonylation of benzene, where $k_2 = 0.0118$, the relative rate of $k_T / k_B = 8.0 \pm 1.0$ obtained.

The same study also looked at the observed isomer distribution in the benzenesulfonylation of toluene (See Table 3).[8]

Table 3. Isomer distribution in the benzenesulfonylation of toluene, catalysed by $AlCl_3$ at 25 °C

% *ortho*	% *meta*	% *para*
28.4	8.7	62.9

Utilizing the selectivity relationship that Jenson and Brown had developed, the partial rate factors and the toluene / benzene relative rates could be calculated directly from the isomer distribution (See Table 4).

Table 4. Observed and calculated values for the partial rate factors for the $AlCl_3$ catalysed benzenesulfonylation of toluene in benzenesulfonyl chloride solution at 25 °C

	Partial rate factors			Relative rate k_T / k_B
	o_f	m_f	p_f	
Observed *	6.8	2.1	30.2	8.0 ± 1.0
Calculated **	7.3	2.3	33	8.7

* Reference 8

** Reference 9

Jenson and Brown also looked at a series of benzenesulfonyl chloride sulfonylations carried out in nitrobenzene.[6] For the reactions in nitrobenzene, for a given concentration of $AlCl_3$ third order kinetics were observed for reactions involving less reactive aryl substrates. When more reactive substrates were used, the reactions were observed to be second order. Due to the changes in the order of reaction, and the difficulty associated with working in nitrobenzene, it proved difficult to study an exhaustive list of aryl substrates. They did however calculate relative rates for a series of reactions with monoalkylbenzenes at 25°C (See Table 5). [6]

Table 5. Rate constants and relative rates for the $AlCl_3$ catalysed benzenesulfonylation of monoalkylbenzenes in nitrobenzene* at 25 °C.

Compound	Rate Constant, k_3 $l.^2$ $mole^{-2}$ min^{-1}.	Relative Rate
Benzene	0.00221, 0.00247, 0.00242	1.00
Toluene	0.0205, 0.0218	9.0
Ethylbenzene	0.0160, 0.0162	6.8
Isopropylbenzene	0.0111, 0.0114	4.8
t-Butylbenzene	0.0081, 0.0034	3.5

* The concentrations of benzenesulfonyl chloride, aluminium chloride ($AlCl_3$) and alkylbenzene all equal 0.222M.

It should be noted that when an attempt was made to extend the study to include polymethylbenzenes, it was found that the third order rate constants calculated increased over the duration of the reaction. Due to this, a series of reactions were studied comparing only the initial rates (See Table 6). [6]

Table 6. Rate constants and relative rates for the $AlCl_3$ catalysed benzenesulfonylation of methylbenzenes in nitrobenzene solution at 25 °C.

Compound	Rate Constant, k_δ, $l.^2$ $mole^{-2}$ $min.^{-1}$	Relative Rate *
Benzene	0.00235	0.11
Toluene	0.0212	1.00
1,2,4,5-Tetramethylbenzene	0.0178, 0.0173,	0.84
o-Xylene	0.041, 0.043	2.0
p-Xylene	0.045, 0.042	2.1
m-Xylene	0.047, 0.052	2.4
Pentamethylbenzene	0.058, 0.055	2.7
1,2,3-Trimethylbenzene	0.064	3.0
1,2,4-Trimethylbenzene	0.071	3.4
1,3,5-Trimethylbenzene	0.069, 0.072	3.3

* The relative rates were calculated using initial rates of reaction.

Truce and Vriesen investigated Friedel Crafts reactions of methanesulfonyl chloride with benzene and certain substituted benzenes. [10] It was found that the para / meta ratio for the reaction with toluene was low, indicating that the methanesulfonyl chloride exhibits comparatively low selectivity. Truce and Vriesen also found that chlorobenzene, bromobenzene and fluorobenzene all afford only the *para* isomer of the corresponding methyl aryl sulfone.

The ratio of rates of reaction, for the reaction of *p*-bromobenzenesulfonyl chloride with toluene and benzene was found to be 3.7. No other rate ratios were calculated in the original study, and the data provided does not allow for subsequent calculations of this kind to be performed due to the fact that the reactions were allowed to run to completion, with different reaction times.

Holt and Pagdin carried out a study on the reaction of a series of polymethylbenzenesulfonyl chlorides with benzene. [11] The reactions were carried out in 1,2-dichloroethane solvent, and will be considered in greater detail in Chapter 4. In the paper, Holt and Pagdin review previous sulfonylations of benzene that have been carried out, and summarise early Friedel-Crafts sulfonylation reactions used in the preparation of diaryl sulfones. The reaction data is only concerned with the synthesis of the sulfones, and is therefore of limited use in this current study. The data collected by Holt and Pagdin are shown below (Table 7).

Table 7. Sulfone yields collected by Holt and Pagdin from the synthesis of diaryl sulfones using $AlCl_3$ catalysed Friedel-Crafts reactions

Sulfonyl chloride	Benzene derivative	Orientation of substituents	Yield (%)
$C_6H_5SO_2Cl$	C_6H_6	-	90
$C_6H_5SO_2Cl$	$C_6H_5CH_3$	2-	5.5
$C_6H_5SO_2Cl$	$C_6H_5CH_3$	4-	74
$C_6H_5SO_2Cl$	$C_6H_5CH_2CH_3$	4-	81
$C_6H_5SO_2Cl$	1,3-$C_6H_4(CH_3)_2$	2,4-	98
$C_6H_5SO_2Cl$	1,4-$C_6H_4(CH_3)_2$	2,5-	92
$C_6H_5SO_2Cl$	1,2,4-$C_6H_3(CH_3)_3$	2,4,5-	76
$C_6H_5SO_2Cl$	1,3,5-$C_6H_3(CH_3)_3$	2,4,6-	70
$C_6H_5SO_2Cl$	1,4-$C_6H_4(CH_2CH_3)_2$	2,5-	53
$C_6H_5SO_2Cl$	1,2,4-$C_6H_3(CH_2CH_3)_3$	2,4,5-	32
$C_6H_5SO_2Cl$	1,4-$C_6H_4(CH(CH_3)_2)_2$	2,5-	61
$C_6H_5SO_2Cl$	C_6H_5Cl	4-	80
p- $CH_3C_6H_4SO_2Cl$	C_6H_6	4-	81
p- $CH_3C_6H_4SO_2Cl$	$C_6H_5CH_3$	4,4'-	72
p- $CH_3C_6H_4SO_2Cl$	1,3-$C_6H_4(CH_3)_2$	2,4,4'-	70
p- $CH_3C_6H_4SO_2Cl$	1,4-$C_6H_4(CH_3)_2$	2,5,4'-	80
p- $CH_3C_6H_4SO_2Cl$	1,3,5-$C_6H_3(CH_3)_3$	2,4,6,4'-	72

Kobayashi *et al.* investigated the *p*-toluenesulfonylation of toluene, chlorobenzene and benzene.[12] The reactions were carried out using *p*-toluenesulfonyl chloride in methylene chloride, with $AlCl_3$ as catalyst, over the temperature range 0 - 20°C. The reaction was found to be third order, with the rate = k_3[*p*-$CH_3C_6H_4SO_2Cl$][$AlCl_3$][ArH]. Although overall relative reactivities were not calculated, partial rate factors for *para*-substitution were calculated. These were found to be 52.5 ($C_6H_5CH_3$), 0.224 (C_6H_5Cl), and 0.164 (C_6H_5Br). In these reactions it was believed that the abstraction of the proton from the complex was the rate-determining step. Substitution was observed exclusively at the *para-* position with halobenzenes, however with toluene *ortho-* and *meta-* substituted products were also observed (13.4% and 8.6% respectively).

Olah *et al.* studied sulfonylation of benzene and toluene with alkyl- and arylsulfonyl halides and sulfonic anhydrides.[13] The reactions were catalysed using $AlCl_3$ and SbF_5, and relative rates were worked out under both competitive and non-competitive conditions.

The general procedure for competitive sulfonylation used an excess of the aromatic substrate as solvent. To a mixture of benzene (0.1 mol.), toluene (0.1 mol.), and $AlCl_3$ (0.022 mol.), 0.02 mol. of sulfonyl chloride was added dropwise with stirring, over a period of 5 minutes in a constant temperature bath (25 °C or 60 °C). The reactions were allowed to proceed for a further 20 minutes (or 2 hr at 60°C). The reaction mixture was then poured onto ice-water, extracted into ether and dried over Na_2SO_4, concentrated and analysed by gas chromatography or NMR spectroscopy.

The procedure used for non-competitive kinetic studies was as follows. A mixture of 0.2 mol. of benzene (or toluene) and 0.170 g of methyl *p*-tolyl sulfone (or 0.156 g methyl phenyl sulfone in the case of toluene), added as internal standard, was placed in a 100 ml round-bottom flask equipped with stirring bar and heated to constant temperature. $AlCl_3$ (10 ml of 1 M) in nitromethane solution was added to the mixture, and after reaching constant temperature a known quantity of a given sulfonyl chloride was added with vigorous stirring.

Most of the work that Olah and co-workers carried out used a range of sulfonyl halides, although they did compare methanesulfonylation using both methanesulfonyl chloride and methanesulfonic anhydride. In the case of methanesulfonylation, the sulfonyl chloride gave k_T/ k_B as 4.2, and using similar conditions the analogous anhydride gave a similar value of 4.0. Both of these results were achieved under the same conditions at 60 °C (See Table 8).

Table 8. $AlCl_3$ catalysed methanesulfonylation of toluene and benzene

Sulfonylating Agent	Catalyst	k_T / k_B	*ortho*	*meta*	*para*	Reaction Conditions	Analytical Method
CH_3SO_2Cl	$AlCl_3$	4.2	54.7	16.6	29.3	60°C, 2 hr	G. C.
$(CH_3SO_2)_2O$	$AlCl_3$	4.0	53.0	14.1	32.9	60°C, 2 hr	G. C.
$(CH_3SO_2)_2O$	$AlCl_3$	4.0	52	48 Total		60°C, 2 hr	NMR

Sulfonylation reactions using methanesulfonyl chloride were also carried out in nitromethane. Using non-competitive conditions at 80 °C, a lower degree of selectivity observed with $k_T/ k_B = 3.3$. The same relative rate was determined by Olah *et al.* using competitive conditions, giving a value of $k_T/ k_B = 3.8$.[13]

DeHaan *et al.* competitively determined the relative rates for the tosylation of benzene and toluene in dichloromethane.[14] The work was carried out using weighted competition conditions, with the less reactive substrate present in higher concentration than the more reactive one. The relative rates obtained are shown in Table 9.[15]

Table 9. Competitively determined rate constant ratios for $AlCl_3$ catalysed *p*-toluenesulfonylation of benzene and toluene in dichloromethane at 25 °C

$[C_6H_6]$	$[CH_3C_6H_5]$	$[CH_3C_6H_4SO_2Cl]$	$[AlCl_3]$	k_T / k_B
0.6948	0.1173	0.0761	0.0393	31 ± 1
0.8473	0.0778	0.0689	0.0303	29 ± 2

The results in Table 9 were achieved using vacuum-line kinetic procedures.[15] In order to avoid the chloromethylation of toluene or benzene, the temperature-equilibrated arene was added to a solution of *p*-toluenesulfonyl chloride and $AlCl_3$. It should be noted that this procedure might not be suitable for work involving *p*-toluene sulfonic anhydride due to the possibility of an "intramolecular" or "unimolecular" reaction taking place (See Chapter 4). The product analysis for this study was carried out using both GC and IR methods.

In the same study DeHaan *et al.* also analysed the product isomer percentages for the competitive reactions. These results are shown below (Table10).

Table 10. Product isomer percentages for the $AlCl_3$ catalysed *p*-toluenesulfonylation of benzene and toluene in dichloromethane at 25 °C *

$[C_6H_6]$	$[CH_3C_6H_5]$	$[CH_3C_6H_4SO_2Cl]$	$[AlCl_3]$	% *ortho*	% *meta*	% *para*
0.6948	0.1173	0.0761	0.0393	12.5 ± 0.5	3.8 ± 0.5	83.6 ± 0.8
0.8473	0.0778	0.0689	0.0303	13 ± 1	4.1 ± 0.5	84 ± 3

* The product analysis was carried out using GC and IR methods.

The product isomer percentage for the $AlCl_3$ catalysed reaction of *p*-toluenesulfonyl chloride with toluene in dichloromethane under non-competitive conditions was also analysed. The isomer distribution is shown below (Table 11).

Table 11. Sulfone product isomer percentages for the $AlCl_3$-catalysed reaction of *p*-toluenesulfonyl chloride with toluene in dichloromethane

	% *ortho*	% *meta*	% *para*
	12.6± 0.3	4.5 ± 0.4	82.9 ± 0.5
	15.1± 0.5	4.4 ± 0.5	80.5 ± 0.8
	14.9 ± 0.4	4.4 ± 0.5	80.7 ± 0.8
	12.5 ± 0.5	3.9 ± 0.4	83.6 ± 0.7
	14.2 ± 0.4	4.5 ± 0.5	81.3 ± 0.4
Average ± S. D.	14 ± 1	4.3 ± 0.2	82 ± 1

The results of DeHaan *et al.* are in contrast to those of Kobayashi *et al.* who reported non-competitively determined k_T / k_B ratios in the range 8 – 10, with no *meta* sulfone product being formed. The work of Kobayashi *et al.* was also carried out in dichloromethane with $AlCl_3$ catalyst. [12]

DeHaan also looked briefly at the SbF_5 catalysed *p*-toluenesulfonylation of toluene and benzene in dichloromethane. Rate constant ratios and product isomer distributions were determined competitively (Table 12 and 13 respectively). The product analysis was carried out using GC and IR methods.

Table 12. Competitively determined rate constant ratios for the $AlCl_3$ catalysed *p*-toluenesulfonylation of benzene and toluene in dichloromethane at 25 °C

[C_6H_6]	[$CH_3C_6H_5$]	[$CH_3C_6H_4SO_2Cl$]	[$AlCl_3$]	k_T / k_B
0.6948	0.1173	0.0761	0.0393	31 ± 1
0.8473	0.0778	0.0689	0.0303	29 ± 2

Table 13. Competitively determined rate constant ratios and product isomer percentages for the SbF_5 catalysed *p*-toluenesulfonylation of benzene and toluene in dichloromethane at 25°C

[C_6H_6]	[$CH_3C_6H_5$]	k_T / k_B	[SbF_5]	% ortho	% meta	% para
0.789	0.200	40 ± 4	0.0313	10.3 ± 0.4	4.7 ± 0.2	85.0 ± 0.5

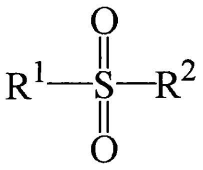
3.4 Routes to aryl sulfones

In order to follow the competition reactions, it was necessary to obtain samples of unsymmetrical sulfone products likely to be formed in the reactions. In each of the competition reactions toluene would be used as the standard and the symmetrical di-*p*-

tolyl sulfone is readily available from commercial sources. The unsymmetrical sulfones likely to be formed in the competition reactions were not readily available from commercial sources and were synthesised. These sulfones were then used to obtain response factors for quantitative analysis and retention times for qualitative analysis.

Although the competition reactions that have been studied primarily involve the formation of unsymmetrical diaryl sulfones, a brief overview of synthetic routes to aryl sulfones is presented.

Sulfones have the general chemical structure **1**, where the substituent groups R^1 and R^2 can take the form of any alkyl, aryl, alkenyl or alkynyl groups.



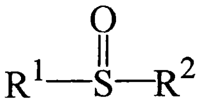
$$R^1-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-R^2$$

1

Although sulfides **2** and sulfoxides **3** can be oxidised to form sulfones, these routes have not been considered here. A review of sulfone formation including oxidative reactions has recently been published by Ward and Diaper.[16]

R^1-S-R^2

2



$$R^1-\overset{\overset{\displaystyle O}{\|}}{S}-R^2$$

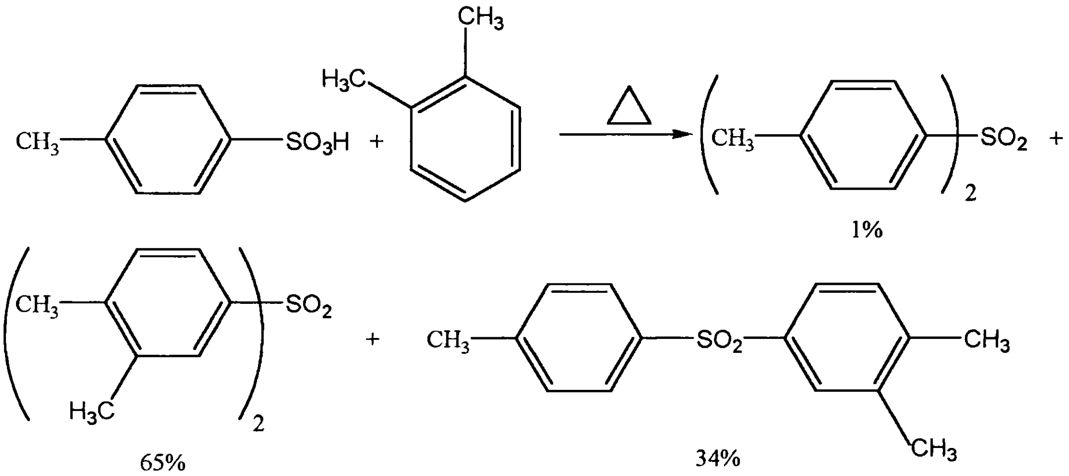
3

3.4.1 Condensation of sulfonic acids with aryl substrates

Condensation of sulfonic acids with aryl substrates in the presence of a dehydrating agent has been proved to be a successful synthetic route to sulfones (Eqn. 5).[17, 18, 19]

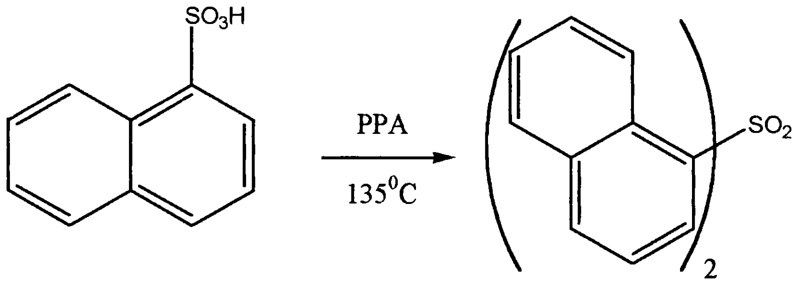
$$\mathrm{Ar^1SO_3H + Ar^2H \xrightarrow{\text{dehydrating agent}} Ar^1SO_2Ar^2 + H_2O} \tag{5}$$

Attempts to carry out similar reactions in the absence of dehydrating agents have been shown to give a mixture of products due to trans-sulfonation (Scheme 1). [20]



Scheme 1

The reactions may be facilitated by removal of water, which may be aided by the addition of P_4O_{10},[21] or by passing a gaseous hydrocarbon stream through the hot reaction mixture.[22] Polyphosphoric acid (PPA) has been found to assist the formation of sulfones, however early work carried out at higher temperatures resulted in relatively low yields of desired products (Scheme 2).[23]



Scheme 2

Graybill synthesised a range of diaryl sulfones using polyphosphoric acid as a dehydrating agent.[17] Benzenesulfonic acid or *p*-toluenesulfonic acid was stirred with the aryl substrates in PPA at 80°C for 8 hours. Although this was found to be a satisfactory method of forming sulfones where active aromatic hydrocarbons were used, in cases involving deactivated aromatic substrates such as chlorobenzene, the reactions did not proceed under the same conditions.

It was later found that the addition of P_4O_{10} to the PPA prior to mixing resulted in an increased yield. It is believed that the improvement was due to the ability of P_4O_{10} to absorb water from the reaction. It has also been found to be advantageous to carry out the reactions under a dry inert atmosphere.[18]

Due to the difficulty associated with handling PPA an alternative set of reaction conditions were developed by Eaton *et al.*[24] A 1:10 (w/w) solution of P_2O_5 in methanesulfonic acid was stirred with the required reagents. The reaction medium was found to act as a good solvent as well as a dehydrating agent, along with being far easier to handle than PPA mixtures. Further studies have been successfully carried out by Ueda *et al.* [19] and Ward and Diaper [25] using the same reagent combination to form diaryl sulfones.

Organometallic reagents have also been employed to form aryl sulfones in moderately good yields.[26] Treatment of an aryltrimethylstannane with a preformed arenesulfonyl chloride-aluminium chloride complex in dichloromethane has been found to give good yields of diaryl sulfones (Equation 6).

$$XC_6H_4SnMe_3 + YC_6H_4SO_2Cl.AlCl_3 \longrightarrow XC_6H_4SO_2C_6H_4Y \qquad (6)$$

Examples of sulfones formed using this technique were as follows (Table 14).

Table 14. Preparation of diaryl sulfones by destannylation

X	Y	Yield (%)
H	H	62
p-Me	H	62
H	*p*-Me	61
p-OMe	H	65
p-F	H	58
H	*p*-Me_3Si	57
H	*p*-Ph	53

Similarly arylmethanesilanes gave the expected di-*p*-substituted sulfone products when treated with arylsulfonyl chloride-aluminium chloride complexes, however in some cases contamination by isomeric products was evident.[26]

Olah *et al.* have recently reported the first truly convenient route to diaryl / aryl alkyl sulfones using sulfonic acids as starting materials. The sulfonylation of aromatics with a suitable arene- or alkanesulfonic acid was easily achieved using Nafion-H, a perfluorinated resinsulfonic acid catalyst.[27]

3.4.2 Friedel-Crafts type sulfonylation and similar reactions

The method of aryl sulfone formation that is better documented than any other is Friedel-Crafts type sulfonylation.[28] It has been widely used for the preparation of aryl sulfones and typically involves the reaction between an arene and a sulfonyl halide in the presence of a Lewis acid catalyst.[29] The original reaction using $AlCl_3$ as catalyst affords satisfactory yields, typically 60-90% (Equation 7).[30]

$$ArSO_2Cl + Ar'H \xrightarrow{AlCl_3} ArSO_2Ar' + HCl \qquad (7)$$

Böeseken *et al.*[31] reported methanesulfonyl chloride to react with benzene in the presence of excess $AlCl_3$ to give methyl phenyl sulfone in a conversion that was "not large." Truce and Vriesen further investigated this field and found that a maximum yield was achieved when a single equivalent of aluminium chloride was used in the reaction.[10] It was proposed that the reason for the reduction in sulfone yield was that the sulfonyl chloride-aluminium chloride complex decomposes in the presence of excess $AlCl_3$ (Equation 8).

$$CH_3SO_2Cl.AlCl_3 \xrightarrow{AlCl_3} CH_3Cl.AlCl_3 + AlCl_3.SO_2 \qquad (8)$$

It was proposed that the ease with which sulfonyl chlorides decompose in the presence of Lewis acids is a function of the stability of the sulfonyl ion and the stability of the carbonium ion. In most of the sulfonylation reactions that have been reported, an excess of catalyst has not been found to have a detrimental effect on the sulfone yield.

A range of diaryl sulfones have been synthesised using substituted arenesulfonyl halides.[10,13,32] The reactivity of a substituted arenesulfonyl halide is influenced by the nature of the substituent. Electron donating groups *para* to the to the SO_2Cl moiety have a rate increasing influence.[33] In the opposite case, electron-withdrawing groups retard the rate of reaction. Due to the reactivity of the sulfonyl halides, even sulfonyl chlorides substituted with *p*-NO_2 moiety are reactive.

Substituents on the aryl substrate exert orienting effects similar to those observed in Friedel-Crafts acylation, although differences between arylsulfonylation and alkylsulfonylation have been observed. In the cases of electron-withdrawing groups on aromatic hydrocarbons in reactions with arylsulfonyl chlorides, an *ortho* directing influence is observed. In similar reactions with methanesulfonyl chloride, only the *para* product is observed.

Where electron-donating substituents are present on the aromatic hydrocarbon, reactions with arylsulfonyl chlorides give a high proportion of the *para* substituted isomer.

A mechanism proposed by Brown *et al.*[34] involves formation of an initial complex between the Lewis acid catalyst and the sulfonyl chloride (Equation 9). The second step of the sequence is ionisation of the sulfonyl chloride, to the sulfonium cation (Equation 10). Subsequently the sulfonium cation attacks the aromatic hydrocarbon producing the sulfone (Equation 11), and then goes on to form a complex with $AlCl_3$. This complex is stronger than the initial complexation with the sulfonyl chloride, which is why one equivalent of catalyst is required.

The rate-determining step is dependent on the reactivity of the aromatic hydrocarbon. Where the aryl substrate is reactive, the second step of the sequence is rate-determining (Equation 10); where the aryl substrate is less reactive, the rate-determining step is the final product-forming step (Equation 11).

$$RSO_2Cl + AlCl_3 \rightleftharpoons RSO_2Cl.AlCl_3 \tag{9}$$

$$RSO_2Cl.AlCl_3 \rightleftharpoons RSO_2^+ + AlCl_4^- \tag{10}$$

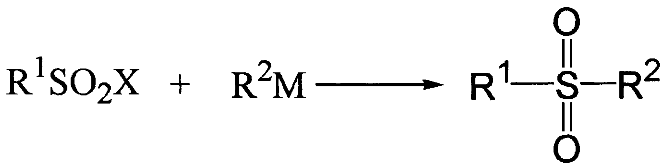
$$RSO_2^+ + AlCl_4^- + ArH \rightleftharpoons ArSO_2R.AlCl_3 + HCl \tag{11}$$

The reaction is usually carried out in excess aromatic hydrocarbon. If however it is carried out in a complexing solvent such as nitromethane, the first step of the reaction sequence is different. Initially the solvent forms a complex with the catalyst, which then goes on to react with the sulfonyl chloride.

Along with sulfonyl halides, sulfonic anhydrides can perform sulfonylation reactions with Lewis acid catalysts.[35]

Recently Fe(III) exchanged montmorillonite clay has been successfully used to catalyse the synthesis of diaryl sulfones.[36] Other environmentally friendly catalysts have been investigated including graphite, which although successful for acylation reactions,[37] has so far proved ineffective in sulfonylation reactions.[38]

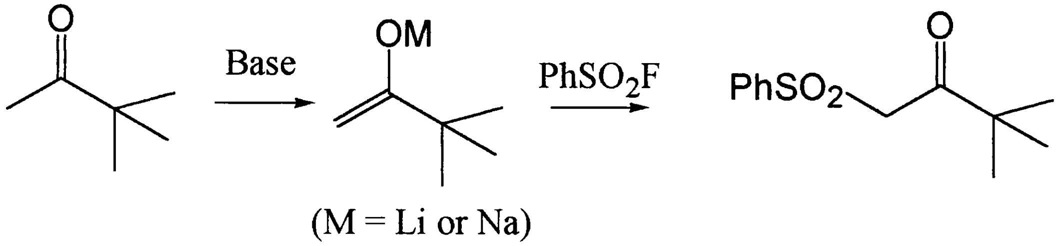
Sulfonyl halides and sulfonate esters can also be treated with a range of organometallic reagents to form aryl sulfones.[39, 40, 41, 42, 43, 44, 45, 46] Organometallic reagents used include organolithium, organocopper, and Grignard reagents. For this type of reaction the sulfonyl fluoride and phenyl sulfonate ester are preferred (Equation 12). This is to reduce the competition from side reactions.



$$R^1SO_2X + R^2M \longrightarrow R^1-\overset{\overset{\large O}{\|}}{\underset{\underset{\large O}{\|}}{S}}-R^2 \tag{12}$$

(R^1, R^2 = alkyl or aryl; X = F or OPh; M = Mg, Li, or Cu)

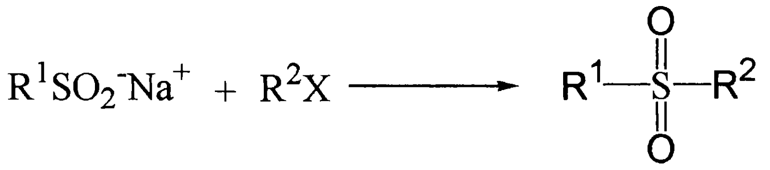
Lithium and sodium enolates react with arenesulfonyl fluorides to form alkylaryl sulfones (Scheme 3).[47]



Scheme 3

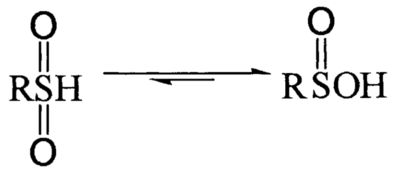
3.4.3 Synthesis of sulfones from sulfinic acids

The alkylation of sulfinic acid salts has been used to prepare arylalkyl sulfones (Equation 13).[48, 49, 50]



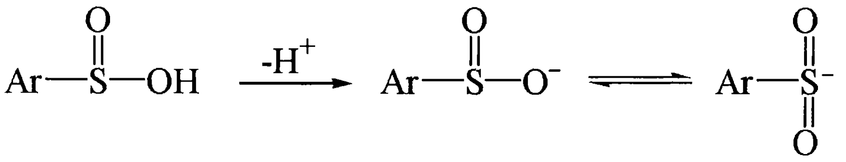
$$R^1SO_2^-Na^+ + R^2X \longrightarrow R^1{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{-}R^2 \qquad (13)$$

Sulfinic acids **4** are believed to exist predominantly as the hydroxy tautomer **5**. The free acids are not very stable and tend to disproportionate to the sulfonic acid and the thiolsulfonate. As a result they tend to be used as the stable sodium salts. Sulfinic acids **4** have been shown to exist primarily in the enolised form **5**.



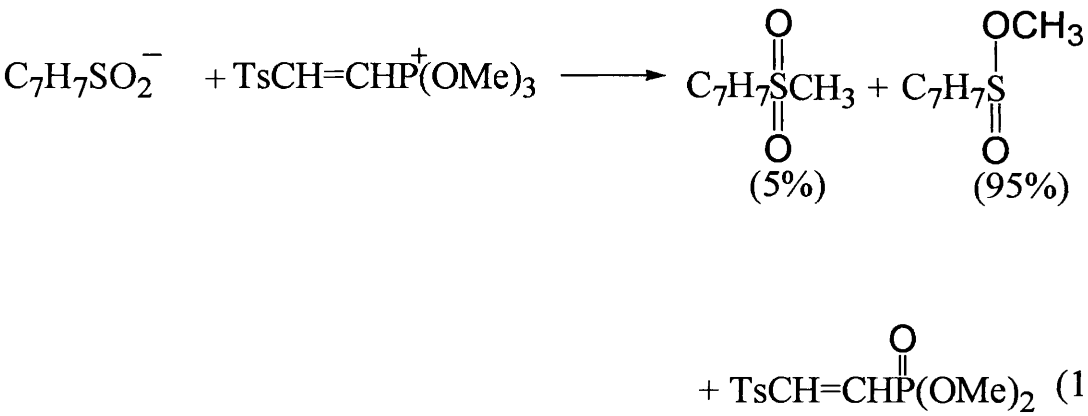
4 **5**

This leads to a competing reaction that can lead to unwanted side products is that of alkylation of the oxygen centre rather than the sulfur centre. This is possible due to the ambient nature of the sulfinate anion (Equation 14).



$$\mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{S}{-}OH} \xrightarrow{-H^+} \mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{S}{-}O^-} \rightleftharpoons \mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{\overset{\overset{\displaystyle O}{\|}}{S^-}}} \qquad (14)$$

Due to the fact that a lot of work is carried out in either water or alcoholic media, the negatively charged oxygen is tightly hydrogen bonded, and thus the sulfur becomes the reactive nucleophilic centre. In reactions where this is not the case, the use of soft electrophiles leads to the almost exclusive formation of sulfone products. Reactions using hard electrophiles result in competition with oxygen alkylation occurring alongside sulfur alkylation. An example of this is shown below (Equation 15).[51]



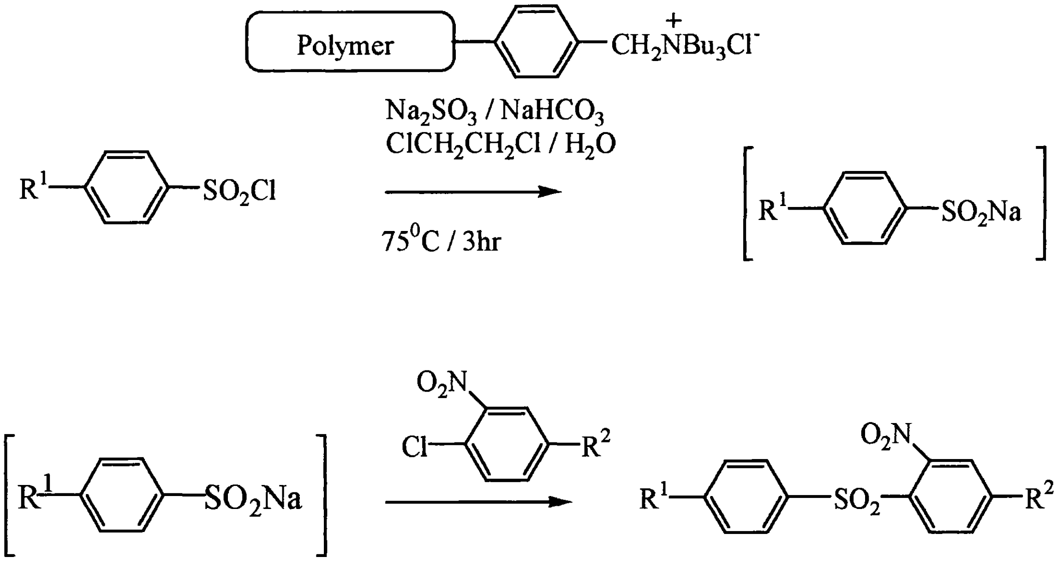
$$\mathrm{C_7H_7SO_2^-} + \mathrm{TsCH{=}CH\overset{+}{P}(OMe)_3} \longrightarrow \underset{(5\%)}{\mathrm{C_7H_7\underset{\underset{\displaystyle O}{\|}}{\overset{\overset{\displaystyle O}{\|}}{S}}CH_3}} + \underset{(95\%)}{\mathrm{C_7H_7\underset{\underset{\displaystyle O}{\|}}{\overset{\overset{\displaystyle OCH_3}{|}}{S}}}}$$

$$+ \mathrm{TsCH{=}CH\overset{\overset{\displaystyle O}{\|}}{P}(OMe)_2} \qquad (15)$$

Phase transfer catalysts have been used in the synthesis of aryl sulfones. Liquid-liquid phase transfer catalysis of the alkylation of sodium *p*-toluenesulfinate with a range of alkyl halides has been successfully carried out, although the method does have limitations.[52] The reaction is carried out in a mixture of benzene, water and acetone at reflux, with tetra-*n*-butylammonium bromide or iodide present as the phase transfer catalyst (Equation 16). In the absence of the phase transfer catalyst the reaction does not proceed.

$$CH_3CH_2I + ArSO_2Na \xrightarrow[H_2O\ /\ C_6H_6\ /\ (CH_3)_2CO]{TBAB} CH_3CH_2SO_2Ar + NaI \qquad (16)$$

More recently polymer supported phase transfer catalysts, including tri-*n*-butylammonium chloride on polystyrene have been used to promote the arylation of aromatic sulfinate salts to form unsymmetrical diaryl sulfones (Scheme 4). The polymer supported phase transfer catalysts are easier to recover and therefore more economically viable, however this is still not an ideal route for the preparative synthesis of sulfones. [53]



(R^1 = F, CH_3; R^2 = CHO, $COCH_3$, NO_2)

Scheme 4

Sulfinic acids have been shown to add successfully to α,β-unsaturated olefins, yielding the corresponding sulfones, the reaction being catalysed by either a buffer solution or weak acids. These reactions are Michael-type additions, with the sulfur atom apparently being the nucleophilic centre of the sulfinic acid. It is believed that this is due to protonation of the terminal oxygen, and the thermodynamic stability of the sulfone product. Several examples are shown below (Eqns. 17, 18 and 19).[54]

$$p\text{-}\mathrm{CH_3C_6H_4SO_2Na} + \mathrm{CH_2{=}CHCN} \xrightarrow{\mathrm{H_3BO_3}} p\text{-}\mathrm{CH_3C_6H_4SO_2CH_2CH_2CN} \qquad (17)$$

$$\mathrm{PhSO_2H} + \mathrm{CH_2{=}CHCOOH} \xrightarrow{\mathrm{H_3BO_3}} \mathrm{PhSO_2CH_2CH_2COOH} \qquad (18)$$

$$p\text{-}\mathrm{CH_3C_6H_4SO_2Na} + \mathrm{CH_2{=}CHCOOCH_3} \xrightarrow{\mathrm{CH_3COOH}} p\text{-}\mathrm{CH_3C_6H_4SO_2CH_2CH_2COOCH_3} \qquad (19)$$

3.5 Synthesis of diaryl sulfones

Having reviewed a range of different synthetic routes to unsymmetrical diaryl sulfones, the synthesis of the required sulfones was carried out. Initially the sulfones were synthesised using the traditional Friedel-Crafts type sulfonylation methods. For the synthesis of 4-bromophenyl-*p*-tolyl sulfone, 4-chlorophenyl-*p*-tolyl sulfone and 4-methoxyphenyl-*p*-tolyl sulfone, the Friedel-Crafts route worked well. These reactions were carried out by reacting toluene with the appropriate *para*-substituted benzenesulfonyl chloride. $AlCl_3$ was used as the catalyst in these reactions.

The synthesis of 4-*iso*propylphenyl-*p*-tolyl sulfone proved to be more problematic Thus, several products were observed on reacting cumene with *p*-toluenesulfonic anhydride (See 3.7). It was therefore decided to attempt the synthesis using Eaton's acid. This was carried out using a 10:1 mixture of methanesulfonic acid / phosphorus pentoxide (w/w). This acts as the dehydrating agent in the condensation of *p*-toluenesulfonic acid with *iso*propylbenzene. The procedure was successful with only a single product obtained although in low yield (16%). The method was simple to carry out, and gave only a single product isomer, the work up of which was straightforward. Later analysis of the products from the attempted synthesis of 4-*iso*propylphenyl-*p*-tolyl sulfone by the Friedel-Crafts method using LC-MS showed that the main product formed was indeed the desired sulfone. The by-products formed were shown to be of the same molecular mass. It was believed that these other products were the 2- and 3- substituted isomers. This problem could possibly have been overcome by starting with the 4-*iso*propylbenzenesulfonyl chloride and reacting it with toluene, however the sulfonyl chloride was not readily available. The synthesis of 4-fluorophenyl-*p*-tolyl sulfone also proved problematic. It was carried out using the

Friedel-Crafts type reaction between 4-fluorobenzenesulfonyl chloride and excess toluene, catalysed by $AlCl_3$. Although the sulfone was formed, a large quantity of a by-product was also formed. The by-product was found to be the corresponding 4-fluorobenzenesulfonyl chloride hydrolysis product, 4-fluorobenzenesulfonic acid.

Several methods of removing the acid by-product were attempted, with only limited success. Extracting the product mixture into dichloromethane, and then washing with aqueous $NaHCO_3$ (10%) did remove some of the acid by-product, but only a small fraction (~20-30% by NMR). Following this the sulfone was again dissolved in dichloromethane, and washed with water. It was hoped that the acid would be soluble enough in the water to be separated from the sulfone product. This however proved unsuccessful. A similar procedure was attempted, washing with Na_2CO_3. This proved to be an unsatisfactory technique due to the fact that the sulfone product appeared to be cleaved, producing *p*-toluenesulfonic acid. The NMR of the mixture also suggested that small quantities of further impurities were present after this process.

The most successful method of removing the acid appears to be partial recrystallisation. The method is slow, but did provide small quantities of the pure sulfone product. The synthesis of the complete range of unsymmetrical sulfones is summarised below (Table 15).

Table 15. Synthesis of unsymmetrical sulfones for use as reference standards in HPLC.

Reagent A	Reagent B	Catalyst	Yield of desired product (%)
4-Bromobenzene sulfonyl chloride	Toluene	$AlCl_3$	5
4-Chlorobenzene sulfonyl chloride	Toluene	$AlCl_3$	20
4-Methoxybenzene sulfonyl chloride	Toluene	$AlCl_3$	51
4-Toluenesulfonic acid	Cumene	CH_3SO_3H / P_2O_5	16
Benzenesulfonyl chloride	Toluene	$AlCl_3$	60
4-Fluorobenzene sulfonyl chloride	Toluene	$AlCl_3$	10

3.6 Method development and analytical methodology for competition reactions

The aim of this study was to investigate the relative reactivity of different aromatic substrates in the presence of activated aromatic sulfonic anhydrides. It has been shown that the reaction between toluene and *p*-toluenesulfonic anhydride can be catalysed by a number of different acidic catalysts, both Lewis and Brønsted acids (See Chapter Two). For the competition reactions, in order to enable us to calculate relative rates of sulfonylation it was decided to initially use $AlCl_3$ as catalyst. $AlCl_3$ had been shown to promote good reactivity of *p*-toluenesulfonic anhydride with toluene under convenient conditions. By understanding the influence of substituents in the sulfonylation leading to sulfone production, it was hoped that the information obtained would be of use in the development of LAB feedstocks.

Having decided to study competition reactions and consider the overall reactivity of aryl substrates towards *p*-toluenesulfonic anhydride, a method of analysis to follow the reaction.

Following the successful use of HPLC in the analysis of the initial sulfonylation studies, it seemed that use of a similar system would be appropriate to follow the competition reactions. In order to follow the reactions then either the formation of products or the disappearance of starting material would have to be followed.

In order to decide which approach to follow, the nature of the competition reactions was taken into consideration. When using competitive conditions to calculate the relative rates of reaction, then the reactions must be considered fair. In order for this to be the case then a large excess of reagent, approximately 10-fold, of the competing substrates over the common reagent, must be used. This ensures that if one substrate is significantly more reactive than the other, then an unfair competition does not evolve in the latter stage of the reaction. Effectively the relative concentration of reagents is thus: Substrate A: Substrate B: Common Reactant = 10:10:1. If a ratio of 1:1:1 was used, and substrate A was significantly more reactive than Substrate B then a situation could arise where the effective ratio of reagents late in reaction was 0.1:1:0.1, distorting the competition. The reaction would no longer be pseudo first order. Using a large 10-fold excess of competing substrates keeps this distortion of results to a minimum, with the largest possible excess of one substrate over the other being 10%.

Taking this into account, if we were to follow the disappearance of starting material, at most, approx 10% reduction in the concentration of the starting materials would be observed. If the formation of reaction products was monitored then a change of up to 100% would be seen. Due to the fact that observing a large change in a small quantity is easier than observing a small change in a large quantity, then following the formation of reaction products appeared the most obvious way to follow the competition reactions.

In order to calculate relative rates of sulfonylation in the competition reactions, then the rates have to be measured relative to a standard substrate. Toluene was used due to the knowledge of its reaction that had been gained in the initial studies (Chapter 2).

As in the initial studies it was decided to use an inert internal standard to calculate the concentration of the reaction products. Due to the success of using 2-nitrotoluene as the internal standard in the initial sulfonylation studies, it was decided where possible to use the same standard again. The only possible complication could be if the reaction products displayed similar retention properties when analysed by HPLC. In order to use 2-nitrotoluene as the internal standard, response factors for the unsymmetrical sulfones were required. These were obtained relative to 2-nitrotoluene using the same techniques as used for di-*p*-tolyl sulfone (See Chapter 2 Appendix 1). The response factors obtained are shown below (Table 16). Details of the response factor calculations are given in Chapter Three Appendix.

Table 16. HPLC response factors for use in competition reactions measured relative to 2-nitrotoluene

Substituent X	Response Factor
H	0.194
CH_3	0.189
$CH(CH_3)_2$	0.171
Br	0.203
Cl	0.197
OCH_3	0.323

In order for the competition reactions to be truly comparable, then the concentrations of the starting materials must be identical. The reactions were initially carried out by mixing standard solutions of all the individual components of each reaction: Substrate A, substrate B, $AlCl_3$, internal standard and *p*-toluenesulfonic anhydride. Although the component ratios were approximately the same for each reaction, they were not reproducible. It was found that no matter how much care was taken in measuring out the starting materials, the exact amount of each substrate used could never be accurately reproduced. This was overcome by preparing a pre-mixed solution containing both competing substrates and the internal standard. This meant that only three solutions had to be mixed: The competing substrates including the internal standard, the $AlCl_3$ catalyst and the sulfonic anhydride solutions, respectively. Due to the fact that a large excess of the competing substrates over the sulfonic anhydride was being used, the exact ratio of the substrates to anhydride was consistent.

Another consideration when looking at the competition reaction is medium effects. The fact that the reactions are carried out in solution has to be taken into consideration. If the reactions are carried out in dilute conditions then the medium effects can be considered negligible. The use of dilute conditions would also make the sampling of the reactions for HPLC analysis simpler and more reproducible.

The temperature of each of the competition reactions must be identical and reproducible. This was achieved using a water bath set at 25.0 °C. The solutions of starting materials used in the reactions were placed in sealed flasks and submerged in the water bath up to the neck. The temperature was allowed to equilibrate for approximately 1 hour with stirring. Using trial samples the temperature was found to be stable at 25.0 °C after less than 15 minutes. The stirring was carried out using magnetic stirring bars and submersible magnetic stirrers.

In early trials it was found that if the $AlCl_3$ catalyst was added to the *p*-toluene sulfonic anhydride in the absence of any aryl substrate then the formation of di-*p*-tolyl sulfone was observed. This was an unexpected result that had implications in the competition reactions. If another route to the di-*p*-tolyl sulfone exists other than the Friedel-Crafts type sulfonylation, then the figures obtained for the competition reactions could be inaccurate. The figures could be distorted by product formed via another competing reaction. An investigation was therefore carried out looking at this possibility. It was discovered that in the presence of an aryl substrate, the yield of sulfone product from the *intra*molecular reaction was negligible. Di-*p*-tolyl sulfone was not produced via this route. This was even the case when an inert, unreactive substrate such as 2-nitrotoluene was present. Full details of the study of the unimolecular reaction are given in Chapter Four, however for the purposes of the competition reactions this alternative pathway can be discounted. By adding the catalyst to the reaction as the final component, the possibility of this reaction occurring can be eliminated.

3.7 Competition reactions using a range of aromatic substrates in sulfonylation reactions with *p*-toluenesulfonic anhydride

The competition reaction between toluene and benzene reacting with *p*-toluenesulfonic anhydride was the first competition studied. Due to the large amount of data available on the relative reactivities of toluene and benzene, it was hoped that the results from the study would provide confirmation that the techniques developed were giving reasonable results. Although the actual relative reactivities obtained would be new, groups using *p*-toluenesulfonyl chloride and methane sulfonic anhydride as the sulfonylating agents had obtained similar data.

The competition between toluene and benzene gave a relative rate $k_{Me} / k_H = 9.1$ This is close to the value of $k_{Me} / k_H = 8.0$ observed by Brown *et al.* using non-competitive conditions and benzenesulfonyl chloride as the sulfonylating agent. Using *p*-toluenesulfonyl chloride Kobayashi *et al.* calculated a relative rate under non-competitive conditions of $k_{Me} / k_H = 10.0$, however it has since been observed that $k_{Me} / k_H = 17.0$ for the same reaction under competitive conditions by Olah *et al.*

In the competition reaction between *iso*propylbenzene and toluene the observations were different to those expected. In the reaction between toluene and *p*-toluene sulfonic anhydride, substitution of the hydrogen in the position *para* to the methyl group is the only reaction observed. Only the di-*p*-tolyl sulfone is observed as a reaction product. In the reaction between *p*-toluenesulfonic anhydride and *iso*propylbenzene, three reaction products were observed. These are believed to be the substitution products due to reaction at the *ortho, meta* and *para* positions to the *iso*propyl group. It was considered that these products could have been formed via one of two routes, the first being reaction at each of the respective positions, the second being via reaction at the position *para* to the *iso*propyl group, followed by rearrangement to give the product mixture. The possibility of rearrangement was investigated using a pure sample of 4-*iso*propylphenyl-*p*-tolyl sulfone. The rearrangement was attempted, however it could not be achieved using a range of conditions (See section 3.7).

In order to measure the total reactivity of the *iso*propylbenzene response factors for the 2,4'- and 3,4'- substituted unsymmetrical sulfones were required. Difficulty was experienced in synthesising these sulfones. Several different routes to the sulfones were attempted, but without success (See section 4.6). Due to the similarities in the response factors for the sulfones, it was decided that an estimate of the reactivity could be made using the response factor for 4-*iso*propylphenyl-*p*-tolyl sulfone.

The relative reactivity of *iso*propylbenzene was found to be lower than expected, with an overall relative reactivity of $k_{i\mathrm{PB}} / k_{\mathrm{Me}} = 0.43$. This figure was obtained using the sum of the yields of the three different isomeric sulfone products. The 4-*iso*propylphenyl-*p*-tolyl sulfone was positively identified by LC-MS and co-injection. Using data obtained by Brown and co-workers under non-competitive conditions, it has been possible to calculate a value of $k_{i\mathrm{PB}} / k_{\mathrm{Me}} = 0.53$. This is in good agreement with this study, carried out using competitive conditions.

The relative reactivity at the position *para* to the *iso*propyl group can be compared to that of the position *para* to the methyl group in toluene. The result gives $k_{i\mathrm{PB}\,(para)} / k_{\mathrm{Me}\,(para)} = 0.29$, again lower than the expected figure based on other electrophilic substitution reactions studied by other groups.

The reactions involving bromobenzene and chlorobenzene proved to be more difficult to study. Initially trial reactions were carried out at higher concentration than that used for the competition reactions. These were used to analyse the isomer distribution in the reactions between halobenzenes and *p*-toluenesulfonic anhydride. In these reactions only the 4-substituted unsymmetrical sulfones were formed. The 2- or 3-halophenyl-*p*-tolyl sulfone products were not observed. This is in agreement with the work of Truce and Vriesen.[10] They found that in the methanesulfonylation of chlorobenzene, bromobenzene and fluorobenzene only the *para* isomer was formed. In this study it was found that no reaction between fluorobenzene and *p*-toluenesulfonic anhydride was observed. The observed yields for the other reactions are given below (See Tables 17 and 18).

Table 17. Isomer distribution for *p*-toluenesulfonic anhydride sulfonylation of bromobenzene catalysed by $AlCl_3$ at 25.0 °C.

Substrate	Mol. Eq.	Mol. Eq. $AlCl_3$	Yield of 2-, 3- and 4-bromophenyl-*p*-tolyl sulfone (%)		
			2-	3-	4-
Bromobenzene	0.7	0.3	-	-	18.9
Bromobenzene	1.5	0.7	-	-	33.9
Bromobenzene	1.7	8.3	-	-	76.7

Table 18. Isomer distribution for *p*-toluenesulfonic anhydride sulfonylation of chlorobenzene catalysed by $AlCl_3$ at 25.0 °C.

Substrate	Mol. Eq.	Mol. Eq. $AlCl_3$	Yield of 2-, 3- and 4-chlorophenyl-*p*-tolyl sulfone (%)		
			2-	3-	4-
Chlorobenzene	0.7	0.3	-	-	5.0
Chlorobenzene	1.5	0.7	-	-	7.6
Chlorobenzene	1.7	8.3	-	-	21.3

In the competition reactions bromobenzene was observed to be less reactive than the alkylbenzene substrates considered. For the competition reactions between bromobenzene and toluene, reactions were carried out using both $AlCl_3$ and $SnCl_4$ catalysts. The actual yields of 4-bromophenyl-*p*-tolyl sulfone observed were very low ($\leq 1\%$). This made the measurement of the of the sulfone yield difficult.

A chromatogram from a sulfonylation competition reaction between bromobenzene and toluene with very little sulfone product can be seen compared to a sample spiked with pure di-*p*-tolyl sulfone and 4-bromophenyl-*p*-tolyl sulfone (See Figure 2).

The reaction yields are given below (See Tables 19 and 20).

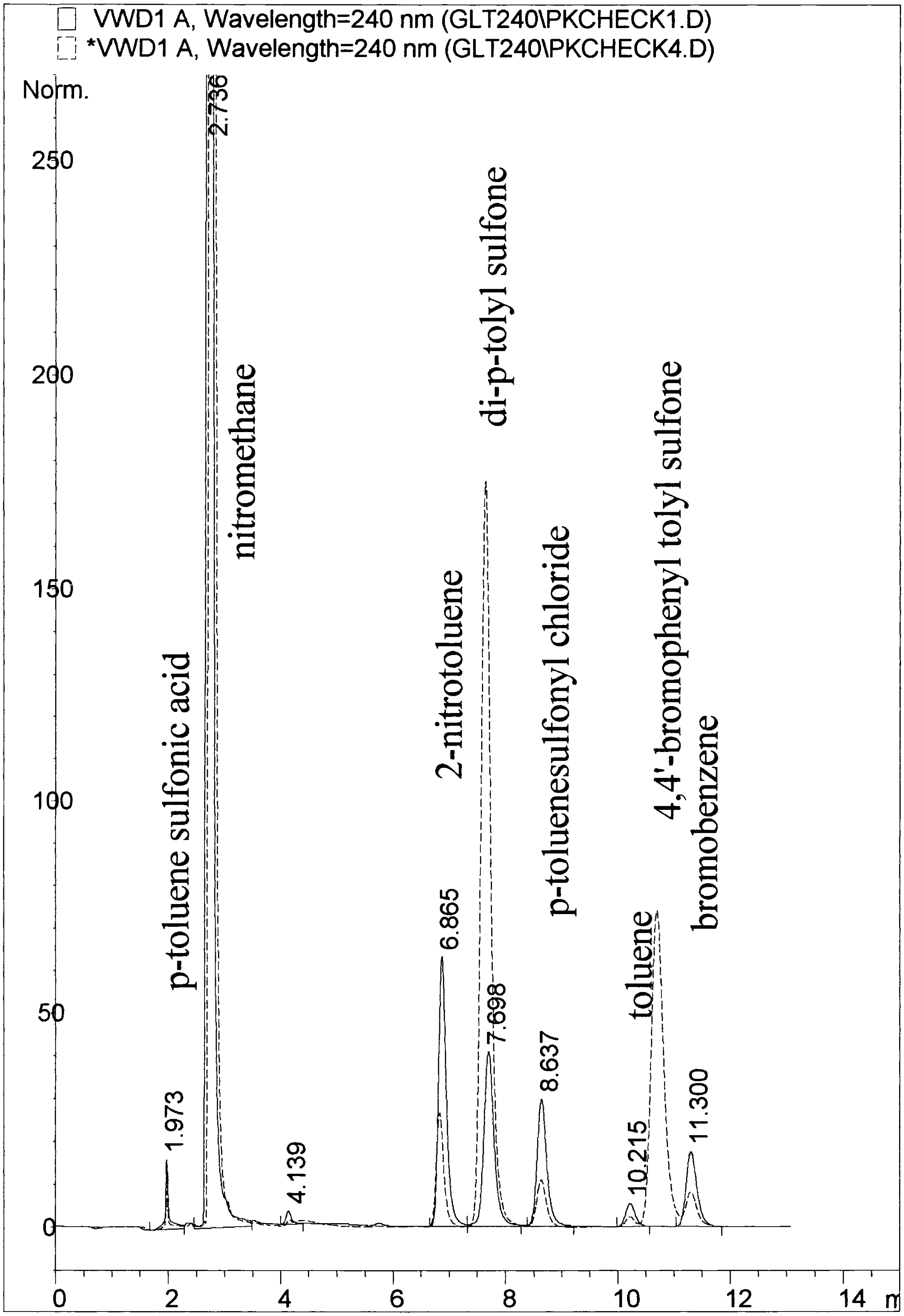


Figure 2. Overlaid chromatograms showing large co-injected di-*p*-tolyl sulfone and 4-bromophenyl-*p*-tolyl sulfone peaks.

Table 19. Relative reactivity of bromobenzene compared to toluene in sulfonylation by *p*-toluenesulfonic anhydride catalysed by $AlCl_3$ at 25.0 °C

Substrate	Mol. Eq.	Mol. Eq. $AlCl_3$	Yield di-*p*-tolyl sulfone (%)	Yield of 4-bromo-*p*-tolyl sulfone (%)	k_{Br} / k_{Me}
Bromobenzene	10.0	5.0	6.3	0.13	0.021
Bromobenzene	10.0	5.0	16.2	0.37	0.023
Bromobenzene	10.0	5.0	11.0	0.22	0.020
				Mean =	0.021

Table 20. Relative reactivity of bromobenzene compared to toluene in sulfonylation by *p*-toluenesulfonic anhydride catalysed by $SnCl_4$ at 25.0 °C

Substrate	Mol. Eq.	Mol. Eq. $SnCl_4$	Yield di-*p*-tolyl sulfone (%)	Yield of 4-bromo-*p*-tolyl sulfone (%)	k_{Br} / k_{Me}
Bromobenzene	10.0	5.0	18	0.35	0.020
Bromobenzene	10.0	5.0	18.1	0.36	0.020
Bromobenzene	10.0	5.0	18.1	0.35	0.019
Bromobenzene	10.0	5.0	17.9	0.31	0.017
Bromobenzene	10.0	5.0	21.9	0.45	0.021
				Mean =	0.019

The values from the reactions involving $AlCl_3$ catalyst lead to a value of $k_{rel} = 0.021$. The results for the reactions catalysed by $SnCl_4$ give a similar value of $k_{rel} = 0.019$. It is clear that the bromobenzene is significantly less reactive than the substrates considered so far in the sulfonylation competition reactions.

The competition reaction between chlorobenzene and toluene reacting with *p*-toluenesulfonic anhydride also proved to be problematic. In the current study, using the reaction technique developed for the competition reactions it was possible to observe the formation of 4-chlorophenyl-*p*-tolyl sulfone, however due to the small quantities formed the sulfone peak was not easy to measure. Di-*p*-tolyl sulfone was detected in much larger quantities. The sulfone yields and k_{rel} values are given below (See Table 21).

Table 21. Relative reactivity of chlorobenzene compared to toluene in sulfonylation by *p*-toluenesulfonic anhydride catalysed by $AlCl_3$ at 25.0 °C

Substrate	Mol. Eq.	Mol. Eq. $AlCl_3$	Yield di-*p*-tolyl sulfone (%)	Yield of 4-chloro-*p*-tolyl sulfone (%)	k_{Cl} / k_{Me}
Chlorobenzene	10.0	5.0	10.7	0.16	0.015
Chlorobenzene	10.0	5.0	10.8	0.17	0.016
Chlorobenzene	10.0	5.0	17.5	0.26	0.015
Chlorobenzene	10.0	5.0	15.0	0.24	0.016
Chlorobenzene	10.0	5.0	23.0	0.32	0.014
				Mean =	0.015

It appears that *p*-toluenesulfonic anhydride reacts with $AlCl_3$ to form *p*-toluenesulfonyl chloride (Equation 20).

$$\begin{aligned}(CH_3C_6H_4SO_2)_2O + AlCl_3 \longrightarrow\ & CH_3C_6H_4SO_2Cl \qquad (20)\\ & + CH_3C_6H_4SO_2O.AlCl_2\end{aligned}$$

It was found that quenching of the reactions in ethanol is not a rapid process, with the sulfonyl chloride surviving the quenching process when analysis was carried out immediately. The fact that the reaction stops at the sulfonyl chloride is an unexpected result. In the reactions a five-fold excess of $AlCl_3$ was used. Another possible explanation of the observation is that the reaction is being terminated by the presence of moisture (Equation 21).

$$2AlCl_3 + 3H_2O \longrightarrow Al_2O_3 + 6HCl \qquad (21)$$

The *p*-toluenesulfonic anhydride would then react with the HCl to form the sulfonyl chloride (Equation 22).

$$(CH_3C_6H_4SO_2)_2O + HCl \longrightarrow CH_3C_6H_4SO_2Cl + CH_3C_6H_4SO_3H \qquad (22)$$

The reaction was observed to stop at the sulfonyl chloride that was stable over time in the reaction. A test was carried out to ascertain whether the reaction had stopped due to hydrolysis of the $AlCl_3$ or whether a competing reaction between the $AlCl_3$ and the *p*-toluenesulfonic anhydride was taking place. The introduction of active $AlCl_3$ to the reaction mixture was observed to have no effect on the reaction system. This confirms that the reaction had not stopped due to hydrolysis of the catalyst. If this had been the case then the reaction would be expected to start again upon addition of new $AlCl_3$.

It is believed that the competing reaction (Equation 20) takes place. Sulfonyl chlorides have been found to be significantly less reactive than the corresponding sulfonic anhydrides, resulting in what appears to be the termination of the reaction.[55] Over a longer time the sulfonyl chlorides would be seen to react, however this would then distort the relative rates of sulfonylation.

Following the observations made in the reaction of chlorobenzene and toluene with *p*-toluenesulfonic anhydride it was feared that similar observations would be made in the competition reaction between fluorobenzene and toluene. Preliminary investigations were carried out to see whether any 4-fluorophenyl-*p*-tolyl sulfone could be detected. As feared only the di-*p*-tolyl sulfone was detected. Due to the very low reactivity of fluorobenzene and the relatively high reactivity of toluene a relative rates could not be calculated under the current conditions.

The relative rates were all measured relative to toluene in the current study. The rates can be calculated so that they can be considered relative to benzene. This has been done and the results are shown below (See Table 22). The rates relative to benzene can easily be compared to the Hammett and electrophilic substituent constants. This is shown below (See Table 23). The results are represented graphically in a Hammett plot (See Figure 3).

Table 22. Conversion of relative rates of sulfonylation from toluene standard to benzene standard

Substituent X	k_X / k_{Me}	k_X / k_H
Methyl	1	9.11
*Iso*propyl	0.43	3.913
Hydrogen	0.11	1
Chloro	0.015	0.137
Bromo	0.021	0.189

Table 23. Comparison of relative rates of sulfonylation relative to benzene with Hammett and Electrophilic substituent constants

Substituent X	σ_p	σ_p^+	k_X / k_B
Methyl	-0.170	-0.311	9.11
*Iso*propyl	-0.151	-0.280	3.91
Hydrogen	0	0	0
Chloro	0.227	0.114	0.137
Bromo	0.232	0.150	0.189

Hammett plot of log (k_X / k_H) against Hammett constants

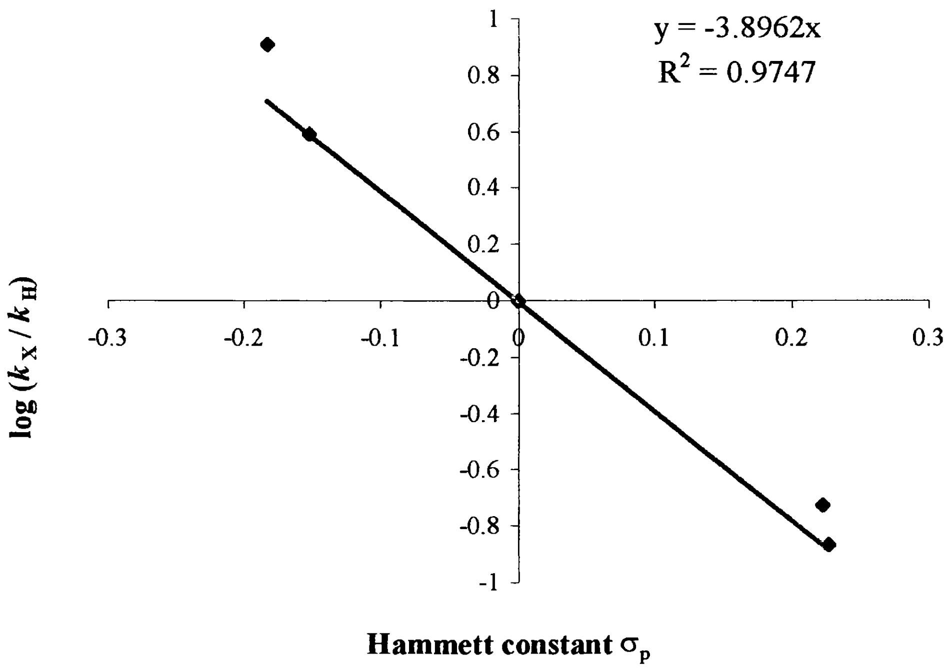


Figure 3

The relative rates of sulfonylation can be seen to be relatively consistent with the Hammett and electrophilic substituent constants, apart from the reactions involving chlorobenzene. Chlorobenzene can be seen to be less reactive than the substitution constants predict, with the reactivity lower than that of bromobenzene, although the reactivities are close as expected. As predicted by the Hammett and electrophilic substituent constants, the reactivity of chlorobenzene and bromobenzene are observed to be much lower than that of the alkyl-substituted benzene derivatives. The order of reactivity observed in the reaction series was toluene > *iso*propylbenzene > benzene > bromobenzene > chlorobenzene. Although the chlorobenzene and bromobenzene are in the reverse order to that which the substitution constants predict, they are very close and the sulfone yields involved are very low.

It can also be seen that toluene is slightly more reactive under the Friedel-Crafts conditions than the constants predict, however the relative rate is close to the predicted value, and the order of reactivity is in agreement with the predicted results.

It is possible to obtain the reaction constant ρ, by measuring the gradient of the Hammett Plot. It was found that $\rho = -3.8962$. The reaction constant is independent of the substituents, and is dependant on the nature of the reaction.

The sulfonylation competition reaction between 4-methoxybenzene and toluene catalysed by $AlCl_3$ was not attempted due to time constraints.

3.8 Isomer formation and isomer distribution in sulfonylation reactions

During the synthesis of the unsymmetrical diaryl sulfones, the reaction of *p*-toluenesulfonic anhydride in with *iso*propylbenzene catalysed by $AlCl_3$ resulted in the formation of several different reaction products. These products were readily separated by HPLC (See Figure 4).

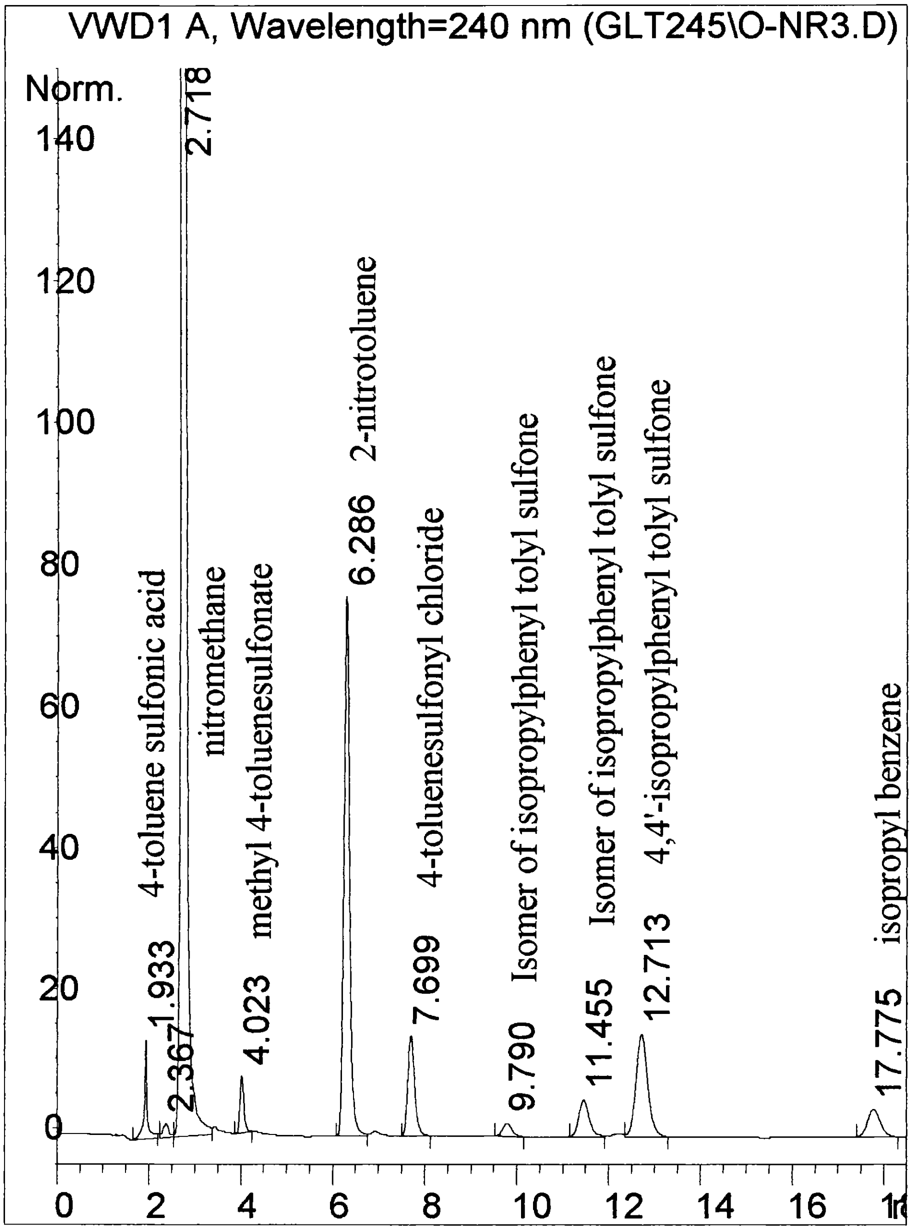


Figure 4. Chromatogram showing the separation of isomers of *iso*propylphenyl tolyl sulfone using HPLC

In order to confirm the identity of the reaction peaks LC-MS was employed. The LC-MS results indicated that two of the peaks were of equal mass, the same as the 4-*iso*propylphenyl-*p*-tolyl sulfone. These were the 2- and 3-*iso*propylphenyl-*p*-tolyl sulfones respectively. The isomer ratios are given below (See Table 24).

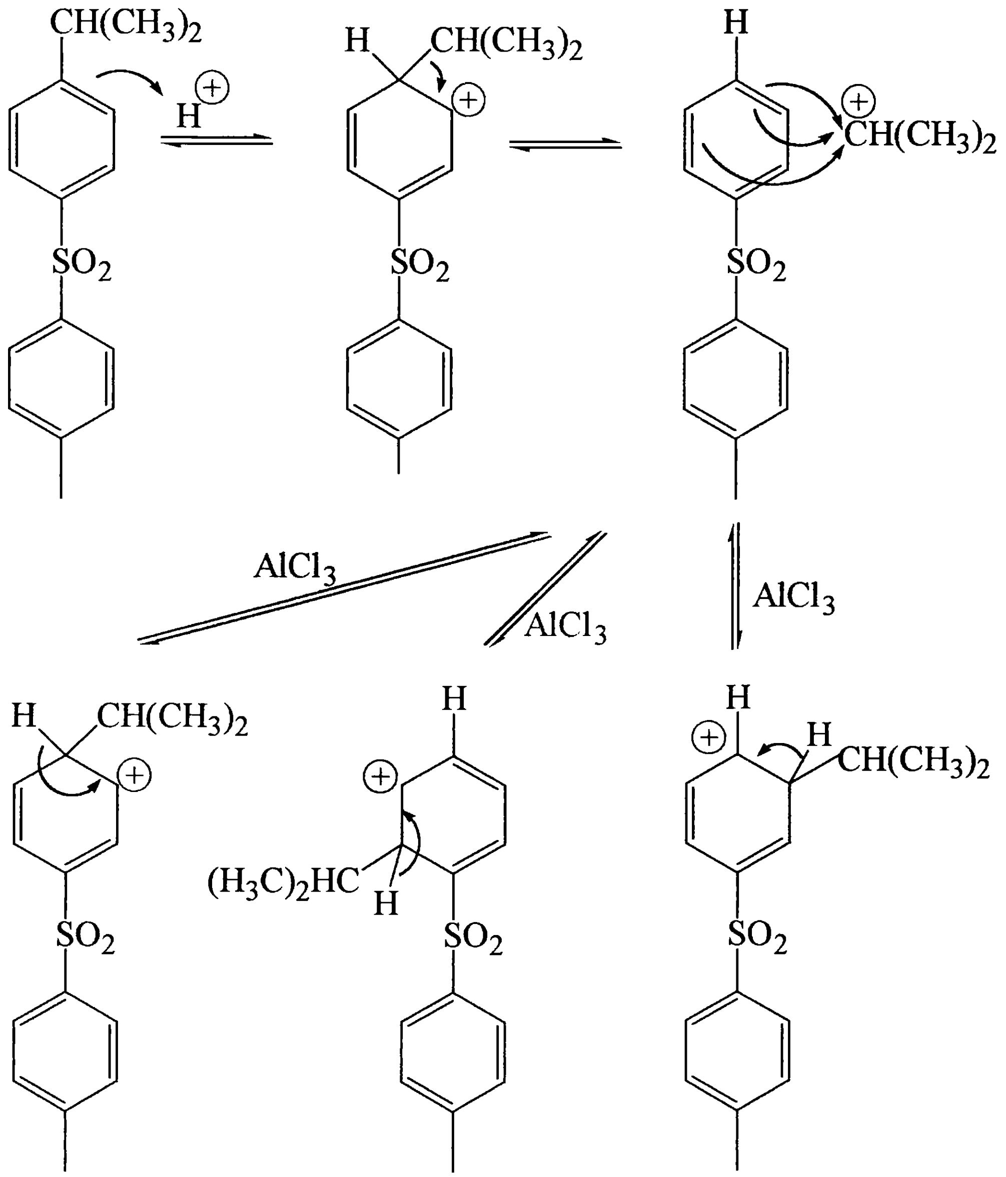
Table 24. Product isomer distribution in the reaction between *p*-toluenesulfonic anhydride and *iso*propylbenzene catalysed by $AlCl_3$ at 25 °C

Sulfonylating Agent	Catalyst	(%) *ortho*	(%) *meta*	(%) *para*	Reaction Conditions
$(p\text{-}CH_3C_6H_6SO_2)_2O$	$AlCl_3$	26.0	5.0	69.0	25°, 3 hr
$(p\text{-}CH_3C_6H_6SO_2)_2O$	$AlCl_3$	22.9	6.9	70.2	25°, 3 hr

Due to the fact that reactions involving *p*-toluenesulfonic anhydride appear regularly to only produce the di-*p*-substituted product, another approach to explain the observations was considered. The possibility was investigated that initially only the 4-*iso*propylphenyl-*p*-tolyl sulfone was formed, which then underwent dealkylation and realkylation *in situ*. The acidic conditions due to the presence of the Lewis acid $AlCl_3$, could possibly promote the isomerisation reaction.

In order to mimic the original reaction conditions, a sample of 4-*iso*propylphenyl-*p*-tolyl sulfone was subjected to similar acidic conditions. The sulfone was added to dry nitromethane to form a standard solution, which was then mixed with a standard solution of $AlCl_3$ in nitromethane. This was initially carried out using 5 equivalents of $AlCl_3$ with respect to the quantity of di-*p*-substituted sulfone. Further dry nitromethane was added to the reaction mixture to dilute the reaction mixture, in order to bring the concentration into line with the competition reactions. The reaction mixtures were allowed to equilibrate at 25.0 °C, and were allowed to react over a period of 18 hours. Samples were regularly taken over this period, however no reaction was observed. The reaction was repeated employing twice as much $AlCl_3$ catalyst, but still no isomerisation was observed. The reaction was then repeated for a third time, adding a large excess of solid $AlCl_3$ to the reaction, again to no avail.

It was noted that under the current reaction conditions, no source of protons was present. This was in contrast to the original synthetic conditions, where for every molecule of sulfonic anhydride that reacts to produce a molecule of sulfone, a molecule of the by-product *p*-toluenesulfonic acid if formed. The protic acid could therefore bring about the isomerisation process (See Scheme 5).



Scheme 5

The reaction conditions were then modified to take into account this new consideration. The revised reaction conditions used the same standard solutions of sulfone and $AlCl_3$ (0.03 M and 0.15 M respectively) and included a third standard solution of *p*-toluenesulfonic acid. Again these reactions were attempted several times employing slightly different conditions, however the 4-*iso*propylphenyl-*p*-tolyl sulfone was recovered unaffected every time.

It is therefore concluded that the different isomers are formed by electrophilic substitution at the different positions during the sulfonylation process and not by rearrangement.

3.9 Effects of changes in reaction concentration on reaction yield in sulfonylation reactions

Due to the relatively low yields of sulfone products, a brief investigation was carried out into the effect of increasing the overall reaction concentration. The ratio of the reagents to each other was maintained, with all concentrations increased by the same factor. It was hoped that the reaction yields would be seen to increase.

The tests were carried out using both *p*-toluenesulfonic anhydride and *p*-toluenesulfonyl chloride as sulfonylating agents. Toluene was used as the aryl substrate in all of the reactions. The reactions were carried out using the same technique as for the competition reactions, however only a single substrate was present. The reactions were allowed to proceed for 3 hours and were then analysed by HPLC. The results of the reactions are shown below (See Table 25 and Table 26). Graphical representation is also given (See Figures 5 and 6).

Table 25. Effect of reaction concentration on the yield of sulfone in sulfonylation of toluene with *p*-toluenesulfonic anhydride, catalysed by $AlCl_3$ at 25.0 °C.

[Sulfonylating agent]	[Toluene]	[$AlCl_3$]	Yield di-*p*-tolyl sulfone (%)
0.06	0.6	0.15	36.3
0.15	1.5	0.75	43.4
0.30	3.0	1.5	45.0

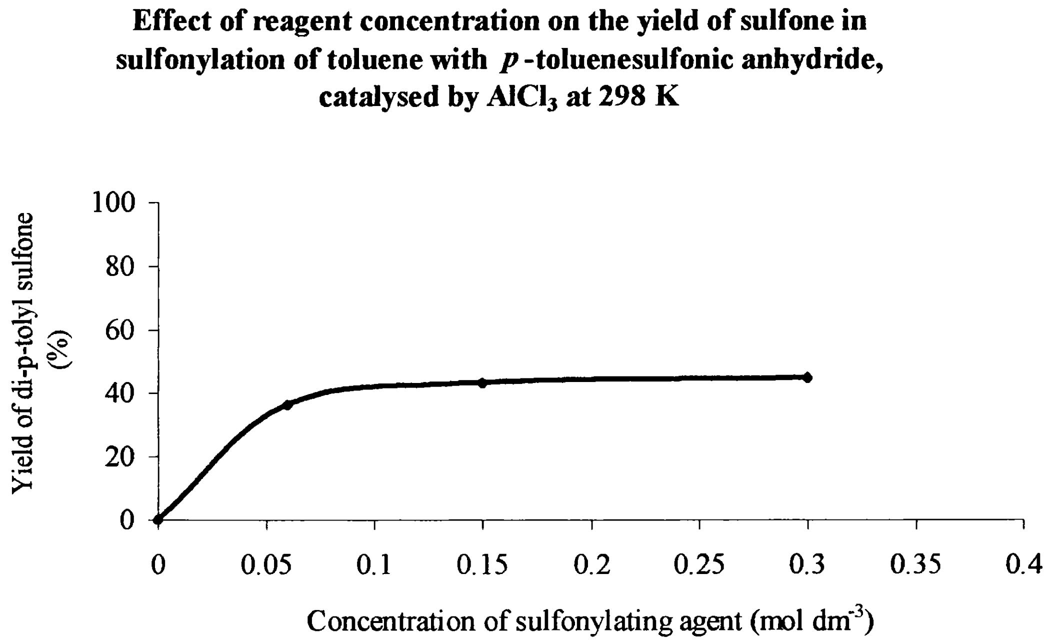

Effect of reagent concentration on the yield of sulfone in sulfonylation of toluene with *p*-toluenesulfonic anhydride, catalysed by $AlCl_3$ at 298 K

Figure 5

Table 26. Effect of reaction concentration on the yield of sulfone in sulfonylation of toluene with *p*-toluenesulfonyl chloride, catalysed by $AlCl_3$ at 25.0 °C.

[Sulfonylating agent]	[Toluene]	[$AlCl_3$]	Yield di-*p*-tolyl sulfone (%)
0.06	0.6	0.15	81.6
0.15	1.5	0.75	93.5
0.30	3.0	1.5	95.7

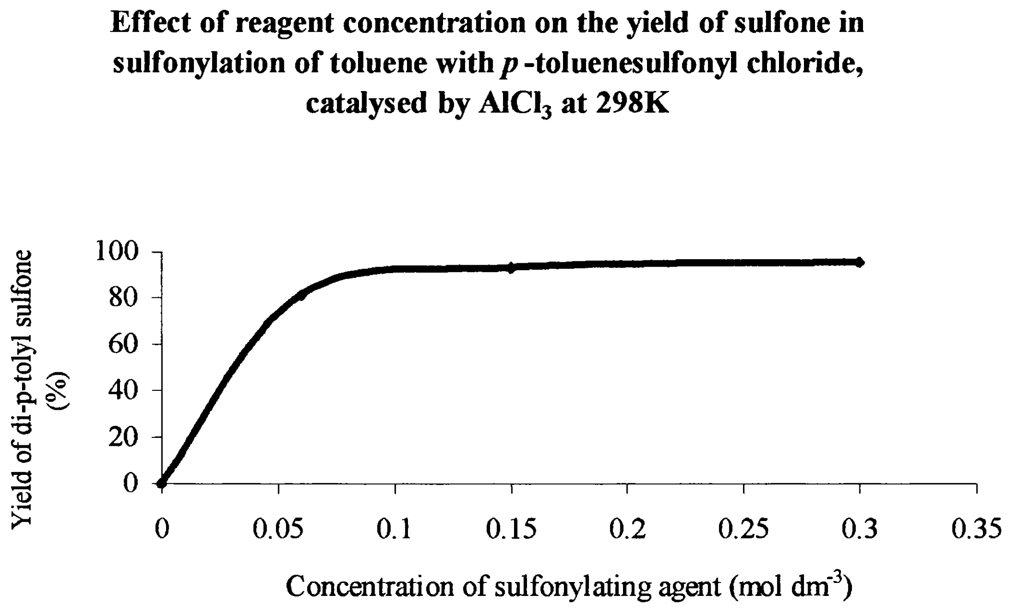


Figure 6

It was observed that the final yield of sulfone does increase with increasing reaction concentration. This helps to explain the low concentrations of sulfone measured in the sulfonylation competition reactions (Section 3.6). The surprising observation was that the yield of sulfone was higher in the reactions involving the sulfonyl chloride rather than the sulfonic anhydride.

3.10 Summary and Perspectives

The results of this study show that the competition reactions involving the sulfonic anhydrides give relative rates of reaction that can be measured, however due to the nature of the reactions this is not straightforward. The reaction series could be extended given more time to include higher alkylbenzenes and the other halobenzenes, however time constraints prevented this. The effect of different substituents on the benzene ring of the sulfonylating agent offers scope for further investigation, and this will be considered in Chapter 5.

From the reactions considered in this study it can be seen that changing the substituent has a large effect on the reactivity of the aryl substrate, and the relative rates of reaction can be seen to change markedly.

Experimental

Preparation of benzene *p*-tolyl sulfone

To a dry flask containing benzenesulfonyl chloride (10.0 g, 56.6 mmol) was added a solution of aluminum chloride (8.0 g, 60.0 mmol) in toluene (20.0 ml, 0.186 mol). The solution was added cautiously over 10 minutes whilst stirring, with dry N_2 gas passed over the reaction mixture to remove any HCl gas evolved during the addition. The reaction mixture was then heated and allowed to reflux for 18 hours.

The reaction was then cooled and added to an excess of iced water (100 ml). This was then basified to pH 8 / 9 using 3M NaOH (aq). The water and excess toluene was then removed by azeotropic distillation. The azeotropic distillation was repeated until the product appeared dry.

The dry material was then added to water (50 ml), then the organic sulfone product extracted into CH_2Cl_2 (4 x 50 ml). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The product was then recrystallised from a minimum of hot ethanol, leaving colourless crystals.

Yield: 7.9g, 60%.

Melting Point: Lit. Value 127°C,[19] Experimental Value 125.5-126.5°C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.40 (3H, s, Me), 7.30 (2H, d, $J_{2,3}$ = 8.4 Hz, 3-H), 7.50 (2H, d, $J_{3',2'}$ = 8.0 Hz, 3'-H), 7.54 (1H, m, 4'-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.55 (Me), 127.48 (C-2), 127.70 (C-2'), 129.21 (C-3'), 129.91 (C-3), 132.99 (C-4'), 138.62 (C-1), 141.96 (C-1'), 144.16 (C-4).

Mass Spectrum: EI m/z 232 (M^+, 65%), CI (NH_3) m/z 250 (M + 18, 100%)

Preparation of 4-bromophenyl-*p*-tolyl sulfone

To a dry flask containing 4-bromobenzenesulfonyl chloride (10.0 g, 39.1 mmol) was added a solution of aluminum chloride (5.5 g, 41.1 mmol) in toluene (20.0 ml, 0.186 mol). The solution was added cautiously over 10 minutes whilst stirring, with dry N_2 gas passed over the reaction mixture to remove any HCl gas evolved during the addition. The reaction mixture was then heated and allowed to reflux for 18 hours.

The reaction was then cooled and added to an excess of iced water (100 ml). This was then basified to pH 8 / 9 using 3M NaOH (aq). The water and excess toluene was then removed by azeotropic distillation. The azeotropic distillation was repeated until the product appeared dry.

The dry material was then added to water (50 ml), then the organic sulfone product extracted into CH_2Cl_2 (4 x 50 ml). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The product was then recrystallised from a minimum of hot ethanol, leaving colourless crystals.

Yield: 0.1g, 5.3%.

Melting Point: Lit. Value 135-136 °C,[36] Experimental Value 134 °C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.32 (3H, s, Me), 7.23 (2H, d, $J_{2',3'}$ = 8.0 Hz, 3'-H), 7.54 (2H, d, $J_{3,2}$ = 8.4 Hz, 3-H), 7.70 (4H, m, 2-H, 2'-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.59 (Me), 127.70 (C-2'), 128.20 (C-4), 129.4 (C-2), 130.05 (C-3'), 132.52 (C-3), 138.14 (C-1,), 141.05 (C-1), 144.53 (C-4').

Mass Spectrum: EI m/z 312 (^{81}Br, M^+, 100%), 310(^{79}Br, M^+, 96%), CI (NH_3) m/z 330 (^{81}Br, M + NH_4, 65%), 328 (^{79}Br, M + NH_4, 59%), 250 (M-81, 100%)

Preparation of 4-chlorophenyl-*p*-tolyl sulfone

To a dry flask containing 4-chlorobenzenesulfonyl chloride (10.0 g, 47.1 mmol) was added a solution of aluminum chloride (10.0 g, 75.1 mmol) in toluene (20.0 ml, 0.186 mol). The solution was added cautiously over 10 minutes whilst stirring, with dry N_2 gas passed over the reaction mixture to remove any HCl gas evolved during the addition. The reaction mixture was then heated and allowed to reflux for 18 hours.

The reaction was then cooled and added to an excess of iced water (100 ml). This was then basified to pH 8 / 9 using 3M NaOH (aq). The water and excess toluene was then removed by azeotropic distillation. The azeotropic distillation was repeated until the product appeared dry.

The dry material was then added to water (50 ml), then the organic sulfone product extracted into CH_2Cl_2 (4 x 50 ml). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The product was then recrystallised from a minimum of hot ethanol, leaving colourless crystals.

Yield: 2.5g, 20%.

Melting Point: Lit. Value 123°C,[19] Experimental Value 122°C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.41 (3H, s, Me), 7.32 (2H, d, $J_{2',3'}$ 8.2, 2'-H), 7.48 (2H, d, $J_{3,2}$ 8.4, 2-H), 7.82 (2H, d, $J_{2,3}$ 8.4, 3-H), 7.87 (2H, d, $J_{2',3'}$ 8.2, 3'-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.56 (Me), 127.68 (C-2'), 128.96 (C-2), 129.54 (C-3), 130.05 (C-3'), 138.23 (C-1'), 139.65 (C-1), 140.53 (C-4), 144.50 (C-4').

Mass Spectrum: EI m/z 266 (^{35}Cl, M^+, 35%), 139 (100%); CI(NH_3) m/z 286 (^{37}Cl, M+NH_4, 40%), 284 (^{35}Cl, M + NH_4, 100%), 250 (^{37}Cl, M-16, 84%).

Preparation of 4-fluorophenyl-*p*-tolyl sulfone

To a dry flask containing 4-fluorobenzenesulfonyl chloride (10.1 g, 51.9 mmol) was added a solution of aluminum chloride (9.4 g, 70.7 mmol) in toluene (20.0 ml, 0.186 mol). The solution was added cautiously over 10 minutes whilst stirring, with dry N_2 gas passed over the reaction mixture to remove any HCl gas evolved during the addition. The reaction mixture was then heated and allowed to reflux for 18 hours.

The reaction was then cooled and added to an excess of iced water (100 ml). This was then basified to pH 8 / 9 using 3M NaOH (aq). The water and excess toluene was then removed by azeotropic distillation. The azeotropic distillation was repeated until the product appeared dry.

The dry material was then added to water (50 ml), then the organic sulfone product extracted into CH_2Cl_2 (4 x 50 ml). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The product was then recrystallised from a minimum of hot ethanol, leaving colourless crystals.

Yield (Crude product): 1.2g, 9.7%.

Melting Point: Lit. Value 95°C,[36] Experimental Value 91.0 - 92.5°C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.41 (3H, s, Me), 7.17 (2H, m, 3-H), 7.32 (2H, d, $J_{3',2'}$ = 8.0 Hz, 3'-H), 7.82 (2H, d, $J_{2',3'}$ = 8.0 Hz, 2'-H), 7.87 (2H, m, 2-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.55 (Me), 116.61 (C-3), 127.61 (C-2'), 130.00 (C-2), 130.24 (C-3'), 138.08 (C-1), 138.48 (C-1'), 144.35 (C-4'), 166.57 (C-4).

NMR spectrum shows acid by-product present.

Mass Spectrum: EI m/z 250 (M^+, 100%); CI(NH_3) m/z 268 (M + 18, 40%).

Preparation of 4-*iso*propylphenyl-*p*-tolyl sulfone

In a dry flask under an atmosphere of N_2, methanesulfonic acid (41.4 g, 0.43 mol) was mixed with phosphorus pentoxide (3.96 g, 27.9 mmol) and stirred for two hours at room temperature. To this was added *p*-toluenesulfonic acid (3.25 g, 18.9 mmol) and *iso*propylbenzene (2.09 g, 17.4 mmol). This reaction mixture was then allowed to stir for 1 week under an atmosphere of N_2 gas. The reaction mixture was a thick yellow liquid, clear in appearance.

This was then poured onto ice-water and the solid collected by filtration. The crude product was then recrystallised from a minimum of hot ethanol, and collected by suction filtration. A second recrystallisation was required, followed by drying under vacuum.

Yield: 0.831g, 17.4%.

Melting Point: Lit. Value 155 °C [19], Experimental Value 151 – 152 °C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 1.24 (6H, d, $J_{\alpha,\beta}$ = 6.8 Hz, Me), 2.40 (3H, s, Me), 2.95 (1H, sc, $J_{\alpha,\beta}$ = 6.8 Hz, $CH(CH_3)_2$), 7.30 (2H, d, $J_{2',3'}$ = 8.4 Hz, 3'-H), 7.34 (2H, d, $J_{2,3}$ = 8.4 Hz, 3-H), 7.84 (2H, d, $J_{2',3'}$ = 8.4 Hz, 2'-H), 7.85 (2H, d, $J_{2,3}$ = 8.4 Hz, 2-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.54 (Me), 23.59 ($(CH_3)_2$), 34.16 ($CH(CH_3)_2$), 127.33 (C-2), 127.61 (C-2'), 127.63 (C-3), 129.83 (C-3'), 139.01 (C-1), 139.27 (C-1'), 143.91 (C-4'), 154.57 (C-4).

Mass Spectrum: EI m/z 274 (M^+, 21%), CI (NH_3) m/z 231 (M – 43, 100%), 292 (M + NH_4, 55%).

Preparation of 4-methoxyphenyl-*p*-tolyl sulfone

To a dry flask containing 4-methoxybenzenesulfonyl chloride (10.0 g, 48.5 mmol) was added a solution of aluminum chloride (7.0 g, 52.5 mmol) in toluene (20.0 ml, 0.186 mol). The solution was added cautiously over 10 minutes whilst stirring, with dry N_2 gas passed over the reaction mixture to remove any HCl gas evolved during the addition. The reaction mixture was then heated and allowed to reflux for 18 hours.

The reaction was then cooled and added to an excess of iced water (100 ml). This was then basified to pH 8 / 9 using 3M NaOH (aq). The water and excess toluene was then removed by azeotropic distillation. The azeotropic distillation was repeated until the product appeared dry.

The dry material was then added to water (50 ml), then the organic sulfone product extracted into CH_2Cl_2 (4 x 50 ml). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The product was then recrystallised from a minimum of hot ethanol, leaving colourless crystals.

Yield: 6.2g, 51%.

Melting Point: Lit. Value 104 °C, [19] Experimental Value 102.5 – 103 °C

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.39 (3H, s, Me), 3.84 (3H, s, OCH_3), 6.96 (2H, d, $J_{2,3}$ = 9.0 Hz, 3-H), 7.28 (2H, d, $J_{3',2'}$ = 8.0 Hz, 3'-H), 7.80 (2H, d, $J_{2',3'}$ = 8.0 Hz, 2'-H), 7.87 (2H, d, $J_{2,3}$ = 9.0 Hz, 2-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.52 (Me), 56.63 (OMe), 114.44 (C-3), 127.3 (C-2'), 129.7 (C-2), 129.8 (C-3'), 133.5 (C-1), 139.4 (C-1'), 143.0 (C-4'), 163.2 (C-4).

Mass Spectrum: EI m/z 262 (M^+, 100); CI(NH_3) m/z 231 (M – CH_3O, 100%), 280 (M + NH_4, 37%).

Typical competition reaction procedure:

Competition reaction between toluene and cumene reacting with *p*-toluenesulfonic anhydride, catalysed by $AlCl_3$ (5.0 eq.) and carried out at 25 °C (2-nitrotoluene used as internal standard).

To dry and distilled nitromethane (100 ml), was added toluene (2.7573 g, 0.03 mol.), cumene (3.6067 g, 0.03 mol.) and 2-nitrotoluene (0.1250 g, 9.11×10^{-4} mol.) to form a standard solution. A similar dry solution of $AlCl_3$ in nitromethane (0.15 M) was prepared. A third solution of *p*-toluenesulfonic anhydride (0.03 M) was prepared. The solutions having been sealed were placed in a water bath (with the tops of the volumetric flasks above the water level) to equilibrate to 25.0 °C. It should be noted that all samples containing nitromethane were kept in the dark to avoid radical formation. This was achieved by wrapping the volumetric flasks in aluminum foil.

Having allowed the solutions to equilibrate, 2.0 ml of each of the three solutions was injected into the reaction flask. The reaction flask was partly submerged in the water bath to keep the reaction at 25.0 °C, and contained a stirrer under an inert atmosphere of N_2 (g).

The reaction was allowed to run and was sampled after 3 hours. An aliquot (approx. 0.2 ml) was removed by dry needle and syringe, then added to ethanol (approx. 7 ml). This was then shaken thoroughly and analysed by HPLC.

Typical HPLC conditions.

Column Packing:	Excil 5µ ODS II C18
Eluent*:	66.4% Methanol
	33.6% (90:10) Water : Methanol
Flow Rate:	1.0 ml / min
Wavelength	240 nm
Run Time:	20 mins

* The eluent composition was changed depending on the aryl substrate used.

Attempted rearrangement of 4-*iso*propylphenyl-*p*-tolyl sulfone by $AlCl_3$

To dry and distilled nitromethane (100 ml), was added 4-*iso*propylphenyl-*p*-tolyl sulfone (0.2072 g, 7.57×10^{-4} mol.) to form a standard solution. A similar dry solution of $AlCl_3$ in nitromethane (0.15 M) was prepared. A third blank solution of nitromethane was also prepared. The solutions having been sealed were placed in a water bath (with the tops of the volumetric flasks above the water level) to equilibrate to 25.0 °C. It should be noted that all samples containing nitromethane were kept in the dark to avoid radical formation. This was achieved by wrapping the volumetric flasks in aluminum foil.

Having allowed the solutions to equilibrate, 2.0 ml of each of the three solutions was injected into the reaction flask. The reaction flask was partly submerged in the water bath to keep the reaction at 25.0 °C, and contained a stirrer under an inert atmosphere of N_2 (g). The solution containing the catalyst was added as the last component.

The reaction was allowed to run and was sampled regularly for 18 hours. An aliquot (approx. 0.2 ml) was removed by dry needle and syringe, then added to ethanol (approx. 7 ml). This was then shaken thoroughly and analysed by HPLC. The starting material was observed to survive the attempted rearrangement unaffected.

Attempted rearrangement of 4-*iso*propylphenyl-*p*-tolyl sulfone by $AlCl_3$ and *p*-toluenesulfonic acid

A similar procedure was used as for the attempted rearrangement with $AlCl_3$. The blank nitromethane solution was replaced with a solution of *p*-toluenesulfonic acid. The reaction was allowed to run for 18 hours with regular sampling. Again the 4-*iso*propylphenyl-*p*-tolyl sulfone was recovered unaffected.

Appendix

Calculation of response factors for unsymmetrical sulfones

The response factor for each unsymmetrical sulfone was calculated using two standard solutions. One of the internal standard *o*-nitrotoluene, the other of *p*-substituted sulfone. The details of the solutions are shown below (Table 1).

Table 1. Details of standard solutions used to calculate factor for each sulfone

Solution	**Compound**	**Mol. Weight (A. M. U.)**	**Quantity (g)**	**Volume (L)**	**Molarity (mol dm^{-3})**
A	*o*-nitrotoluene	137.14	0.0397	0.25	1.16 x 10^3
B	$(CH_3)_2CH$	274.33	0.055	0.20	1.00 x 10^3
C	H	232.33	0.0465	0.20	1.00 x 10^3
D	OMe	262.33	0.0525	0.20	1.00 x 10^3
E	Cl	266.783	0.0534	0.20	1.00 x 10^3
F	Me	246.33	0.0621	0.25	1.00 x 10^3
H	Br	311.02	0.0318	0.10	1.02 x 10^3

Aliquots of varying sizes of each solution were accurately measured using a Finnpipette fixed volume mechanical pipette. These were then mixed thoroughly, and analysed by HPLC using the stated conditions. Measurements were repeated to give a set of results, from which a mean value of α could be obtained (Tables 2 - 7).

Table 2. Co-injection data to calculate response factor for 4-*iso*propylphenyl-*p*-tolyl sulfone

Vol. A* (ml)	Conc. A (mol dm^{-3})	Area A	Vol. B** (ml)	Conc. B (mol dm^{-3})	Area B	Response Factor B
1	5.790×10^{-4}	533.5	1	5.012×10^{-4}	2754.4	0.167686
1	5.790×10^{-4}	539.4	1	5.012×10^{-4}	2783.1	0.167773
2	7.720×10^{-4}	686.9	1	3.341×10^{-4}	1726.6	0.172212
2	7.720×10^{-4}	755.1	1	3.341×10^{-4}	1915.3	0.170657
2	7.720×10^{-4}	695.3	1	3.341×10^{-4}	1762.0	0.170799
3	8.685×10^{-4}	778.5	1	2.506×10^{-4}	1315.3	0.170807
3	8.685×10^{-4}	794.8	1	2.506×10^{-4}	1333.9	0.171944
3	8.685×10^{-4}	790.8	1	2.506×10^{-4}	1327.3	0.171925
1	3.860×10^{-4}	359.5	2	6.683×10^{-4}	3571.3	0.174283
1	3.860×10^{-4}	357.8	2	6.683×10^{-4}	3629.3	0.170715
1	3.860×10^{-4}	361.1	2	6.683×10^{-4}	3683.7	0.169721
3	8.685×10^{-4}	803.3	1	2.506×10^{-4}	1373.0	0.168844
3	8.685×10^{-4}	794.4	1	2.506×10^{-4}	1348.4	0.170004
3	8.685×10^{-4}	795.9	1	2.506×10^{-4}	1330.2	0.17266
					Mean =	0.170716

* Standard solution of *o*-nitrotoluene

** Standard solution of *iso*propylphenyl tolyl sulfone

Table 3. Co-injection data to calculate response factor for phenyl-*p*-tolyl sulfone

Vol. A* (ml)	Conc. A (mol dm^{-3})	Area A	Vol. C** (ml)	Conc. C (mol dm^{-3})	Area C	Response Factor C
1	5.790×10^{-4}	538.1	1	5.004×10^{-4}	2340.6	0.19868
1	5.790×10^{-4}	558.1	1	5.004×10^{-4}	2484.7	0.19413
1	5.790×10^{-4}	559.1	1	5.004×10^{-4}	2482.8	0.194635
2	7.720×10^{-4}	441.4	1	3.336×10^{-4}	997.7	0.191157
2	7.720×10^{-4}	738.1	1	3.336×10^{-4}	1648.4	0.193481
2	7.720×10^{-4}	747.9	1	3.336×10^{-4}	1678.2	0.192572
3	8.685×10^{-4}	807.1	1	2.502×10^{-4}	1228.8	0.189232
3	8.685×10^{-4}	802.8	1	2.502×10^{-4}	1219.0	0.189708
3	8.685×10^{-4}	653.3	1	2.502×10^{-4}	984.8	0.191128
3	8.685×10^{-4}	834.6	1	2.502×10^{-4}	1235.8	0.194549
1	3.860×10^{-4}	380.2	2	6.672×10^{-4}	3285.7	0.200008
1	3.860×10^{-4}	339.9	2	6.672×10^{-4}	2985.7	0.196788
1	3.860×10^{-4}	373.7	2	6.672×10^{-4}	3218.0	0.20071
					Mean =	0.193839

* Standard solution of *o*-nitrotoluene

** Standard solution of phenyl-4-tolyl sulfone

Table 4. Co-injection data to calculate response factor for 4-methoxyphenyl-*p*-tolyl sulfone

Vol. A* (ml)	Conc. A (mol dm^{-3})	Area A	Vol. D** (ml)	Conc. D (mol dm^{-3})	Area D	Response Factor D
1	5.790×10^{-4}	528.0	1	5.003×10^{-4}	1359.2	0.335708
1	5.790×10^{-4}	549.4	1	5.003×10^{-4}	1400.9	0.338906
1	5.790×10^{-4}	580.5	1	5.003×10^{-4}	1441.7	0.347974
1	5.790×10^{-4}	578.5	1	5.003×10^{-4}	1533.0	0.326092
1	5.790×10^{-4}	552.4	1	5.003×10^{-4}	1474.7	0.323683
1	5.790×10^{-4}	544.5	1	5.003×10^{-4}	1453.0	0.323823
2	7.720×10^{-4}	743.4	1	3.335×10^{-4}	990.5	0.324271
2	7.720×10^{-4}	724.9	1	3.335×10^{-4}	963.5	0.325068
2	7.720×10^{-4}	753.3	1	3.335×10^{-4}	1000.8	0.32523
3	8.685×10^{-4}	838.3	1	2.502×10^{-4}	760.8	0.317425
3	8.685×10^{-4}	828.8	1	2.502×10^{-4}	749.0	0.318739
3	8.685×10^{-4}	807.3	1	2.502×10^{-4}	725.2	0.320673
1	3.860×10^{-4}	373.2	2	6.671×10^{-4}	1891.7	0.340936
1	3.860×10^{-4}	384.8	2	6.671×10^{-4}	1971.3	0.33733
1	3.860×10^{-4}	379.7	2	6.671×10^{-4}	1947.5	0.336962
					Mean =	0.322778

* Standard solution of *o*-nitrotoluene

** Standard solution of 4-methoxyphenyl-4-tolyl sulfone

Table 5. Co-injection data to calculate response factor for 4-chlorophenyl-*p*-tolyl sulfone

Vol. A* (ml)	Conc. A (mol dm^{-3})	Area A	Vol. E** (ml)	Conc. E (mol dm^{-3})	Area E	Response Factor E
1	5.790×10^{-4}	529.4	1	5.790×10^{-4}	2389.4	0.221579
1	5.790×10^{-4}	554.0	1	5.790×10^{-4}	2533.4	0.218693
1	5.790×10^{-4}	532.2	1	5.790×10^{-4}	2438.4	0.218243
2	7.720×10^{-4}	740.1	1	3.336×10^{-4}	1658.7	0.192818
2	7.720×10^{-4}	720.2	1	3.336×10^{-4}	1602.3	0.19425
2	7.720×10^{-4}	731.9	1	3.336×10^{-4}	1630.0	0.194042
3	8.685×10^{-4}	824.6	1	2.502×10^{-4}	1276.1	0.186178
3	8.685×10^{-4}	816.5	1	2.502×10^{-4}	1235.9	0.190353
3	8.685×10^{-4}	809.4	1	2.502×10^{-4}	1233.4	0.189048
1	3.860×10^{-4}	368.6	2	6.672×10^{-4}	3371.3	0.189001
1	3.860×10^{-4}	359.6	2	6.672×10^{-4}	3374.7	0.184193
1	3.860×10^{-4}	366.9	2	6.672×10^{-4}	3407.5	0.186123
					Mean =	0.197044

* Standard solution of *o*-nitrotoluene

** Standard solution of 4-chlorophenyl-4-tolyl sulfone

Table 6. Co-injection data to calculate response factor for di-*p*-tolyl sulfone						
Vol. A* (ml)	**Conc. A (mol dm^{-3})**	**Area A**	**Vol. F** (ml)**	**Conc. F (mol dm^{-3})**	**Area F**	**Response Factor F**
2	7.720×10^{4}	735.2	1	3.361×10^{4}	1605	0.199419
2	7.720×10^{4}	761.8	1	3.361×10^{4}	1646	0.201447
2	7.720×10^{4}	701.6	1	3.361×10^{4}	1520	0.200994
3	8.685×10^{4}	801.7	1	2.521×10^{4}	1218	0.191014
3	8.685×10^{4}	797.7	1	2.521×10^{4}	1206	0.19202
3	8.685×10^{4}	798.8	1	2.521×10^{4}	1206	0.192317
1	3.860×10^{4}	370.7	2	6.723×10^{4}	3541	0.182336
1	3.860×10^{4}	371.7	2	6.723×10^{4}	3592	0.180227
1	3.860×10^{4}	367.1	2	6.723×10^{4}	3529	0.18116
1	3.860×10^{4}	360.3	2	6.723×10^{4}	3445	0.18217
1	3.860×10^{4}	360.5	2	6.723×10^{4}	3465	0.181208
					Mean =	0.18943

* Standard solution of *o*-nitrotoluene

** Standard solution of di-*p*-tolyl sulfone

Table 7. Co-injection data to calculate response factor for 4-bromophenyl-*p*-tolyl sulfone						
Vol. A* (ml)	**Conc. A (mol dm^{-3})**	**Area A**	**Vol. H** (ml)**	**Conc. H (mol dm^{-3})**	**Area H**	**Response Factor H**
3	8.685×10^{-4}	750.4	1	2.556×10^{-4}	1071.5	0.206145
3	8.685×10^{-4}	916.7	1	2.556×10^{-4}	1310.9	0.205811
3	8.685×10^{-4}	831.1	1	2.556×10^{-4}	1177.3	0.207792
1	5.790×10^{-4}	545.6	1	5.112×10^{-4}	2337.2	0.206106
1	5.790×10^{-4}	543.4	1	5.112×10^{-4}	2341.6	0.204897
2	7.720×10^{-4}	692.7	1	3.408×10^{-4}	1537.2	0.198953
2	7.720×10^{-4}	447.8	1	3.408×10^{-4}	980.8	0.20157
				Mean =		0.2044676

* Standard solution of *o*-nitrotoluene

** Standard solution of 4-bromophenyl-4-tolyl sulfone

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Chapter Four

*Intra*molecular sulfonylation reaction and associated reactions

4.1 Introduction to *intra*molecular reaction between *p*-toluenesulfonic anhydride and $AlCl_3$ to form di-*p*-tolyl sulfone

During background investigations for the initial studies of the Friedel-Crafts type sulfonylation reactions between an aryl substrate and *p*-toluenesulfonic anhydride, it was observed that the predicted sulfone product could possibly be formed by reaction between *p*-toluenesulfonic anhydride and $AlCl_3$ in the absence of an aryl substrate. The reaction was investigated in nitromethane, using similar conditions to those used for the initial study and competition reactions.

Having observed the possible formation of the di-*p*-tolyl sulfone under these conditions, it was decided to investigate the reaction further, to determine whether the new route of formation of diaryl sulfones was a major contributor to the di-*p*-tolyl sulfone yield in the initial studies and the competition reaction (See Chapters Two and Three).

Although Friedel-Crafts type sulfonylation reactions have been extensively studied, reactions in the absence of an aryl substrate have only briefly been looked at by Christensen.[1] Christensen found that attempts to form di-*p*-iodophenyl sulfone by reacting SO_3 gas with *p*-iodobenzenesulfonic anhydride were unsuccessful, with no sulfone product observed. Christensen also unsuccessfully attempted to form di-*p*-iodophenyl sulfone from the reaction between *p*-iodobenzenesulfonic anhydride and iodobenzene in the absence of a catalyst. This led Christensen to the conclusion that in order to form diaryl sulfones from diaryl sulfonic anhydrides three components were required, the sulfonic anhydride, an aryl substrate and a catalyst.

Although the reactions were to be carried out in nitromethane, aromatic sulfonic anhydrides are not readily soluble in nitromethane alone. However Christensen found that when nitromethane was acidified using H_2SO_4, then the solubility increased greatly (See Table 1).

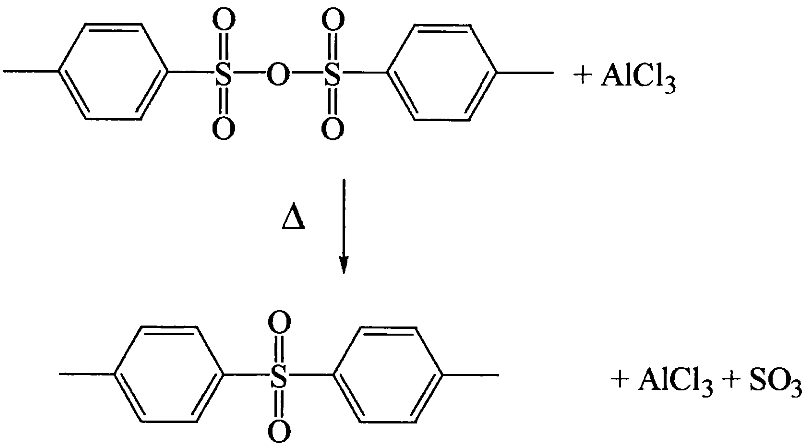
Table 1. Solubility of *p*-iodobenzenesulfonic anhydride in nitromethane solvents at 0°C.

Solvent	Method 1*	Method 2**
Pure nitromethane	1.2 mg/g	2.1 mg/g
0.3m H_2SO_4 (101%)		26 mg/g
0.6 m H_2SO_4 (101%)		35 mg/g
1.8 m H_2SO_4 (101%)	17 mg/g (4 h)	
1.8 m H_2SO_4 (101%)	4 mg/g (1 h)	
2.1 m H_2SO_4 (101%)	22 mg/g (4 h)	
2.1 m H_2SO_4 (101%)	14 mg/g (1 h)	

* Method 1 employs constant temperature

** Method 2 involves cooling from a warm solution

Following the observation in the initial study that di-*p*-tolyl sulfone appeared to be formed in the absence of an aryl substrate, it was decided to investigate the possibility that an *intra*molecular reaction of *p*-toluene sulfonic anhydride forming ditolyl sulfone under suitable conditions was occurring. It was also necessary to identify the different product isomers formed if any (See Equation 1).



(1)

4.2 Reaction and analytical method development

The reaction of *p*-toluenesulfonic anhydride in nitromethane catalysed by $AlCl_3$ to form ditolyl sulfone was first identified by HPLC during the initial studies of sulfonylation with *p*-toluenesulfonic anhydride. Due to the problems that had been encountered in separating the different isomers of ditolyl sulfone, the first challenge was to identify whether or not the reaction gave ditolyl sulfone. The product isomer ratio would then be investigated further if the reaction was found to be successful.

In the first reaction of this type, di-*p*-tolyl sulfone was found to have the same retention time as the product peak from the reaction between *p*-toluenesulfonic anhydride and $AlCl_3$ in nitromethane. Furthermore, the reaction could not be analysed quantitatively as no internal standard was included for the first reaction. In addition it was found that the presence of any aromatic substrate appeared to suppress the reaction, and an external standard had to be added to the reaction mixture after quenching with ethanol in order to analyse the reaction quantitatively. The external standard used was 2-nitrotoluene, as used in the initial study (See Chapter Two).

In order to identify the reaction product, initially the reaction was analysed using LC-MS, and HPLC by co-injection. The results did show that ditolyl sulfone was being formed, however it was not clear which isomer was being formed.

4.3 Investigation into the product isomer distribution in the *intra*molecular reaction of *p*-toluenesulfonic anhydride with $AlCl_3$ in nitromethane

In order to determine the product isomer distribution in the formation of the ditolyl sulfone, a sample of the sulfone had to be isolated. In order to do this a reaction was carried out at a higher concentration than in the earlier studies (See Chapters One and Two). The early attempts to isolate the sulfone proved problematic, with difficulties being experienced in separating and drying the product. Following the reaction of $AlCl_3$ with *p*-toluenesulfonic anhydride in nitromethane, the mixture was quenched with cold water. Attempts to remove the water / nitromethane mixture under vacuum were unsuccessful due to foaming problems that could not be overcome. The excess liquor was removed by evaporation using heat alone, however attempts to extract the sulfone from any acid by-product gave poor results. The problems stemmed from the quenching stage, and the fact that water is totally miscible with nitromethane. In order to try to overcome this problem, it was decided to take a new approach to the quenching process. The nitromethane was removed from the reaction *in situ*, using vacuum distillation. The reaction mixture was quenched with cold water, and neutralised. An organic extraction using dichloromethane was carried out to separate any sulfone product from any acid by-products present. The organic extracts were combined and dried, and reduced under vacuum to leave a crystalline product that was successfully recrystallised from hot ethanol. The product was analysed by Mass Spectrometry, ^1H NMR and melting point. The product was confirmed as di-*p*-tolyl sulfone. After a single recrystallisation the product was 100% pure, with only the single isomer being observed. The Mass Spectrometry data were analysed for any traces of chlorine isotope patterns, however no trace of the corresponding sulfonyl chloride could be seen.

The reaction yield was 45% (measured by HPLC using 2-nitrotoluene as an external standard). Due to time constraints the yield was not optimised.

4.4 Proposed mechanism for the *intra*molecular reaction

The mechanism for the formation of di-*p*-tolyl sulfone via the *intra*molecular reaction has been considered. Several reaction pathways have been proposed, of which two are given below (See Figures 1 and 2).

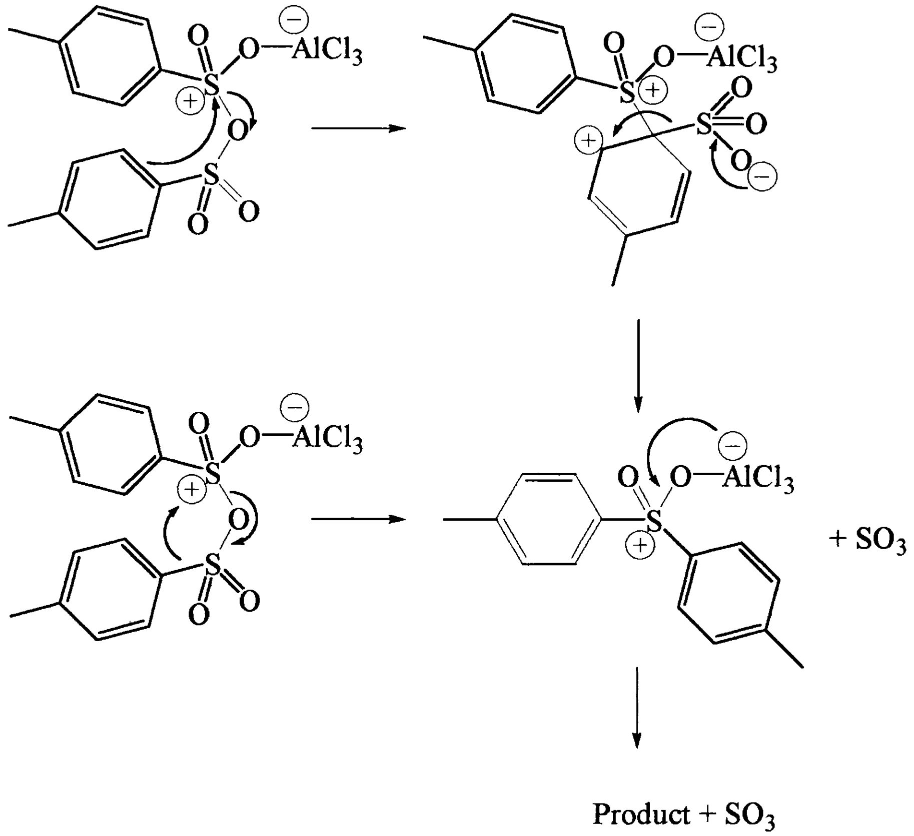


Figure 1

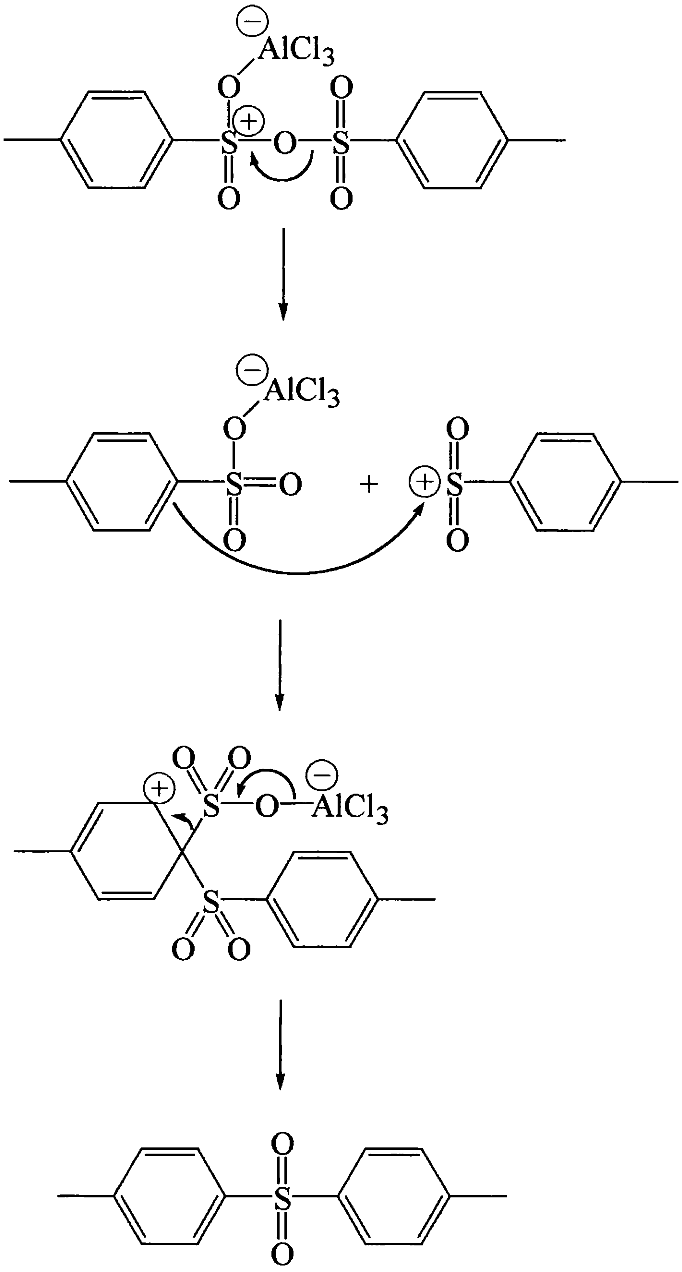


Figure 2

In order to determine whether or not the reaction is truly *intra*molecular, it was necessary to carry out crossover reactions. In order to do this a second aromatic sulfonic anhydride was required. It was hoped that the crossover reaction would help to identify and clarify whether the *intra*molecular reaction is truly *intra*molecular or *inter*molecular (See Figure 3).

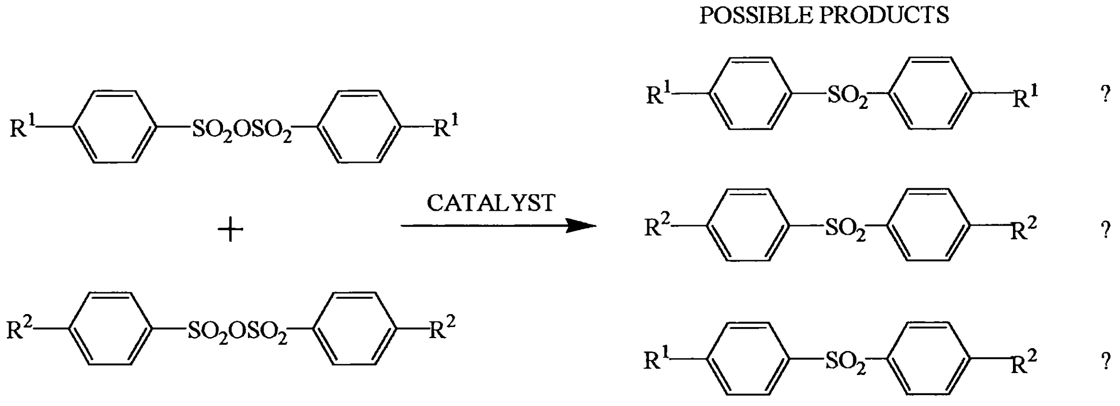


Figure 3

4.5 Crossover reaction between two different aromatic sulfonic anhydrides catalysed by SO_3

In order to establish whether the route to the sulfones is truly *intra*molecular (See Figure 1), or whether the mechanism involves the cleavage of the sulfonic anhydride to form separate *sulfo* cations and anions (See Figure 2), a crossover reaction was attempted.

The first attempted crossover reaction was performed using SO_3 as the catalyst, since this would provide a better model of the industrial sulfonation process. The reaction was carried out using batch sulfonation apparatus at Unilever Research, Port Sunlight. For the purposes of the reaction a second aromatic sulfonic anhydride was required. It was decided to use *p*-bromobenzenesulfonic anhydride. This was synthesised as part of the study of relative rates of sulfonylation using different sulfonic anhydrides (See Chapter Five). Both *p*-toluene- and *p*-bromobenzenesulfonic anhydrides were added to nitromethane and charged to the reactor. Due to the relatively poor solubility of aromatic sulfonic anhydrides in pure nitromethane the reaction mixture was heterogeneous at the start of the reaction. SO_3 gas was added to the reaction mixture (2 mole equivalents relative to the total amount of anhydride) and the reaction was allowed to proceed for 1 hour. The reaction was carried out at 20 °C. The expected formation of the sulfone products was not observed. Due to time constraints the reaction was not repeated at higher temperatures using SO_3. The crossover reaction was then attempted using $AlCl_3$ catalyst.

4.6 Crossover reaction between two different aromatic sulfonic anhydrides catalysed by $AlCl_3$

Similar reactions were attempted using $AlCl_3$ as catalyst. The reactions were carried out using varying amounts of catalyst at different temperatures. At 20 °C the reactions between $AlCl_3$ and the sulfonic anhydrides were seen to form the corresponding sulfonyl chlorides. This appears to be a side reaction (See Chapter Three), competing with the Friedel-Crafts type reaction of the sulfonic anhydride. The sulfonyl chloride products were stable in the reaction solution at 20 °C, and the addition of further $AlCl_3$ was not observed to change the reaction products.

Three reactions were carried out using 1.0, 2.0 and 5.0 mole equivalents of $AlCl_3$ relative to the total amount of sulfonic anhydride in the reaction. The formation of sulfone products was not observed at 20 °C in any of the reactions over a period of one hour. The reaction using 5.0 equivalents of $AlCl_3$ was repeated under reflux, for a period of one hour. This reaction was seen to produce di-p-tolyl sulfone and di-*p*-bromophenyl sulfone. Small traces of the corresponding sulfones were present in the reaction mixture. The crossover product of 4-bromophenyl-*p*-tolyl sulfone was not observed in the reaction mixture, suggesting that the mechanism of sulfone formation is truly *intra*molecular (See Figure 1).

4.7 Competition reactions between Friedel-Crafts sulfonylation of aryl substrates and the *intra*molecular route to diaryl sulfones using *p*-toluenesulfonic anhydride

Once the new route to diaryl sulfones from aromatic sulfonic anhydrides had been revealed, a new concern arose, whether or not the *intra*molecular route to diaryl sulfones was competing with the Friedel-Crafts type sulfonylation route. As the *intra*molecular route had not been previously identified, there was no published literature available on this reaction. A series of reactions had to be devised to investigate the competition between the two routes.

In order to establish the importance of the reaction, a range of aryl substrates was used in competition with the *intra*molecular reaction. The range of aryl substrates was chosen to provide a wide range of reactivities. The aryl substrates chosen included: cyclohexylbenzene, bromobenzene, 1-phenyldodecane, 2-nitrotoluene, 2-chlorotoluene, 1-phenylhexane, and phenylacetone. Along with using a range of aryl substrates, a number of different catalysts were considered. These included $AlCl_3$, $TiCl_4$ and trifluoromethanesulfonic acid (triflic acid). The triflic acid was unsuccessful as a catalyst for both the Friedel-Crafts *inter*molecular and the *intra*molecular reaction. The $AlCl_3$ and $TiCl_4$ catalysts were more successful for the Friedel-Crafts reactions.

The reactions were carried out using similar techniques to both the initial studies and the competition reactions, although a wider range of concentrations and dilutions was considered. The results were measured using 2-nitrotoluene as an external standard.

The results using $TiCl_4$ are given below (See Tables 2-6).

Table 2. Competition between $TiCl_4$ catalysed Friedel-Crafts sulfonylation of cyclohexylbenzene with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25 °C

Substrate	Mol. Eq.	Mol. Eq. $TiCl_4$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	$k_{Intra} / k_{F\text{-}C}$
Cyclohexylbenzene	1.1	0.14	0.5	2.9	0.17241
Cyclohexylbenzene	1.0	0.69	0.1	29.4	0.00340
Cyclohexylbenzene	1.0	0.72	0.2	22.9	0.00873
Cyclohexylbenzene	1.2	2.26	0.1	38.8	0.00258

Table 3. Competition between $TiCl_4$ catalysed Friedel-Crafts sulfonylation of bromobenzene with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C

Substrate	Mol. Eq.	Mol. Eq. $TiCl_4$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	$k_{Intra} / k_{F\text{-}C}$
Bromobenzene	2.4	2.01	1.2	40.3	0.029777
Bromobenzene	1.1	0.57	0.2	7.9	0.025316
Bromobenzene	1.2	0.13	0.2	25.9	0.007722

Table 4. Competition between $TiCl_4$ catalysed Friedel-Crafts sulfonylation of 1-phenylhexane with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C

Substrate	Mol. Eq.	Mol. Eq. $TiCl_4$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	$k_{Intra} / k_{F\text{-}C}$
1-phenylhexane	2.7	0.16	0.1	2.7	0.037037
1-phenylhexane	0.9	0.34	0.1	5.3	0.018868
1-phenylhexane	0.8	7.65	0.1	34.2	0.002924

Table 5. Competition between $TiCl_4$ catalysed Friedel-Crafts sulfonylation of 1-phenyldodecane with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25 °C

Substrate	Mol. Eq.	Mol. Eq. $TiCl_4$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	k_{Intra} / $k_{F\text{-}C}$
1-phenyldodecane	1.2	0.54	0.2	17.6	0.01136
1-phenyldodecane	1.3	0.87	0.1	27.6	0.00362
1-phenyldodecane	1.4	0.95	0.1	34.3	0.00292
1-phenyldodecane	1.0	3.45	0.3	38.4	0.00781

Table 6. Competition between $TiCl_4$ catalysed Friedel-Crafts sulfonylation of 2-chlorotoluene with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C

Substrate	Mol. Eq.	Mol. Eq. $TiCl_4$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	k_{Intra} / $k_{F\text{-}C}$
2-chlorotoluene	1.5	0.52	0.2	25.0	0.008
2-chlorotoluene	1.1	0.67	0.1	23.3	0.004292
2-chlorotoluene	1.1	1.15	0.2	39.1	0.005115

The results show that with $TiCl_4$ catalyst, the yield of di-*p*-tolyl sulfone due to the *intra*molecular reaction route is negligible. It can be seen that even in the reactions featuring the unreactive aryl substrates where no unsymmetrical sulfone is formed, the *intra*molecular route appears to be inhibited.

The reactions catalysed by $AlCl_3$ show similar results. Again it can be seen that in the reactions where unreactive substrates are used the *intra*molecular reaction is suppressed. The results using $AlCl_3$ are shown below (See Tables 7-11).

Table 7. Competition between $AlCl_3$ catalysed Friedel-Crafts sulfonylation of cyclohexylbenzene with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C					
Substrate	**Mol. Eq.**	**Mol. Eq. $AlCl_3$**	**Yield di-*p*-tolyl sulfone (%)**	**Yield unsymmetrical sulfone (%)**	**$k_{Intra} / k_{F\text{-}C}$**
Cyclohexylbenzene	1.1	0.24	0.3	10.2	0.026258
Cyclohexylbenzene	1.2	0.29	0.3	13.2	0.023495
Cyclohexylbenzene	1.1	3.95	0.6	11.1	0.053779

Table 8. Competition between $AlCl_3$ catalysed Friedel-Crafts sulfonylation of bromobenzene with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C					
Substrate	**Mol. Eq.**	**Mol. Eq. $AlCl_3$**	**Yield di-*p*-tolyl sulfone (%)**	**Yield unsymmetrical sulfone (%)**	**$k_{Intra} / k_{F\text{-}C}$**
Bromobenzene	0.7	0.32	0.3	18.9	0.016186
Bromobenzene	1.5	0.70	0.4	33.9	0.011705
Bromobenzene	1.7	8.33	0.5	76.7	0.006397

Table 9. Competition between $AlCl_3$ catalysed Friedel-Crafts sulfonylation of 1-phenylhexane with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C					
Substrate	**Mol. Eq.**	**Mol. Eq. $AlCl_3$**	**Yield di-*p*-tolyl sulfone (%)**	**Yield unsymmetrical sulfone (%)**	**$k_{Intra} / k_{F\text{-}C}$**
1-phenylhexane	1.5	0.55	0.3	23.2	0.013264
1-phenylhexane	1.5	0.65	0.2	20.6	0.00949
1-phenylhexane	1.3	1.36	0.4	23.5	0.019009
1-phenylhexane	1.0	2.53	0.3	23.2	0.012298

Table 10. Competition between $AlCl_3$ catalysed Friedel-Crafts sulfonylation of 1-phenyldodecane with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C

Substrate	Mol. Eq.	Mol. Eq. $AlCl_3$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	$k_{Intra} / k_{F\text{-}C}$
1-phenyldodecane	1.1	0.90	0.4	22.3	0.019776
1-phenyldodecane	1.0	0.99	0.3	29.0	0.011082
1-phenyldodecane	1.3	1.79	0.6	29.6	0.019077

Table 11. Competition between $AlCl_3$ catalysed Friedel-Crafts sulfonylation of phenylacetone with *p*-toluenesulfonic anhydride and the *intra*molecular reaction at 25°C

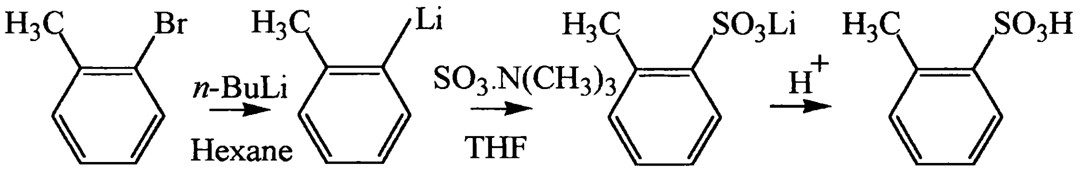
Substrate	Mol. Eq.	Mol. Eq. $AlCl_3$	Yield di-*p*-tolyl sulfone (%)	Yield unsymmetrical sulfone (%)	$k_{Intra} / k_{F\text{-}C}$
Phenylacetone	1.8	0.27	0.1	3.5	0.032834
Phenylacetone	1.1	1.17	0.2	12.7	0.012804
Phenylacetone	1.4	5.55	0.2	28.3	0.007326
Phenylacetone	1.6	6.29	0.0	45.2	-

It can be seen from the results that the sulfone yield due to the *intra*molecular reaction is negligible, and will not affect the results of the competition reactions featured in Chapters Three and Five.

4.8 Attempted synthesis of 2,4'- substituted unsymmetrical sulfones

The synthesis of 2,4'- and 3,4'-substituted unsymmetrical sulfones was required in order to obtain response factors for the different sulfones, especially ditolyl sulfone to help to identify the sulfone product formed in the *intra*molecular reaction. In the case of *iso*propylphenyl tolyl sulfone and ditolyl sulfone as several isomers of each had been observed in Chapter Three. Having earlier reviewed the routes to diaryl sulfones and successfully synthesised di-*p*-substituted diaryl sulfones, it was believed that the most suitable route to the 2,4'-substituted sulfones would be by condensation using Eaton's acid. Initially toluene was used in order to produce ditolyl sulfone. This would involve the reaction of 2-toluenesulfonic acid with an aryl substrate. It was hoped that this would help us to find a route to the desired sulfones that could be adapted for other aryl substrates.

It was found that 2-toluenesulfonic acid is not commercially available, so it was decided to synthesise the required 2-toluenesulfonic acid using butyllithium metallation followed by reaction with sulfur trioxide-trimethylamine complex (STTAC), $SO_3.N(CH_3)_3$. This route is based on a similar reaction developed by Smith *et al.* to form 4-toluenesulfonic acid starting from 4-bromotoluene (See Scheme 1).[2]



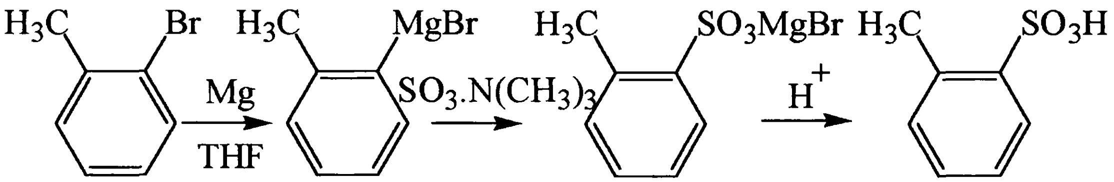
Scheme 1

The reaction was carried out by adding *n*-butyllithium to 2-bromotoluene at –78 °C. This solution was then used in the second stage of the reaction, when it was added to a suspension of STTAC in dry THF. The reaction was allowed to proceed for three hours whilst allowing warming to room temperature. The reaction was worked up according to the published literature, however a crystalline product was not recovered.[2]

The problems were believed to be due to the purity of the STTAC. Smith *et al.* found that when impure samples of STTAC had been used, reactions produced a mixture of reaction products. Smith *et al.* found that commercially available STTAC was only approximately 50% pure. Our sample was found by ^{1}H NMR to be 48% pure. The ^{1}H NMR of the crude complex shows two proton peaks, at $\delta = 3.06$ and 2.77. It is believed that the two peaks are due to STTAC ($\delta = 3.06$) and $SO_2.ON(CH_3)$, ($\delta = 2.77$).[2]

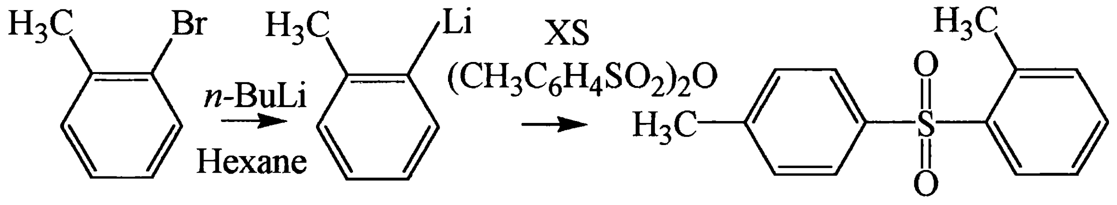
The reported method of purification is to recrystallise the sulfur trioxide complex from cold water. The purification by recrystallisation was attempted using several techniques, however purity greater than 75% could not be achieved (See Experimental).

The lithiation of bromotoluene was attempted again using the recrystallised form of STTAC, and again a dark brown oil containing no sulfonic acid was recovered. The reaction was adapted to use a Grignard reagent (See Scheme 2). The product again contained no sulfonic acid.



Scheme 2

It was decided to attempt a metallation reaction followed by sulfonylation to directly form the desired sulfones. This would eliminate the problems associated with the purity of the STTAC. The metallation of *o*-bromotoluene, followed by direct coupling with excess *p*-toluenesulfonic anhydride was attempted (See Scheme 3).



Scheme 3

As had been experienced in the attempted lithiation to form the sulfonic acid, the lithiation step of the reaction resulted in a virtually solid reaction mixture that was very difficult to manipulate. Finally having worked up the reaction to form a viscous oil, no sulfone product could be detected. Due to time constraints this method could not be developed and optimised.

4.9 Summary and perspectives

The reaction of aromatic sulfonic anhydrides with $AlCl_3$ in nitromethane has been shown to produce the corresponding aromatic sulfones in the absence of other reagents. The reaction, although interesting is not of particular value due to the difficulty in facilitating the reaction. The reaction cannot be considered a valuable route to diphenyl sulfones due to the difficulty of synthesising and isolating the requisite sulfonic anhydrides.

The reaction has been shown not to be a major factor that would obscure the competition reaction results, permitting further research into the relative rates of sulfonylation. The reaction can also be seen not to invalidate the results achieved in Chapters Two and Three.

Experimental

Preparation of di-*p*-tolyl sulfone from *p*-toluenesulfonic anhydride and $AlCl_3$.

A solution of *p*-toluenesulfonic anhydride (10 g, 30.6 mmol) in dry nitromethane (20 ml) was placed into a dry round bottom flask, under an atmosphere of dry N_2 gas. To this was added $AlCl_3$ catalyst (20 g, 150 mmol). This was added against a positive pressure of nitrogen to prevent moisture getting into the reaction. The reaction exotherm was only slight, and the reaction was then allowed to proceed for 18 hours whilst stirring.

The nitromethane solvent was removed by rotary evaporation, with the resulting solid placed under high vacuum to remove any remaining solvent. The solid was then quenched using excess ice-water (100 ml). This was then neutralised using 3M KOH.

The organic product was extracted using CH_2Cl_2 (5 x 25 ml), the combined organic extracts were then dried over anhydrous $MgSO_4$, filtered and the solvent removed by rotary evaporation. This afforded a pale brown crystalline solid, which was recrystallised from ethanol.

Yield: 3.4g, 45%.

Melting Point: Lit. Value[3] 156°C Experimental Value 154-5°C

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.42 (6H, s, Me), 7.34 (4H, d, $J_{2,3}$ 8, 2-H), 7.85 (4H, d, $J_{2,3}$ 8, 3-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.81 (Me), 127.04 (C-2), 130.23 (C-3), 141.68 (C-4), 146.81 (C-1).

Mass Spectrum: EI m/z 246 (M^+, 68%), 214 (100%); CI (NH_3) m/z 264 ($M + NH_4$, 15%), 207 (40%), 190 (100%).

Attempted crossover reaction between *p*-bromobenzenesulfonic anhydride and *p*-toluenesulfonic anhydride catalysed by SO_3 at 20 °C

To the batch sulfonation reactor was charged a slurry of *p*-bromobenzenesulfonic anhydride (6.857 g, 15 mmol) and *p*-toluenesulfonic anhydride (4.899 g, 15 mmol) in nitromethane (100 ml) under an atmosphere of dry N_2 gas. The reactor cooling jacket temperature was set to 20°C and the reaction mixture was allowed to equilibrate. To this was added SO_3 (2.5 ml, 60 mmol), carried following vaporisation by a stream of dry nitrogen. The rate of transfer of the SO_3 was 10 ml/hr.

The reaction was allowed to proceed for 1 hour and the product was then collected and analysed by HPLC.

Analysis of the reaction mixture by co-injection showed that the reaction mixture contained *p*-bromobenzenesulfonyl chloride and *p*-toluenesulfonyl chloride.

Attempted crossover reaction between *p*-bromobenzenesulfonic anhydride and *p*-toluenesulfonic anhydride catalysed by $AlCl_3$ at 20 °C

A solution of *p*-toluenesulfonic anhydride (4.883 g, 15 mmol) and *p*-bromobenzenesulfonic anhydride (6.86 g, 15 mmol) in dry nitromethane (100 ml) was placed into a dry round bottom flask, under an atmosphere of dry N_2 gas. The reaction was sealed and placed in a water bath at 20°C. To this was added $AlCl_3$ catalyst (7.55 g, 60 mmol). This was added against a positive pressure of nitrogen to prevent moisture getting into the reaction mixture, and the reaction was then allowed to proceed for 1 hour whilst stirring. The reaction was then sampled for analysis. An aliquot (approx. 2 ml) was removed by dry needle and syringe, and then added to ethanol (approx. 10 ml) to quench the reaction; this was then shaken thoroughly and analysed by HPLC. The reaction was repeated using different quantities of $AlCl_3$ (30 mmol and 150 mmol respectively).

In all three reactions the *p*-toluenesulfonyl chloride and *p*-bromobenzenesulfonyl chloride were observed as the reaction products by co-injection.

Attempted crossover reaction between *p*-bromobenzenesulfonic anhydride and *p*-toluenesulfonic anhydride catalysed by $AlCl_3$ at reflux

A solution of *p*-toluenesulfonic anhydride (4.883 g, 15 mmol) and *p*-bromobenzenesulfonic anhydride (6.86 g, 15 mmol) in dry nitromethane (100 ml) was placed into a dry round bottom flask fitted with a condenser under an atmosphere of dry N_2 gas. To this was added $AlCl_3$ catalyst (7.55 g, 60 mmol). This was added against a positive pressure of nitrogen to prevent moisture getting into the reaction mixture. The reaction was sealed and heated in an oil bath to reflux. The reaction was allowed to proceed for 1 hour whilst stirring. The reaction was sampled for analysis. An aliquot (approx. 2 ml) was removed by dry needle and syringe, and added to ethanol (approx. 10 ml) to quench the reaction this was then shaken thoroughly and analysed by HPLC. Di-*p*-tolyl sulfone and di-*p*-bromophenyl sulfone were observed as the reaction products by co-injection of standard solutions.

Typical HPLC conditions

Column Packing:	Excil 5µ ODS II C18
Eluent:	65% Methanol 35% Water
Flow Rate:	1.0 ml / min
Wavelength	240 nm
Run Time:	20 mins

Typical procedure for competition reaction between *intra*molecular reaction and Friedel-Crafts sulfonylation reaction of *p*-toluenesulfonic anhydride:

Competition reaction between *intra*molecular reaction and the Friedel-Crafts reaction between *p*-toluenesulfonic anhydride and bromobenzene in nitromethane at 25°C

A solution of *p*-toluenesulfonic anhydride (0.32 g, 0.98 mmol) and bromobenzene (0.264 g, 1.68 mmol) in dry nitromethane (20 ml) was placed into a dry round bottom flask, under an atmosphere of dry N_2 gas. The reaction was sealed and placed in a water bath at 25°C (with the top of the flask above the water level). To this was added $AlCl_3$ catalyst (1.07 g, 7.89 mmol). This was added against a positive pressure of nitrogen to prevent moisture getting into the reaction, and the reaction was then allowed to proceed for 3 hours whilst stirring. The reaction was then sampled for analysis. An aliquot (approx. 2 ml) was removed by dry needle and syringe, and then added to ethanol (approx. 10 ml) to quench the reaction. To this was added 2-nitrotoluene (0.050 g, 0.365 mmol) as an external standard. This was then shaken thoroughly and analysed by HPLC. Typical HPLC conditions for the reaction are given below, however it should be noted that the eluent composition was varied from 70% methanol down as far as 65% methanol depending on the aryl substrate used in the reaction. All HPLC analysis was carried out isocratically.

Typical HPLC conditions

Column Packing:	Excil 5µ ODS II C18
Eluent:	70 - 65% Methanol 30 - 35% Water
Flow Rate:	1.0 ml / min
Wavelength	240 nm
Run Time:	20 mins

Attempted synthesis of 2-toluenesulfonic acid by reaction of SO_3 with 2-tolyllithium

To 2-bromotoluene (518 mg, 3.1 mmol) was added *n*-BuLi in hexane (2.0.M, 1.56 ml, 3 mmol) over 10 minutes whilst cooling on ice. After 6 hours, the supernatant solution was used in the next stage.

To a dry flask of THF (15 ml) was added the STTAC (431mg, 3.1 mmol) at –78^{0}C. To this the preformed hexane solution of *o*-tolyllithium was added dropwise over 15 minutes. The reaction mixture was stirred at –78^{0}C for 2 hours, then allowed to warm to room temperature over 18 hours.

After the removal of solvent under vacuum, water (10ml) and KOH (3M, 1 ml, 3 mmol) were added, then this aqueous solution was extracted with Et_2O (2 x 15 ml) to remove any unreacted 2-bromotoluene.

The aqueous solution was evaporated to give a white solid, and HCl (6 M, 4 ml, 24 mmol) was added. The mixture was extracted with EtOAc (4 x 20 ml) and the combined organic extract was dried with anhydrous $MgSO_4$, filtered and evaporated to give a moist solid. This was washed further with Et_2O (2 x 10 ml).

The combined Et_2O extracts were concentrated to give brown oil.

Reverse phase HPLC showed that there was a large mixture of products present. It appeared that there were four major components, two of these being believed to be the *o*-bromotoluene and the desired sulfone. Two of the peaks eluted very close together, around the retention time of the sulfone. The second peak could be due to the sulfoxide.

Attempted purification of sulfur trioxide-trimethylamine complex

The crude material (10 g) was dissolved in cold water (800 ml). This was then reduced to 200 ml at room temperature. This second step proved to be troublesome, with a rotary evaporator connected to a tap aspirator being insufficient to reduce the volume of water. Attempts were made using oil pumps to reduce the volume of the solution; however cold finger traps protecting the pumps repeatedly froze solid.

A large trap was designed and made, capable of holding a volume of up to 3 litres. This was an attempt to reduce the chances of the trap freezing and blocking, thus resulting in a block on the vacuum and loss of performance. This unfortunately was not successful as ice rapidly blocked the system.

An experimental set up was designed to maximise the airflow in a fume cupboard, the aim being to increase the rate of evaporation of water at atmospheric pressure. The 800 ml solution was poured into a clean glass baking tray, and a dust cover suspended approximately 3 cm above the rim of the tray. This prevented any debris falling into the tray, and also helped to channel the through draft over the surface of the solution. The time of evaporation from 800 ml to 200 ml was 2 days.

Once the volume had been reduced to approximately 200 ml, white crystals were present in the solution. These were collected by suction filtration and dried under high vacuum in the presence of P_2O_5.

By ^1H NMR analysis the isolated product still contained trimethylamine oxide. The highest level of purity of STTAC achieved using this technique was 75%.

A second sample of the crude sulfur trioxide complex was purified by washing. This material (5 g) was placed into a fluted filter paper and washed with cold distilled water (4 x 15 ml). This was then dried under vacuum and analysed by ^1H NMR. Again a reduction in the trimethylamine oxide content could be seen. The maximum STTAC content achieved using this technique was 72%.

Attempted synthesis of 2-toluenesulfonic acid by reaction of SO_3 with 2-tolylmagnesium bromide

Magnesium turnings (7.1 g, 29.2 mmol) were stirred overnight under an atmosphere of N_2 (g). THF (7 ml) was then added to cover the magnesium turnings with stirring. To this 2-bromotoluene (5 g, 29.2 mmol) was added and the mixture allowed to reflux under it's own heat after starting the reaction with a hot air gun. The reaction was heated for a further 10 minutes until all the magnesium had dissolved and the reaction was allowed to cool to room temperature. The reaction was then cooled over acetone/ice and STTAC (4.06 g, 29.2 mmol) was added in THF (25 ml). Due to poor solubility a further 100 ml of THF was added to the reaction mixture. Due to solubility problems involved in adding the STTAC, it was added as a slurry against a positive pressure of nitrogen. The reaction was then allowed to warm to room temperature overnight.

After removal of solvent under vacuum, water (100 ml) and KOH (3 M, 10 ml, 3 mmol) were added, then this aqueous solution was extracted with Et_2O (2 x 100 ml) to remove any unreacted 2-bromotoluene.

The aqueous solution was evaporated to give a white solid, and HCl (6 M, 40 ml, 240 mmol) was added. The mixture was extracted with EtOAc (4 x 50 ml) and the combined organic extract was dried with $MgSO_4$ and evaporated to give a moist solid. This was washed further with Et_2O (2 x 50 ml).

The combined Et_2O extracts were concentrated to give a brown oil.

Attempted metallation of 2-bromotoluene, followed by direct coupling with excess *p*-toluenesulfonic anhydride to form 2,4'-ditolyl sulfone

To 2-bromotoluene (518 mg, 3.1 mmol) was added n-BuLi in hexane (2.0.M, 1.56 ml, 3 mmol) over 10 minutes with cooling in an ice bath. After 6 hours, the supernatant solution was used in the next stage.

To this *o*-tolyllithium solution was added an excess of *p*-toluenesulfonic anhydride (1.93 g, 6 mmol) at -78^0C for two hours. It was then allowed to reach room temperature over 18 hours. At this stage the reaction mixture appeared to be brown oil. To this oil, water (10 ml) was added to hydrolyse any remaining sulfonic anhydride. This was then neutralised with KOH, until pH 7 was reached. The organic product was then extracted using CH_2Cl_2 (4 x 15 ml).

The combined organic extracts were evaporated under vacuum to give a brown oil. The oil was analysed using reverse phase HPLC, but showed no trace of sulfone. The oil was not investigated further.

References

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Chapter Five

Relative rates of sulfonylation on substituted benzenesulfonic anhydrides

5.1 Introduction to rates of sulfonylation using different sulfonylating agents

Several groups have studied the rates of reaction of different sulfonylating agents, however little attention has been paid to reactions involving the aromatic sulfonic anhydrides. Sulfonylation studies considering the final yields of sulfone have been carried out by several research groups previously, however relative rates of reaction have generally not been included. Where relative rates of arylsulfonylation have been studied, it has been the sulfonyl halides (and more specifically the chlorides) that have been considered.

Olivier first considered the relative reactivities of different sulfonylating agents, investigating the arenesulfonylation of benzene.[1] Having studied the *p*-bromobenzenesulfonylation of benzene catalysed by $AlCl_3$ in detail, Olivier went on to study the reactions of a series of *para*-substituted benzenesulfonyl chlorides with benzene (as an active solvent) and $AlCl_3$ the catalyst.[1]

The rates that Olivier observed indicated that where electron-donating substituents are present in the position *para* to the sulfonyl chloride, the rate is accelerated. Where electron-withdrawing groups are present *para*-substituted relative to the sulfonyl chloride, the rate of reaction is decreased. Olivier found that the order of reactivity could be summarised thus; *p*-methyl > hydrogen > *p*-iodo > *p*-bromo > *p*-chloro > *m*-nitro. The rates observed are shown below (See Table 1).

Table 1. Rates for sulfonylation of benzene with *para*-substituted benzenesulfonyl chlorides.	
Substituent	Rate $k_{0,1}$
p-CH_3	0.00646
H	0.00212
p-I	0.00140
p-Br	0.0011
p-Cl	0.00106
m-NO_2	0.000136

Olivier also studied the relative reactivities of a series of *para-* and *meta-* substituted sulfonyl chlorides with benzene in carbon disulfide solvent. $AlCl_3$ was again used as the catalyst (See Table 2).[1]

Table 2. Relative rates of *para*-substituted benzenesulfonylation of benzene in carbon disulfide with $AlCl_3$ catalyst at 30 °C.	
Substituent	k/k_H
p-CH_3	3.0
H	1.0
p-I	0.5
p-Br	0.4
p-Cl	0.4
m-NO_2	0.06

The observations seem inconsistent with the ionic mechanism earlier proposed for the reaction (See Chapter Two, Equations 9-11). It can be seen that a relatively large change in the structure results in only a small change in the rate of reaction. The predominant effect appears to be the effect on the concentration of sulfonium cation, with the effect of the structure on the ionising equilibrium offset by the effect of the structure on the reactivity of the sulfonium cation.

Jenson and Brown whilst investigating the rates of reaction of a range of arenes with *p*-toluenesulfonyl chloride and benzenesulfonyl chloride, found that the *p*-toluenesulfonyl chloride reacted at approximately four times the rate of benzenesulfonyl chloride. Jensen and Brown believed that the observation could be attributed to two different contributing factors. The first being that the *p*-methyl substituent should stabilise the arenesulfonim cation and favour the ionisation step (See Figure 1).[2]

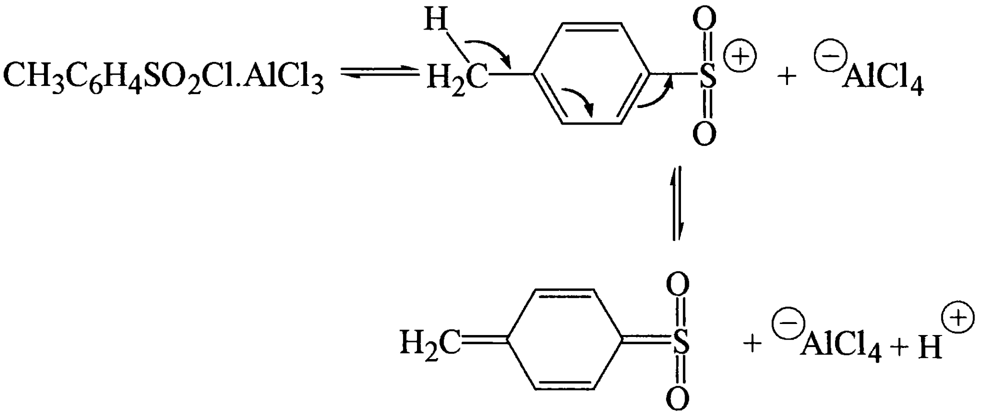


Figure 1

The second is the effect of induction by the methyl group, which should result in a more favourable equilibrium prior to the ionisation step (See Figure 2).

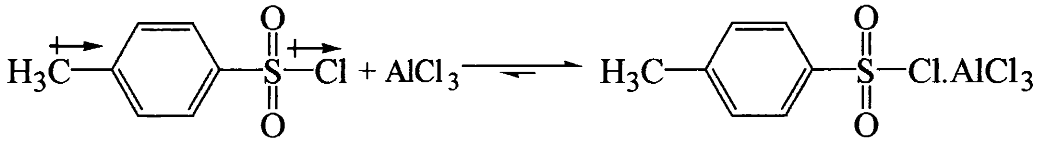
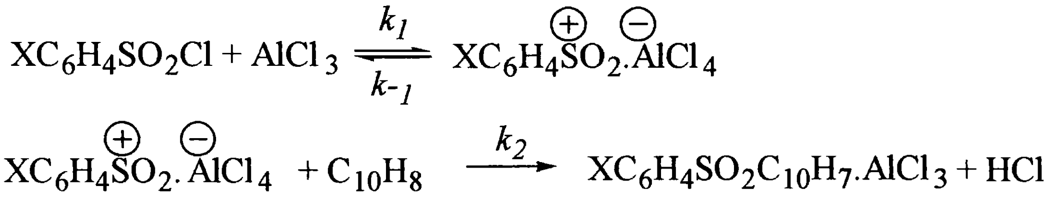


Figure 2

Holt and Pagadin carried out a series of reactions using polymethylbenzenesulfonyl chlorides with benzene in 1, 2-dichloroethane as solvent and $AlCl_3$ as catalyst. Holt and Pagadin found that methyl groups substituted *ortho-* or *para-* to the sulfonyl group resulted in lower sulfone yields from Friedel-Crafts type reactions. This observation is in contrast to results of other groups who found that the presence of methyl groups increased the reactivity of the sulfonyl chlorides.[3]

Olah studied the effect of substituents on the selectivity of sulfonylating agents in the sulfonylation of toluene and benzene, however relative rates of reaction of the sulfonyl chlorides were not included in this work.[4]

Yoshii *et al.* carried out a kinetic study on the Friedel-Crafts reaction of naphthalene with different *para*-substituted benzenesulfonyl chlorides.[5] Rate constants for both the formation of sulfonium cations (k_1) and the formation of sulfones (k_3) were determined separately. The rate constant k_3 is defined as $k_3 = k_1.k_2 / k_{-1}$ (See Figure 3).



$$XC_6H_4SO_2Cl + AlCl_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} XC_6H_4\overset{\oplus}{S}O_2.\overset{\ominus}{A}lCl_4$$

$$XC_6H_4\overset{\oplus}{S}O_2.\overset{\ominus}{A}lCl_4 + C_{10}H_8 \xrightarrow{k_2} XC_6H_4SO_2C_{10}H_7.AlCl_3 + HCl$$

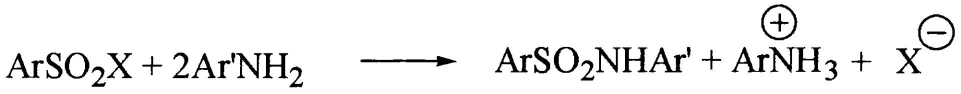
Figure 3

It was again found that the presence of electron donating *para*-substituents resulted in higher rates of reaction. The rates of reaction were calculated at several different temperatures and are given below (See Table 3).

Table 3. Rate parameters for *para*-substituted benzenesulfonylation of naphthalene in nitromethane, catalysed by $AlCl_3$

Substituent	Temperature (°C)	10^2k_1 / l mol^{-1} min^{-1}	k_3 / l^2 mol^{-2} min^{-1}
OMe	2	2.21 ± 0.07	0.90 ± 0.15
	5	3.53 ± 0.10	1.6 ± 0.3
	8	5.08 ± 0.15	1.7 ± 0.3
	11	6.79 ± 0.21	3.8 ± 0.5
Me	5	0.292 ± 0.012	0.083 ± 0.007
	10	0.563 ± 0.020	0.16 ± 0.01
	20	1.98 ± 0.07	0.52 ± 0.06
	30	6.94 ± 0.25	1.3 ± 0.2
H	20	0.524 ± 0.021	0.10 ± 0.01
	30	1.88 ± 0.07	0.28 ± 0.02
	40	5.21 ± 0.18	0.75 ± 0.09
	50	16.4 ± 0.60	1.1 ± 0.1
F	20	0.264 ± 0.008	0.032 ± 0.004
	30	1.06 ± 0.05	0.14 ± 0.01
	40	3.95 ± 0.16	0.62 ± 0.05
	50	13.5 ± 0.50	2.4 ± 0.3
Cl	20	0.229 ± 0.010	0.021 ± 0.002
	30	0.589 ± 0.021	0.076 ± 0.008
	40	2.09 ± 0.07	0.18 ± 0.02
	50	6.03 ± 0.20	0.37 ± 0.04
NO_2	30	0.0141 ± 0.0008	0.0013 ± 0.0003
	40	0.0883 ± 0.0035	0.0023 ± 0.0005
	50	0.141 ± 0.007	0.013± 0.002
	60	0.557 ± 0.035	0.021 ± 0.003

Although a range of *para*-substituted benzenesulfonyl chlorides were considered, the reactivity of substituted benzene sulfonic anhydrides was not included in the study.[5] Litvinenko *et al.* carried out a study of the reactivity of substituted benzenesulfonic anhydrides.[6] The kinetics of the reactions of the arenesulfonic anhydrides with aromatic amines in nitrobenzene were investigated. It was found in the study that the sensitivity of the rate of reaction to the influence substituents in the arenesulfonic anhydride is substantially higher than in the corresponding sulfonyl chlorides and bromides. The general reaction scheme is shown below (See Figure 4).



$$ArSO_2X + 2Ar'NH_2 \longrightarrow ArSO_2NHAr' + Ar\overset{\oplus}{N}H_3 + X^{\ominus}$$

$X = OSO_2Ar$, Br, Cl

Figure 4

In the study Litvinenko has compared the reactivity of derivatives of *p*-toluenesulfonic acid in the reaction with *m*-nitroaniline in nitrobenzene at 25 °C. The results are shown below (See Table 4).[6]

Table 4. Comparison of the reactivities of derivatives of *p*-toluenesulfonic acid (*p*-$CH_3C_6SO_2X$) in the reaction with *m*-nitroaniline in nitrobenzene at 25 °C

Substituent X	k_2. 10^5 l mol^{-1} sec^{-1}
p-$CH_3C_6H_4SO_2O$	163
Br	1.97
Cl	0.055

The rate constants for the reaction of substituted anhydrides with 3-nitroanaline were also calculated. The results are shown below (See Table 5).

Table 5.Rate constants of the reaction of substituted arenesulfonic anhydrides with 3-nitroaniline in nitrobenzene at 25 °C

R in $(RC_6H_4SO_2)_2O$	k_2. 10^2. l mol^{-1} sec^{-1}
4-CH_3	0.160 ± 0.005
H	0.370 ± 0.009
3-NO_2	18.5 ± 0.20
4-Cl	1.27 ± 0.06

The influence of substituents on the rate of reactions of the sulfonic anhydride studied was found to be satisfactorily described by the Hammett–Taft equation.[6]

It is believed that the higher sensitivity of the rates of reaction of the arenesulfonic anhydrides compared with the sulfonyl chlorides is connected with the fact that the substituent appears twice in each molecule of the anhydride. The interaction of the two substituents coincides in direction, thus ensuring an increased sensitivity of the reaction under consideration to structural changes in the molecule results.

It can be assumed that the Friedel-Crafts type reactions of the sulfonic anhydrides will exhibit different characteristics. The reaction is predicted to be more complicated due to the greater complexity of the kinetics with regard to the stability of the sulfonium cation formed in sulfonylation reactions. The reactions with 3-nitroaniline can be more easily understood as nucleophilic substitutions taking place at the sulfur atom.

It is believed that the relative rates of formation of the sulfonium cations will be dominant in determining the relative rates of Friedel-Crafts sulfonylation.

The aim of this study was to obtain relative reactivities for a range of substituted benzenesulfonic anhydrides in the Friedel-Crafts type reactions with toluene. The reactions were carried out in nitromethane and catalysed by $AlCl_3$. In order to carry out such an investigation the synthesis of a range of aromatic sulfonic anhydrides was required.

5.2 Methods of synthesising sulfonic anhydrides

Aromatic sulfonic anhydrides are derivatives of aromatic sulfonic acids. They were first reported in 1884 by Hubner in his partially successful attempt to synthesise phenylsulfonic anhydride from silver benzenesulfonate and benzenesulfonyl chloride. Following the initial reaction Hubner tried to isolate the product by extracting into ether. This resulted in some of the ether combining with the sulfonic anhydride and forming ethyl phenyl sulfonate.[7]

Abrahall improved on the early attempt of Hubner in 1886. It was suggested to Abrahall that the route to the anhydride was as carried out by Hubner, however the final extraction step should be carried out using chloroform rather than ether to avoid the sulfonate formation. The extraction with chloroform proved more successful with the product successfully isolated. Abrahall observed that the sulfonic anhydride was more reactive than the corresponding sulfonyl chloride, contrasting with the prediction made based on the fact that the anhydrides of carboxylic acids are less reactive than the corresponding chlorides. [8]

Billeter used a similar route to form benzenesulfonic anhydride, however the product was then distilled from phosphorus pentoxide and dried under vacuum.[9] This method is expensive and not a convenient route to sulfonic anhydrides.

Meyer and co-workers used the reaction of thionyl chloride with sulfonic acids or their salts. In this series of reactions was found that the sulfonyl chloride could also be obtained. The ratio of anhydride to sulfonyl chloride appears to be dependent upon the presence of trace impurities in the thionyl chloride.[10]

In his work on sulfonamide preparations Shepard desired a more reproducible route to aromatic sulfonic anhydrides.[11] Shepard hoped that the reaction between oxalic acid and activated halogen compounds could be extended to work with benzenesulfonyl chloride as shown below (Equation 1).

$$2C_6H_5SO_2Cl + (COOH)_2 \rightarrow (C_6H_5SO_2)_2O + 2HCl + CO + CO_2 \quad (1)$$

The reaction of benzenesulfonyl chloride with anhydrous oxalic acid was found to give the desired benzenesulfonic anhydride product. The reported yield was 99%. It was concluded in the same paper that oxalic acid shows unique behaviour due to the fact that when a similar reaction was attempted with anhydrous sulfonic acid, no sulfonic anhydride product was formed. Even when higher temperatures were used for longer periods of time no anhydride product was observed.[11]

Lamar Field published a synthetic route to aromatic sulfonic anhydrides involving the condensation of the respective sulfonic acids carried out using a 50% excess of phosphorous pentoxide and an inert support (Equation 2).[12]

$$2RSO_3H \xrightleftharpoons{P_2O_5} (RSO_2)_2O + H_2O \qquad (2)$$

A mixture of Super-cel kieselguhr and Gooch asbestos was used as a support in the reaction. The preparation of benzenesulfonic anhydride was carried out over a period of 5 hours at 100°C with occasional mixing, after which time it was extracted from the reaction mixture using 1,2-dichloroethane. The similar reaction to synthesise *p*-toluenesulfonic anhydride using *p*-toluenesulfonic acid (monohydrate) was also carried out and both the benzenesulfonic anhydride and *p*-toluenesulfonic anhydride were successfully recrystallised from a benzene-ether mixture. In the work by Field melting point ranges of the sulfonic anhydrides were found to be rather broad. It was postulated that this was not due to large amounts of impurities present in the recrystallised product, rather that a small amount of sulfonic acid impurity resulted in a large depression of observed melting point.[12]

In 1953 a valuable route to aromatic sulfonic anhydrides was contributed by Khorana, who obtained sulfonic anhydrides from the corresponding sulfonic acids.[13] This was achieved by reacting them with substituted carbodiimides. Dicyclohexyl carbodiimide was used in the early work in this study, however difficulty was experienced in separating the di-cyclohexyl urea from the sulfonic anhydride products. This problem was overcome by using di-*p*-tolyl carbodiimide in place of the dicyclohexyl carbodiimide and using benzene as a solvent. Using the revised reaction conditions the separation of the product was readily achieved, due to the urea by-product being insoluble in the solvent system. This method was used to prepare the anhydrides of methane-, benzene- and *p*-toluenesulfonic acids in excellent yield.[13]

In a study on the sulfonation of halogen-substituted benzene derivatives, Lukashevich observed that when the reactions were carried out using 65% oleum the anhydrides of the corresponding sulfonic acids could be isolated in reasonable yields.[14] In the study he considered arenes containing bromine, chlorine and iodine. In most cases the arene was added to 65% oleum and allowed to stir at room temperature for 1 or more days, with the anhydride being recovered in approximately 50% yield with respect to the starting arene.[14]

The synthesis of *p*-toluenesulfonic anhydride was achieved by Eglington *et al.* by adding methoxyacetylene to *p*-toluenesulfonic acid in dichloromethane.[15] A vigorous reaction took place with cooling required. Evaporation of the solvent and treatment with potassium hydrogen carbonate resulted in the isolation of the *p*-toluenesulfonic anhydride in 52% yield. [15] The general reaction mechanism is shown below (See Figure 5).

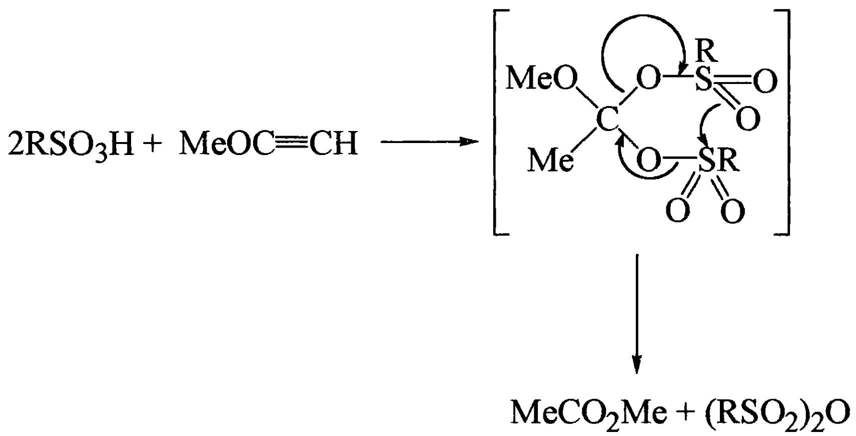


Figure 5

The ozonolysis of diaryl disulfides was shown to be a viable route to diaryl sulfonic anhydrides by Barnard.[16] In the study it was shown that organic monosulfides are oxidised by less than the theoretical amount of ozone to give high yields of the respective sulfone via the sulfoxide. Disulfides were found to give the corresponding sulfonic anhydride via a more complicated route, also producing small amounts of thiolsulfonate and disulfone. Tetrasulfides were surprisingly also found to give sulfonic anhydrides with sulfur dioxide as the by-product. The diaryl sulfonic anhydrides prepared using this method included benzene and di-*p*-chlorobenzene sulfonic anhydride. The paper also includes consideration of mechanisms, and rate data derived from competitive ozonolysis reactions. [16]

Flavell and Ross reported the preparation of aromatic sulfonic anhydrides by the disproportionation of mixed anhydrides.[17] It was demonstrated that the disproportionation of mixed anhydrides was accelerated when carried out in the presence of acetonitrile. The thermal decomposition of mixed anhydrides was found to be a less satisfactory method of preparing sulfonic anhydrides in good yield due to the partial decomposition of the sulfonic anhydrides at the decomposition temperature of the mixed anhydrides. Benzenesulfonic anhydride was prepared from the reaction between benzenesulfonyl chloride and silver acetate in acetonitrile, and the subsequent disproportionation of the mixed anhydride. The reaction was carried out at reflux for 15 hours, after which time silver chloride was filtered off and the solvent was removed under reduced pressure. The reaction afforded a 21% yield with respect to the benzenesulfonyl chloride starting material. A similar reaction using mesitylenesulfonyl chloride was reported to give a 25% yield of pure sulfonic anhydride. [17] Following on from this work, Karger and Mazur found that good yields of sulfonic anhydrides could be achieved by the pyrolysis of mixed carboxylic-sulfonic anhydrides.[18] They found that the method could give a good yield of sulfonic acid product, without experiencing the decomposition noted by Flavell and Ross.[17] In the work carried out by Karger and Mazur, it was observed that the thermal decomposition of the sulfonic anhydrides occurred at approximately 130 °C. They demonstrated that the pyrolysis could give the sulfonic anhydride in preference to the sulfonic acid as long as the reaction temperature was below 130 °C (Equation 3). [18]

$$2C_6H_5C(O)OSO_2C_6H_5 \longrightarrow (C_6H_5CO)_2O + (C_6H_5SO_2)_2O \qquad (3)$$

N. Hesselbjerg Christensen reported that it was possible to prepare iodobenzenesulfonic anhydride from the reaction of iodobenzenesulfonic acid with sulfur trioxide (Equation 4).[19] A series of reactions was carried out and in all instances the corresponding sulfones were not observed.

$$2RSO_3H + SO_3 \longrightarrow (RSO_2)_2O + H_2SO_4 \qquad (4)$$

The results of the dehydration reactions carried out are detailed below (See Table 6). In one of the experiments the sulfonic acid was labelled with ^{35}S and the dehydration had no effect on the specific activity. i.e. There was no sulfur exchange taking place.[19]

Table 6. Reaction between sulfonic acid and sulfur trioxide in nitromethane at 40 °C.

SO_3 added, mmol per mmol sulfonic acid	Yields in % of initial sulfonic acid	
	Sulfonic anhydride	Sulfonic acid (Water-extracted)
0.95	69	Not determined
1.2	73	22
4.0	43	52

The reaction between disulfides and dinitrogen tetroxide was reported by Kunieda and Oae in 1968.[20] In the paper the same reaction methodology was used to react an excess of dinitrogen tetroxide with *p*-toluenethiolsulfinate to form *p*-toluenesulfonic anhydride. This reaction afforded the anhydride in a 94% yield. In the reaction 4.6 mole equivalents of dinitrogen tetroxide were used. The paper does not detail whether or not any work up and separation was necessary however the melting point reported was a lot sharper than in many of the other communications on the subject.[20]

As part of a study on the Reactions of Free Toluene-*p*-sulfonyl Radical, da Silva Corrêa and Waters reported the formation of *p*-toluenesulfonic anhydride.[21] The product being formed as a product in the disproportionation of the *p*-toluene sulfonyl radicals according to Equation 5.

$$6CH_3C_6H_4SO_2\bullet \longrightarrow \begin{array}{c} 2(CH_3C_6H_4SO_2)_2O \\ + \\ CH_3C_6H_4SSO_2C_6H_4CH_3 \end{array} \qquad (5)$$

The desired radicals were formed by the excitation of *p*-toluenesulfonyl iodide in the absence of metal. The irradiation was carried out using warming in either benzene or carbon tetrachloride solvents, with the reactions carried out in the presence of an azo-compound to abstract the free iodine radicals. The reaction details can be seen below

(See Table 7). It should be noted that in each of the reactions the disulfone yield is relatively low.[21]

Table 7. Percentage yields of products of reactions between *p*-$CH_3C_6H_4SO_2I$ and azo-compounds, RN_2R.

	$(CH_3)_2C(CN)N_2C(CH_3)_2CN$		$C_6H_{10}(CN)N_2C_6H_{10}CN$
Product	In C_6H_6	In CCl_4	In C_6H_6
$R_2C(CN)I$	35	32	13
$R_2C(CN)CR_2CN$	-	29	3.7
$CH_3C_6H_4SO_2OSO_2C_6H_4CH_3$	37	27	54
$CH_3C_6H_4SO_2SO_2C_6H_4CH_3$	18	3.0	4.6

Litvinenko *et al.* carried out a study on the reactivity of aromatic sulfonic anhydrides.[22] The paper also included the synthesis of several anhydrides to be used as starting materials. They synthesised the anhydrides of *p*-toluenesulfonic acid and benzenesulfonic acid using the method published in an earlier publication by the same research group.[23] To synthesise *p*-chlorobenzenesulfonic anhydride Litvinenko used direct sulfonation of chlorobenzene in nitromethane.[22] This was very similar to the route that Hesselbjerg Christensen had used to produce *p*-iodobenzenesulfonic anhydride.[19]

In an attempt to prepare a sample of *bis*(tosyloxymethyl) ether for study, Burness *et al.* found the reaction of silver tosylate with *bis*(chloromethyl) ether (BCME) did not give the desired product. After analysis it was determined that the reaction had actually formed *p*-toluenesulfonic anhydride in 36% yield.[24] At first glance this method appears convenient as the reaction needs very little work up, however the BCME is a known carcinogen. It should also be noted that this method gave a product with a wide melting point range compared to some of the other preparative methods. A possible reaction pathway is shown in Figure 6.[24]

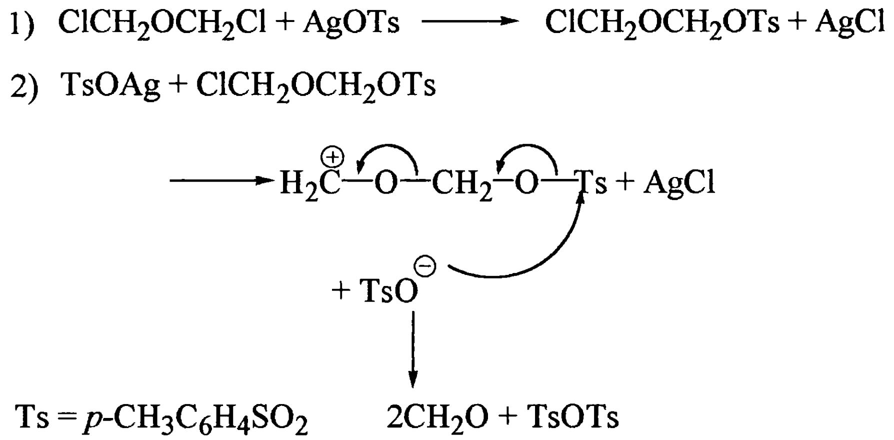


Figure 6

In 1994 Peterli-Roth *et al.* used *p*-toluenesulfonic anhydride in the stereoselective synthesis of (S)-6-methyldeaminosinefungin.[25] The group synthesised *p*-toluenesulfonic anhydride using the route Meyer used in 1923 using the sulfonic acid monohydrate and thionyl chloride.[10] The work up was carried out by the distillation of the excess thionyl chloride, and then crystallising out the sulfonic anhydride from ether. The product was achieved in 80% yield, and had a relatively sharp melting point, however other methods have given sharper melting points.[25] More recently Cerfontain *et al.* expanded on earlier work by the group on the formation of aromatic sulfonic anhydrides and aromatic sulfonic acids.[26] The work centred on the sulfonation of dialkylbenzenes and 1,ω-diarylalkanes.[27] The diaryl sulfonic anhydrides were achieved by reacting the arenes with approximately a 4 fold excess of SO_3 at 0-22 °C.

There are several examples documented in the literature of research teams making unsymmetrical arylsulfonic trifluoromethanesulfonic anhydrides including the work of Effenberger *et al.*[28] These examples have not been considered, as it is only the diaryl sulfonic anhydrides that are of direct relevance to the current study.

5.3 Attempted synthesis of aromatic sulfonic anhydrides

Having reviewed the available literature it was decided to attempt to synthesise a range of aromatic sulfonic anhydrides. The initial attempt was carried out using the method originally developed by Khorana[13] by reaction of a sulfonic acid with a carbodiimide, the carbodiimide acting as a dehydrating agent. In the original publication Khorana had difficulty separating and isolating the sulfonic anhydride when 1,3-dicyclohexyl carbodiimide was used as a starting material. The use of di-*p*-tolyl carbodiimide was found to aid the product separation, however this was not considered due to the high cost of the starting material. The 1,3-dicyclohexyl carbodiimide was used, with the intention of attempting the separation of products if the reaction mixture could be seen to contain the desired sulfonic anhydride.

Problems were encountered in trying to follow the synthetic methods outlined by Khorana. Due to the fact that benzenesulfonic acid was found not to be readily soluble in benzene as described in the original publication, a homogenous starting solution of the acid in benzene could not be achieved. Several attempts were made to dissolve the acid in both benzene and toluene. Attempts were made by heating, then gently cooling the solution as it was hoped that the sulfonic acid would remain in solution long enough to start the reaction, however the mixture crystallised very readily as soon as the cooling process began. Due to the fact that the subsequent reaction needed to be carried out cool, this technique did not offer the desired solution.

It was found that the 1,3-dicyclohexyl carbodiimide was readily soluble in benzene, and by reversing the order of addition of the reagents the problems was overcome. Subsequently the benzene sulfonic acid added was readily taken into the carbodiimide solution for reaction. Shortly after all the acid had been taken into solution, urea started to crystallise out as a by-product. The urea was removed by filtration in the absence of air and moisture, which proved more difficult than anticipated. The very fine nature of the solid lead to a wet slurry that was difficult to filter. Due to these problems it was decided to look at an alternative route to aromatic sulfonic anhydrides.

The route outlined by Shepard [11] to benzenesulfonic anhydride using oxalic acid was considered to be an attractive alternative, using simple techniques along with inexpensive reagents. The reaction was carried out as described in the literature with the oxalic acid and benzenesulfonyl chloride mixture heated to 160 °C under an inert atmosphere for 1 hour. The mixture was then heated to 200 °C for a short period of time. Any volatile material was removed by vacuum distillation. The liquid residue crystallised quickly on cooling, as described in the original work, however the characteristics of the solid product suggested that the acid had been formed rather than the sulfonic anhydride. The product was not recrystallised from ether as detailed in the original work, due to the product being completely insoluble even at high temperature.

The melting point of the crude material of 42-47 °C is characteristic of the sulfonic acid, as is the deliquescence that was observed when the product was exposed to air. Further attempts were made to carry out this experiment, with the heating carried out for both longer and shorter periods of time. On every occasion it was the sulfonic acid product that was isolated and identified. Other methods of isolating any anhydride that may have been formed were also attempted including hot extractions of any anhydride from the acid along with washing away the acid with the aim of leaving any anhydride as a residue, however all attempts proved unsuccessful.

One possible problem that was identified was that the original publication described the organic extraction as having used ‘ether’. Due to the age of the paper it was believed that ‘ether’ referred to was diethyl ether. To avoid any possible misunderstanding the isolation of the product was attempted using petroleum ether. Again the product isolated was found to be benzenesulfonic acid. The product readily deliquesced in air and was found to have a slightly sharper melting point than the earlier isolated products. Due to the problems experienced with this method, a third route was then investigated.

Meyer and Schlegel had outlined a method to form aromatic sulfonic anhydrides via the reaction of thionyl chloride and benzenesulfonic acid.[10] The reaction was carried out in benzene, and again difficulties were experienced in isolating the desired product. The mixture was heated to reflux for 2 hours, with any excess thionyl chloride removed at 50 °C under vacuum. The reaction mixture was allowed to cool and was stored at 0 °C for 1 hour. The desired product was isolated by hot extraction into dry, alcohol free diethyl ether. A small amount of solid was collected, which did not deliquesce on exposure to air. The melting point was a little low for the anhydride, but significantly higher than that of the acid. The product was quite strongly coloured. This information combined with the work of Field[12] that concluded that a small amount of impurity in a sample of sulfonic anhydride could lead to a large depression of melting point, suggested that it was the anhydride that had been formed. The product yield was very low from this reaction and steps were taken to try to improve this. One attempt was to change the reaction solvent, from benzene to nitromethane. This allowed the reaction to be repeated at higher temperature, with any product being formed falling out of solution as a precipitate. In the reaction no anhydride product was observed to crystallise out. Due to the disappointing results obtained from the initial attempts to synthesise aromatic sulfonic anhydrides, direct sulfonation was attempted.

Initially direct sulfonation of an aryl halide was attempted, with oleum as the sulfonating media.

It should be noted at this stage that doubts over the literature methods existed before this was attempted, due to the water sensitive nature of the anhydrides, and the fact that the isolation of the reaction products involved the addition of the reaction products to cold water. The reaction was carried out as outlined by Lukashevich[14], however difficulties were experienced in the isolation of the anhydride as expected. The literature method describes the addition of the reaction mixture to ice cold water, with the hydrolysis of the anhydride being avoided due to the cold conditions and poor solubility of the anhydride in water. When this step was carried out it was observed that the hydrolysis appeared to take place very rapidly, with no solid product precipitate being collected. Several alterations were made to try to improve the final step of the reaction, including very rapid mechanical stirring of the reaction mixture in an attempt to try to avoid localised heating of the water in the presence of the reaction mixture. This however did not overcome the rapid hydrolysis that appeared to be taking place, if indeed any sulfonic anhydride product was being formed at all. The likely explanation is that the reaction was only proceeding as far as the sulfonic acid, and that no anhydride was being formed at all.

It is believed that one of the main problems associated with this reaction was that a supplier of 65% oleum as used in the original publication could not be found. The reactions were attempted using 15-20% oleum, however it is believed that the concentration of SO_3 was not high enough to successfully promote the dehydration of the sulfonic acid to the sulfonic anhydride. It was decided that a higher concentration of SO_3 was needed to achieve the final step of the reaction.

5.4 Synthesis of aromatic sulfonic anhydrides using SO_3

Literature methods for the formation of sulfonic anhydrides outline the use of SO_3 (g), a technique that was not available in U. W. Swansea. However, due to the installation of a new laboratory scale sulfonation facility at Unilever Research Port Sunlight, this approach became viable. Two sulfonation studies were carried out at Unilever, the first was an initial study replicating the work of Field, [12] the second was carried out with further improvements to the experimental technique. Due to the fact that the facility was new, significant advances were made in the understanding of the equipment and the reactions. In the first study the method published by Field was investigated and extended to include other halobenzenes.[12] The reactions were carried out using 10% (w/w) solutions of halobenzene in nitromethane.

To a solution of a given halobenzene in nitromethane, SO_3 was added. This was added as a gas, carried on a stream of dry nitrogen. The amount of SO_3 used was based on the studies of Hesselbjerg-Christensen who found that that a mole ratio of SO_3 / halobenzene equal to approximately 1.6 gave the highest yield of sulfonic anhydride product, recording a yield of 80%. The use of nitromethane as a solvent removes the need for water to be used in the isolation and purification stages of the reaction. The results of the sulfonations of halobenzenes carried out in the first study can be seen below (See Table 8).

Table 8. Summary of synthesis of aromatic sulfonic anhydrides by direct sulfonation using 1.6 mol. eq. SO_3 in nitromethane

Sulfonic anhydride	Temperature (°C)	Yield (%)	M.p. (Lit. Value) (°C)
p-Bromobenzene	10	40	170 - 180 (182)
p-Bromobenzene	20	34	163 – 174 (182)
p-Bromobenzene	40	40	174 – 179 (182)
p-Chlorobenzene	15	6	131 – 136 (141)
p-Chlorobenzene	40	9	127 – 131 (141)
p-Chlorobenzene	20	4	93 – 96 (141)
p-Chlorobenzene	10	8	128 – 131 (141)
p-Fluorobenzene	15	Only sulfonic acid isolated	-
Benzene *	20	Only sulfonic acid isolated	(91.5)

* Starting material used was benzenesulfonic acid

In the first series of reactions using SO_3 gas, an attempt was made to extend the work to include the dehydration reaction between benzenesulfonic acid and SO_3 to form benzenesulfonic anhydride. The first attempt at this work was unsuccessful, however it is believed that this was due to the fact that acid used was partially hydrated. This in turn would have lead to the SO_3 added being converted to sulfuric acid following the reaction with any water present. Literature also states that the presence of any impurities in the sulfonic acid is detrimental to the reaction succeeding.

The second set of direct sulfonation reactions using SO_3 to form sulfonic anhydrides proved to be more successful. It was observed that although Hesselbjerg-Christensen found that 1.6 mole equivalents of SO_3 gave the maximum yield of sulfone, more SO_3

was required than the quantity of that had previously been indicated. This was due to the loss of SO_3 as exhaust fumes (See Fig. 7).

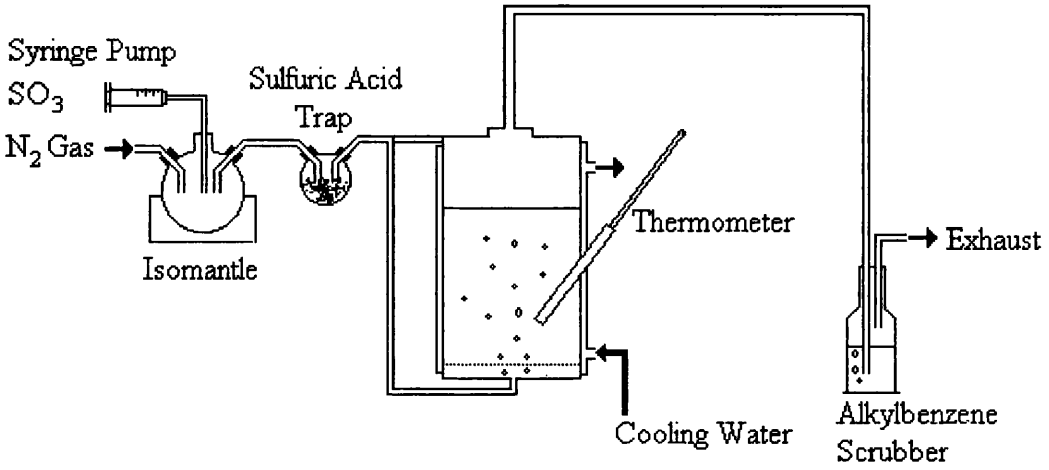


Figure 7

Due to the fact that the nitrogen carrier gas was also used as the method of agitation, the carrier gas must pass through the reaction mixture at a high enough flow rate to affect good agitation. This in return results in some SO_3 gas being carried straight through the reaction mixture without being absorbed into solution. The result is unreacted SO_3, which passes out to the scrubber as exhaust fumes.

In order to overcome the problem two different approaches were considered. The first attempt was to reduce the flow rate of the nitrogen carrier gas. This did appear to reduce the loss of SO_3. Although the approach initially appeared successful, it was found that the agitation was not sufficient to prevent build up of sulfonic anhydride product at the neck of the SO_3 inlet. The result was that product was lost, as it could not be easily be recovered due to accessibility problems. Another problem was that where the sulfonic anhydride was exposed to direct contact with SO_3, very strong discolouring of the product was observed.

A second approach to overcome the problem was then used. An excess of SO_3 slightly larger than the 1.6 mole equivalents previously used was employed. A mole ratio of SO_3 / Aromatic equal to 2 allows for a 20% loss of SO_3, resulting in an estimated mole equivalent somewhere close to the 1.6 mole required for optimum results.

The second series of sulfonation reactions was carried out in which the concentration of halobenzene was increased from 10% to 15% (w/w) of halobenzene in nitromethane. The results of the second study show a large improvement on the first set of results. The yields of the desired sulfonic anhydrides were significantly higher following the revisions made (See Table 9).

Table 9. Summary of synthesis of aromatic sulfonic anhydrides by direct sulfonation using 2.0 mol. eq. SO_3 in nitromethane at 20 °C

Sulfonic anhydride	Yield (%)	M.p. °C (Lit. Value)
p-Bromobenzene	55	170 - 178 (182)
p-Bromobenzene	49	178 - 180 (182)
p-Bromobenzene	58	171 - 175 (182)
p-Chlorobenzene	24	137 - 139 (141)
p-Chlorobenzene	18	135 - 138 (141)
p-Chlorobenzene	20	136 - 139 (141)
p-Iodobenzene	63	217 – 219(221)
p-Iodobenzene	68	215 – 219 (221)
Benzene *	Only sulfonic acid isolated	(91.5)
Benzene **	Only sulfonic acid isolated	(91.5)
p-Fluorobenzene	Only sulfonic acid isolated	Not known
*p-Iso*propylbenzene	Only sulfonic acid isolated	Not known
*p-Iso*propylbenzene	Only sulfonic acid isolated	Not known

* Starting material benzene

** Starting material benzenesulfonicacid

The second series of sulfonation reactions was extended beyond the halobenzenes, with sulfonation of benzene, *iso*propylbenzene and anhydrous benzenesulfonic acid also attempted. The reactions of benzene and *iso*propylbenzene displayed slightly different characteristics to the reactions of the halobenzenes. The target sulfonic anhydrides were not observed to readily crystallise out of the nitromethane reaction solutions. The reactions were allowed to stand for a period of 1 week, sealed under an inert atmosphere until crystallisation was observed. The crystals were later found to be the corresponding sulfonic acids. Due to time constraints this investigation was discontinued

Having obtained samples of several different sulfonic anhydrides a method for the sulfonylation competition reactions could be developed.

5.5 Sulfonylation competition reaction method development

Having successfully used HPLC as the analytical technique for the earlier sulfonylation competition reactions, it was decided to continue with a similar analytical system and to follow the reactions by measuring the formation of sulfone products.

In the earlier sulfonylation studies only a single sulfonic anhydride was used, *p*-toluenesulfonic anhydride, resulting in the formation of di-*p*-tolyl sulfone along with *p*-toluenesulfonyl chloride as a by-product of the reaction. With a system involving two competing sulfonic anhydrides, it was predicted that two different sulfones would be formed, as well as two different sulfonyl chlorides as by-products. A trial series of separations was performed to attempt to separate the mixture of predicted reaction products to check the suitability of the technique as an analytical system for the competition reactions. The trial was carried out using a mixture of *p*-toluenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride, di-*p*-tolyl sulfone, 4-bromophenyl-*p*-tolyl sulfone and *o*-nitrotoluene (The internal standard). The compounds were successfully separated by HPLC using the Excil reverse phase column used for the earlier analysis (See Chapters Two and Three). In contrast to the earlier work, the eluent composition had to be changed from 70:30 methanol: water to 67: 33 methanol: water. The change in eluent composition could theoretically have an effect on the response factors of the different sulfone products. Analysing a mixture of sulfones and *o*-nitrotoluene using varying eluent composition confirmed that the effect was negligible. In changing the eluent composition from 70: 30 to 65:35 methanol: water, no significant change in response factor was observed. As a result it was concluded that the response factors obtained for the sulfones studied in Chapter Three would be used for the current study. The results of the response factor study are given below (See Table 10).

Table 10. Effect of changing eluent composition on response factor of di-*p*-tolyl sulfone at 240 nm

Methanol (%)	Water (%)	Response Factor
70	30	0.1894
69	31	0.1892
68	32	0.1887
67	33	0.1901
66	34	0.1903
65	35	0.1893

In order to promote pseudo first order kinetics and to ensure fair competition between the competing aromatic sulfonic anhydrides, a ten-fold excess of each sulfonic anhydride over the aryl substrate was decided upon. In order to have the final reaction concentration similar to that used in the earlier competition reactions, it was decided to use a concentration of 0.4 moldm^{-3} for each of the starting solutions of anhydride.

This resulted in a reaction concentration of 0.01 $moldm^{-3}$ with respect to the toluene, and 0.1 $moldm^{-3}$ with respect to the sulfonic anhydride.

Reactions were allowed to proceed for three hours, after which time samples were taken and quenched in ethanol, and then analysed by HPLC.

In order to include *p*-iodobenzenesulfonic anhydride in the competition reactions it should be noted that 4-iodophenyl-*p*-tolyl sulfone was synthesised (See Experimental). The response factor was obtained for 4-iodophenyl-*p*-tolyl sulfone using similar techniques as used in the first competition reaction study (Chapter Three). The results are given in Chapter Five Appendix.

5.6 Competition reactions using a range of aromatic sulfonic anhydrides in sulfonylation reactions with toluene

Following the difficulties encountered in trying to isolate the different aromatic sulfonic anhydrides it was only possible to calculate the relative reactivities of a limited number of compounds. Due to the fact that benzenesulfonic anhydride was not successfully isolated, the relative rate of reaction of each anhydride was measured using *p*-toluenesulfonic anhydride as the standard. The reactions were investigated at 25.0 °C.

The first relative rate to be measured was that of *p*-bromobenzenesulfonic anhydride against *p*-toluenesulfonic anhydride, reacting with toluene and catalysed by $AlCl_3$. It was found that $k_{Br} / k_{Me} = 0.43$. This suggests that the effect of the substituent on the rate of reaction is not very large. It suggests that the electron withdrawing properties of the bromine have detrimental effect on the rate of reaction.

The second relative rate investigated was that of *p*-iodobenzenesulfonic anhydride. It was found that the *p*-iodobenzenesulfonic anhydride was not readily soluble in nitromethane. It had been hoped that the *p*-iodobenzenesulfonic anhydride would be soluble enough in nitromethane to make the required starting solution. This was not the case, with the *p*-iodobenzenesulfonic anhydride proving to be almost completely insoluble. Investigation found that with gentle heating the *p*-iodobenzenesulfonic anhydride was taken into solution. It was found that with *p*-toluenesulfonic anhydride and toluene present that the *p*-iodobenzenesulfonic anhydride remained a nitromethane solution long enough start the reaction with the addition of $AlCl_3$. Following the addition of the catalyst the reaction mixture remained homogeneous. The relative rate was found to be k_I / k_{Me} = 0.55. The reactivity of the *p*-iodobenzenesulfonic anhydride being greater than that of *p*-bromobenzenesulfonic anhydride.

The third reaction in the series was that of *p*-chlorobenzenesulfonic anhydride. The solubility of the anhydride in nitromethane was found to be sufficient so that heating of the starting solution was not required to achieve homogeneity. The relative rate of reaction was k_{Cl} / k_{Me} = 0.42. The relative rate was found to be very close to that of bromobenzene.

The relative rates of reaction can be plotted against the Hammett constant σ for each substituent to give the reaction constant, ρ, as the gradient. This is normally calculated relative to benzene, however by letting the rate of reaction of *p*-toluenesulfonic anhydride = 1.0, the plot is possible and shown below (See Figure 8).

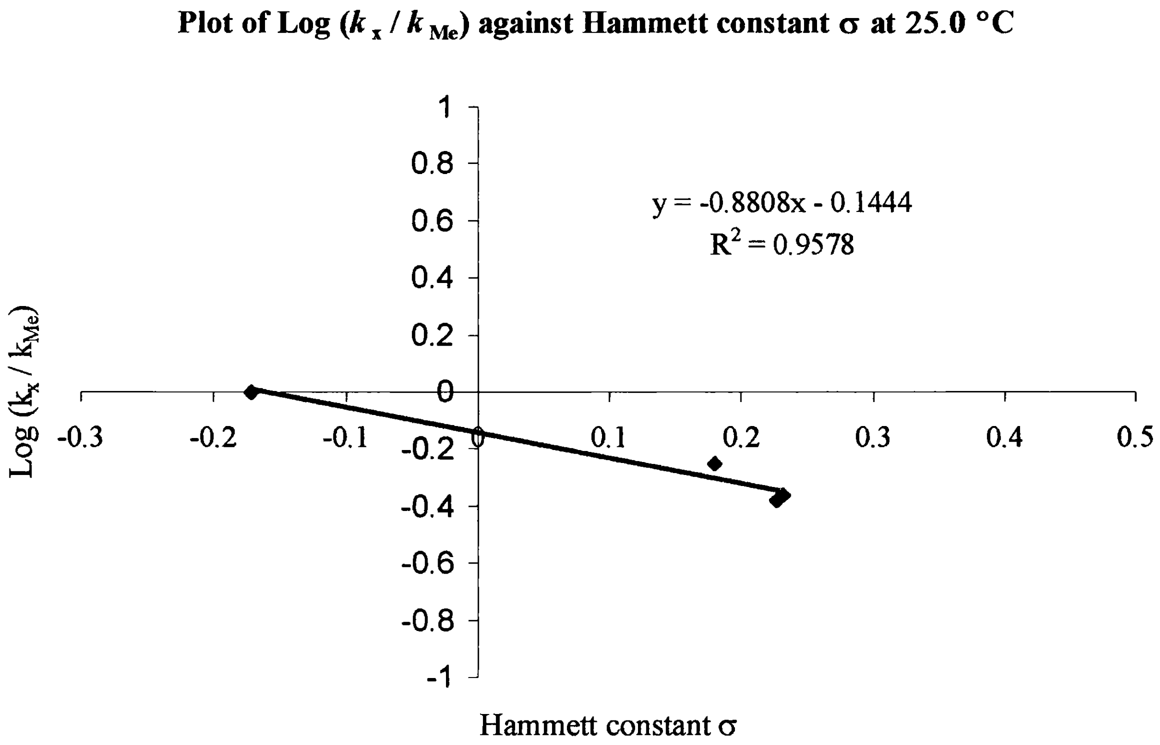


Figure 8. Plot of Log (k_X / k_{Me}) against Hammett constant for the *para*-substituted benzenesulfonylation of toluene in nitromethane at 25 °C, catalysed by $AlCl_3$

From the gradient of the Hammett plot the reaction constant was obtained as $\rho = -0.8808$. If the reaction of benzenesulfonic anhydride is assumed to follow the pattern of the other competitive sulfonylation reactions it is then possible to use the values obtained from the Hammett plot of the competition reactions carried out to predict the relative reactivities of the different sulfonic anhydrides relative to benzenesulfonic anhydride. This includes a predicted reactivity of *p*-toluenesulfonic anhydride relative to benzenesulfonic anhydride. The predicted reactivities are given below (See Table 11).

Table 11. The k_X / k_{Me} and predicted k_X / k_H values for the X-substituted benzenesulfonylation of toluene in nitromethane catalysed by $AlCl_3$ at 25 °C		
Substituent X in C_6H_5X	k_X / k_{Me}	k_X / k_H
Br	0.43	0.61
Cl	0.42	0.59
I	0.55	0.78
CH_3	1.0	1.39

The predicted relative of reactivity of *p*-toluenesulfonic anhydride to benzenesulfonic anhydride was calculated to be k_{Me} / k_H = 1.39.

Having carried out the first study it was decided to investigate the effect of changing the temperature on the relative rates of reaction. The first set of reactions was carried out at 0° C, using the same reagents as used at 25 °C. The results are given below (See Table 12), and have been plotted against the Hammett constant σ (See Figure 9).

Table 12. The k_X / k_{Me} and predicted k_X / k_H values for the X-substituted benzenesulfonylation of toluene in nitromethane catalysed by $AlCl_3$ at 0 °C		
Substituent X in C_6H_5X	k_X / k_{Me}	k_X / k_H
Br	0.43	0.62
Cl	0.44	0.62
I	0.21	0.30
CH_3	1.00	1.42

It should be noted that the line of best fit was calculated excluding the value for iodobenzene due to the very low relative reactivity observed. It is believed that the lower than expected reactivity is due to poor solubility of the anhydride in nitromethane at low temperatures. Having excluded the value for iodobenzene, the results obtained at 0 °C can be seen to be very similar to the results at 25 °C.

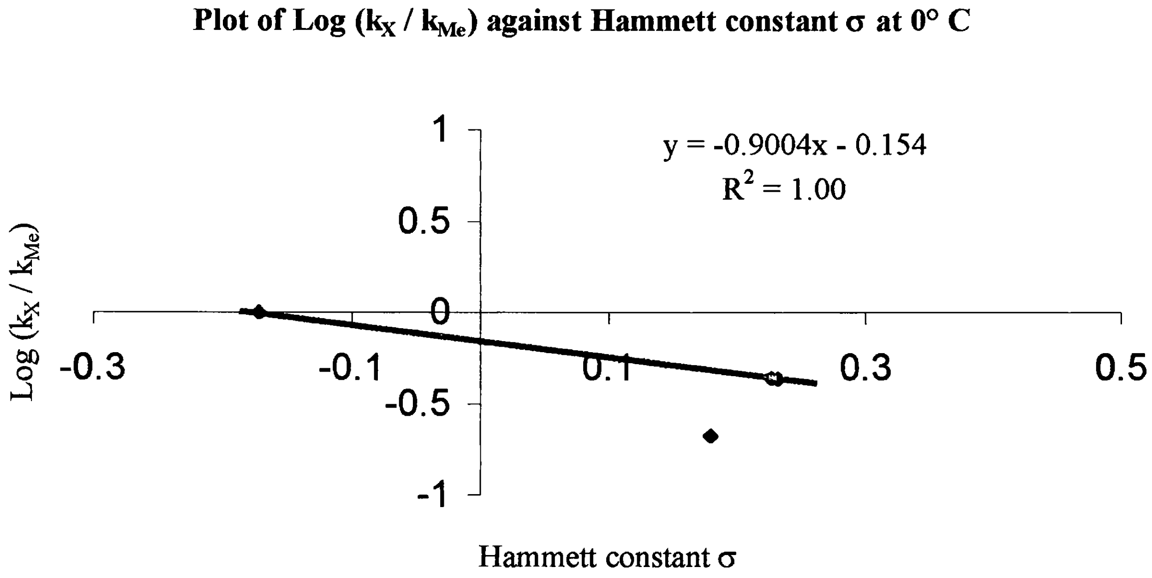


Figure 9. Plot of Log (k_X / k_{Me}) against Hammett constant for the *para*-substituted benzenesulfonylation of toluene in nitromethane at 0 °C, catalysed by $AlCl_3$

The competition reactions were carried out at 60 °C so that the effect of higher temperature could be observed. The reactions show a general trend with the relative rates of reactivity all increasing. The implication is that the selectivity is reduced, with the reaction heading towards diffusion-controlled characteristics The relative reactivity is higher in the reactions of the halobenzenes, suggesting that the increase in temperature favours the formation of the sulfonium cations. It is believed that this is due to the two factors. The increase in temperature promoting the resonance effect, by increasing the delocalisation energy and promoting the donation of electrons to stabilise the resonance structure of the sulfonium cations. The second factor being that increased donation of electrons from the halogens via the resonance effect decreases the stability of the *p*-halobenzenesulfonic anhydride–$AlCl_3$ complex, by making the sulfonyl anion a better leaving group. Despite the increase in resonance effect increasing the reactivity of the *p*-halogenated benzenesulfonic anhydrides, it is still clear in the case of the halobenzenesulfonic anhydrides that the inductive effect dominates over the resonance effect.

A Hammett plot using the values obtained at 60 °C allowed the reaction constant to be calculated. It was found that $\rho = -0.6979$ (See Figure 10).

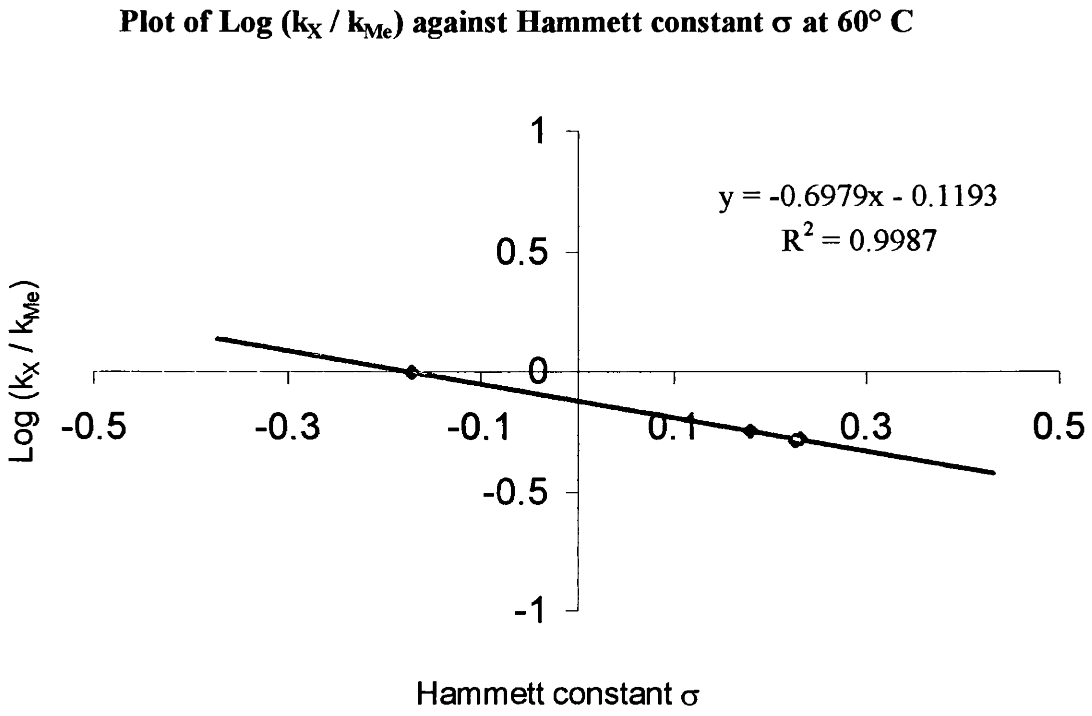


Figure 10 . Plot of Log (k_X / k_{Me}) against Hammett constant for the *para*-substituted benzenesulfonylation of toluene in nitromethane at 60 °C, catalysed by $AlCl_3$

The reactivities relative to benzene have also been predicted (See Table 13).

Table 13. The k_X / k_{Me} and predicted k_X / k_H values for the X-substituted benzenesulfonylation of toluene in nitromethane catalysed by $AlCl_3$ at 60 °C

Substituent X in C_6H_5X	k_X / k_{Me}	k_X / k_H
Br	0.53	0.70
Cl	0.52	0.68
I	0.57	0.75
CH_3	1.00	1.32

Despite the increases in the relative reactivity of the *p*-halobenzenesulfonic anhydrides with temperature, the sulfonylation reaction yields can be seen to be very low with the competing reaction to form the corresponding sulfonyl chlorides dominating the reaction of the sulfonic anhydrides (See Table 13).

Table 14. Yield of different sulfones in the X-substituted benzenesulfonylation of toluene in nitromethane catalysed by $AlCl_3$ at 60 °C

Substituent X in C_6H_5X	$CH_3C_6H_4SO_2C_6H_4CH_3$ (%)	$XC_6H_4SO_2C_6H_4CH_3$ (%)
Br	2.32	1.24
Cl	1.23	0.65
I	1.72	0.98
CH_3	-	-

5.7 Summary and Perspectives

From the data obtained it can be seen that the nature of a substituent in *p*-substituted benzenesulfonic anhydrides has only a relatively small effect on the reactivity of the anhydride in Friedel-Crafts type sulfonylation reactions. This can be explained by the high reactivity of the sulfonic anhydride under the reaction conditions.

The negative ρ values seen for the reaction at different temperatures confirm the fact that the reaction is promoted by increasing the electron donation to the reaction site. At first glance this seems an odd characteristic for a reaction undergoing electrophilic substitution, however it can be simply explained. The limiting factor would appear to be the formation of the sulfonium cation, and not it's subsequent reaction with the electrophile. The formation of the sulfonium cation is dependent on both the leaving ability of the sulfonate anion and initially on the formation of the complex between the sulfonic anhydride and $AlCl_3$. It can be seen that increased electron donation from the substituent helps to promote the complex formation, as well as stabilise the sulfonium cation.

From the relative rates of reaction it is clear that the electron withdrawing inductive effect of the halogen dominates the influence of halogen substituents on substituted benzenesulfonic anhydrides in the sulfonylation reactions.

Considering the results from the previous studies conducted in this project, several conclusions can be reached.

The influence of different substituents on the rate of Friedel-Crafts type sulfonylation reactions is far greater in the aryl substrate than in the aromatic sulfonic anhydride. That is, the change in the rate of reaction when changing the aryl substrate from XC_6H_5 to YC_6H_5 is far greater than when changing the aromatic sulfonic anhydride from $XC_6H_4SO_2OSO_2C_6H_4X$ to $YC_6H_4SO_2OSO_2C_6H_4Y$.

The influence of the substituent in benzene derivatives on the direct sulfonation in SO_3 was greater than expected. It was observed during this study that different substituents have a large effect on the nature of the product from the direct sulfonation reaction by SO_3 in nitromethane. It was observed that in the sulfonations performed on deactivated aromatics such as bromobenzene and chlorobenzene, the reactions favour the formation of the corresponding aromatic sulfonic anhydrides. In the reactions involving more reactive aryl substrates such as benzene and toluene, the reactions favour the formation of the corresponding sulfonic acid products. It is now believed that solubility problems were not the reason for the isolation of different sulfonation products, rather that the different products were formed, depending on the starting materials used.

If the Friedel-Crafts type sulfonylation reaction is considered to be the main route of the formation of sulfone by-product in industrial sulfonation of LAB, then in order to reduce the influence of this reaction pathway, several factors have to be taken into consideration.

The presence of electron deficient benzene derivatives in the LAB feed stock will lead to the formation of aromatic sulfonic anhydrides in the sulfonation process. By reducing the quantity of less reactive aromatic starting material, the quantity of sulfonic anhydride produced should be reduced.

Due to the fact that the influence of different substituents on the reactivity of aromatic sulfonic anhydrides is not great, then the formation of the sulfonic anhydride is believed to be the main contributing factor in the formation of diaryl sulfone via this type of reaction. Even the less reactive sulfonic anhydrides have shown good tendency to undergo Friedel-Crafts reactions. The presence of electron donating substituents will promote the sulfone formation if the aromatic sulfonic anhydride is formed. However, as discussed above the sulfonic anhydride is less likely to be formed when electron rich aromatics are used.

Another factor that should not be ruled out, although it was not observed as a contributing factor in the reactions in nitromethane, is the reaction between pyrosulfonic acids and aryl substrate leading to the direct formation of diaryl sulfones (See Chapter One, Scheme 5).

Based on the observations made during the studies outlined, it is believed that the formation of sulfone by-product is predominantly via the Friedel-Crafts route. The use of more reactive aromatic starting materials may well reduce the influence of this route to the formation of sulfone, however it may also increase the significance of the alternative pathway via the pyrosulfonic anhydride.

There remains plenty of scope for research into the formation of the sulfone by-product, however I believe that this is not as straight forward as it may seem due to the difficulties associated in trying to study the reactions of the pyrosulfonic acid.

Experimental

Attempted synthesis of benzenesulfonic anhydride from the reaction between benzenesulfonic acid and 1, 3-dicyclohexyl carbodiimide

Into a clean dry flask was placed a suspension of benzenesulfonic acid (3.0 g, 18.9 mmol) in benzene (20 ml). To this was added a solution of 1,3-dicyclohexyl carbodiimide (4.68 g, 22.6 mmol) in benzene (20ml). This was carried under an inert atmosphere of dry N_2 (g). The reaction was stirred at room temperature for a period of three hours, during which time the urea by-product was observed to crystallise out of solution as very fine colourless crystals.

An attempt was made to filter the reaction mixture using a sintered glass filter funnel under an inert atmosphere. Due to the nature of the reaction mixture this was unsuccessful, with the slurry blocking the funnel. The reaction product could not be isolated without exposure to air. Due to the difficulties associated with the work-up of the reaction it was discontinued.

Attempted synthesis of benzenesulfonic anhydride from benzenesulfonyl chloride and oxalic acid

Into clean dry flask was placed oxalic acid (4.43 g, 49.2 mmol) fitted with a condenser. To this was added benzenesulfonyl chloride (17.7 g, 100 mmol) whilst stirring. This was carried out under an inert atmosphere of N_2 (g). The reaction mixture was heated to 160 °C and allowed to proceed until all the solid acid had changed in appearance. The reaction mixture changed in appearance from a white solid suspended in a colourless clear liquid to homogenous brown oil. This took a period of approximately 1 hour. The reaction was then heated to 200 °C for a short period of time (~ 15 mins).

The reaction was allowed to cool to 160 °C and a vacuum was applied (3 – 5 mm Hg) to remove any volatile material. This took approximately 30 minutes. The reaction mixture was allowed to cool and was stored at 0 °C for 12 hours. The reaction crystallised readily on cooling. An attempt was made to recrystallise the organic product from dry diethyl ether, however the solid was found to be insoluble in hot ether. The solvent was removed under vacuum, and the melting point of the crude material was measured. The melting point was found to correspond to benzenesulfonic acid. The solid product was also seen to readily deliquesce in air. It was concluded that benzenesulfonic acid had been isolated.

Melting Point; Lit. Value 46 °C [29], Experimental Value 41 – 47 °C.

The reaction was repeated, with the recrystallisation attempted using dry petroleum ether, however the product was again found to be benzenesulfonic acid.

Melting Point; Lit. Value 46 °C [29], Experimental Value 44 – 46 °C.

Attempted synthesis of benzenesulfonic anhydride from benzenesulfonic acid and thionyl chloride

Into a clean dry flask fitted with a stirrer was placed benzenesulfonic acid (3.4 g, 21.5 mmol) under an inert atmosphere of N_2 (g). To this was added benzene as solvent (10 ml) and thionyl chloride (10 ml, 137 mmol). The reaction mixture was heated to reflux for a period of 2 hours. The reaction mixture was allowed to cool, and heated again to 50 °C under vacuum (3 – 4 mm Hg) for 30 minutes to remove any excess thionyl chloride. The reaction was allowed to cool to 0 °C for 1 hour, and attempts were made to recrystallise the product from diethyl ether. A very small quantity of product was isolated that did not deliquesce on exposure to air. The melting point was low for benzenesulfonic anhydride, but significantly higher than that of benzenesulfonic acid. The amount of product collected was insufficient for further analysis.

Melting Point; Lit Value Benzenesulfonic acid 46 °C [29], benzenesulfonic anhydride 92 °C [11], Experimental Value 72 – 76 °C.

The reaction was repeated using nitromethane as solvent with the reflux carried out for a period of 12 hours. The nitromethane was removed along with any excess thionyl chloride under vacuum. The product was again found to be benzenesulfonic acid.

Melting Point; Lit. Value 46 °C [29], Experimental Value 42 – 47 °C.

Attempted synthesis of *p*-chlorobenzenesulfonic anhydride from the reaction of chlorobenzene with oleum

Into a clean dry flask was placed chlorobenzene (20 ml). To this was added a large excess of 15% oleum (100 ml) whilst stirring. The reaction mixture was stirred at room temperature for a period of 12 hours. The reaction mixture was added to ice-water (1000 ml) with vigorous stirring. Solid was supposed to precipitate out of solution, however no solid anhydride product was isolated. Analysis of the reaction mixture by HPLC showed that it only contained *p*-chlorobenzenesulfonic acid. This technique was not investigated further and the product was not isolated.

Preparation of sulfonic anhydrides using SO_3: General procedure – Study One

The sulfonation apparatus was assembled clean and dry and purged with a flow of dry nitrogen. This was passed through the experiment apparatus after set up and throughout the experiment. The gas flow was controlled and measured using a manifold connected to the nitrogen inlet. After passing through the manifold the gas was dried by passing it through silica indicating gel, and through a glass wool filter to remove any solid matter being carried.

Following the drying process, the nitrogen is passed into a heated 250 ml triple-neck flask, where it collects and carries the SO_3 gas from this vaporising flask on into the batch reactor, via a connecting pipe. Between the vaporising flask and the batch reactor, a 10 ml round bottom flask is used, filled with glass wool as a trap to remove any liquid SO_3 or oleum that has been carried over from the vaporising flask.

In order to measure the amount of SO_3 being added to the reaction, a mechanical syringe pump was used to add the instructed amount. The rate of addition was also automated and could be easily adjusted.

The SO_3/N_2 gas mixture enters into the bottom of the batch reactor, and is passed through a drilled base plate, to ensure even distribution of the gas and consequently good agitation. This removes the need for any mechanical method of agitation.

A second stream of dry nitrogen is also available, that does not pass through the SO_3 vaporising flask. This can transferred onto the reactor at any time to provide a clean source of agitation, free from any possible contamination with SO_3.

The batch reactor is a custom designed reaction vessel, which requires a reaction volume of approximately 100 ml in order to work effectively. The vessel is a straight walled reactor, with a water filled outer jacket allowing some control of the reaction temperature. Pumping water through the jacket, in a continuous loop from a temperature controlled water bath, controls the jacket temperature.

The reactor also features a thermometer fitted halfway up the vessel that measures the temperature of the reaction mixture at any given time. The top of the reactor is fitted with an outlet pipe, which then passes through a scrubber to remove excess SO_3 that has passed through the reaction. The scrubber used was a Dreschler flask filled with alkylbenzene feedstock from the industrial sulfonation process. The SO_3 reacts with the alkylbenzene to form a mixture of alkylbenzene sulfonic acids, which can be disposed of appropriately. The scrubber can also be used as a test to check the system for leaks, and to check that the nitrogen is flowing correctly.

The reactor was charged with the prescribed quantities of the benzene derivative and nitromethane solvent, and agitation was started with the 'clean' nitrogen gas stream. The reaction mixture used was a 10% (w/w) solution of substrate in nitromethane.

Liquid SO_3 was measured out and transferred into the vaporising flask using the syringe pump. The amount of SO_3 used was based on the studies of Hesselbjerg-Christensen[19], who found that a mole ratio [SO_3 / C_6H_5I] of approximately 1.6 gave the highest observed yield of sulfonic anhydride product. The recorded yield was approximately 80%. The transfer of the SO_3 to the vaporising flask was carried out slowly, with the vaporised SO_3 carried on the nitrogen stream to the batch reactor, where it bubbled through the reaction mixture. The reaction addition typically took in the region of 15 minutes. After addition of the SO_3 was complete, the nitrogen stream was replaced with the 'clean' stream, continuing with agitation until the reactions were deemed to have reached completion.

Upon addition of SO_3 to the reaction, solid sulfonic anhydride precipitate was observed to crystallise out of solution. The reactions were allowed to continue for between 20 and 40 minutes. This was partly governed by the reaction temperatures, due to the fact that the nitromethane was found to evaporate appreciably into the nitrogen stream when the batch reactor was operated with a jacket temperature of 40 °C or higher.

The solid aromatic sulfonic anhydride product was collected by vacuum filtration. The sulfonic anhydride product was washed with nitromethane and ether, and dried in a vacuum oven at 50 °C overnight. The sulfonic anhydride products were mainly found to be white crystalline solids. The products were stored in a desiccator in the presence of phosphorous pentoxide and silica indicating gel.

Synthesis of *p*-bromobenzenesulfonic anhydride by aromatic sulfonation; Study One

The reactor water jacket temperature was set to 10.0 °C. The batch reactor was charged with bromobenzene (12 g: 0.08 mol) and nitromethane (108g: 1.77mol) and the temperature was allowed to equilibrate. To this was added SO_3 (9.85 g: 0.123 mol) using the method outlined previously. The rate of transfer of the SO_3 was set at 50 ml/hr. No precipitate was observed to crystallise out of solution for the first 10 mins of the reaction, including the addition period. After 20 mins a white precipitate appeared on the top of the walls of the reactor. The reaction was allowed to continue for a further 5mins until no further solid was observed to crystallise out of solution. The solid was collected as previously outlined.

Yield; 7.0 g, 40%.

Melting Point: Lit. Value 182 °C [19] Experimental Value 170 – 180 °C.

Mass Spectrum: EI m/z 456 (^{79}Br, ^{81}Br', M^{+}, 8%), 458 (^{81}Br, ^{81}Br', M^{+}, 5%), 454 (^{79}Br, ^{79}Br', M^{+}, 3%), 155 (^{79}Br, $BrC_6H_4^{+}$, 100%), 157 (^{81}Br, $BrC_6H_4^{+}$, 92%).

Analysis of the molecular ion peak reveals the following isotope pattern; EI m/z 456 (^{79}Br, ^{81}Br', M$^+$, 100%), 458 (^{81}Br, ^{81}Br', M$^+$, 60%), 454 (^{79}Br, ^{79}Br', M$^+$, 50%).

Synthesis of *p*-chlorobenzenesulfonic anhydride by aromatic sulfonation; Study One

The reactor water jacket temperature was set to 15.0 °C. The reactor was charged with chlorobenzene (12 g: 0.11 mol) and nitromethane (108 g: 1.77 mol) and the temperature was allowed to equilibrate. To this was added SO_3 (13.7 g: 0.17 mol) using the method outlined previously. The rate of transfer of the SO_3 was set at 28 ml/hr. No precipitate was observed to crystallise out of solution for the first 20 mins of the reaction, including the addition period. After 20 mins a white precipitate appeared on the top of the walls of the reactor. The reaction was allowed to continue for a further 17 mins until no further solid was observed to crystallise out of solution. The solid was collected as previously outlined.

Yield; 0.82 g, 6 %.

Melting Point: Lit. Value 141 °C [19] Experimental Value 131 – 136 °C.

Mass Spectrum: EI m/z 366 (^{35}Cl, ^{35}Cl', M$^+$, 4%), 368 (^{35}Cl, ^{37}Cl', M$^+$, 3%), 111 (^{35}Cl, $ClC_6H_4^+$, 100%), 175 (^{35}Cl, $ClC_6H_4SO_2^+$, 68%), 113 (^{37}Cl, $ClC_6H_4^+$, 29%), 177 (^{37}Cl, $ClC_6H_4SO_2^+$, 19%).

Attempted synthesis of *p*-fluorobenzenesulfonic anhydride by aromatic sulfonation; Study One

The reactor water jacket temperature was set to 15.0 °C. The reactor was charged with fluorobenzene (12 g: 0.12 mol) and nitromethane (108 g: 1.77 mol) and the temperature was allowed to equilibrate. To this was added SO_3 (16.0 g: 2.00 mol) using the method outlined previously. The rate of transfer of the SO_3 was set at 55 ml/hr. No precipitate was observed to crystallise out of solution for the first 45 mins of the reaction, including the addition period. The reaction mixture was collected and stored under an inert atmosphere of dry N_2 (g) for 1 week. A small amount of crystalline solid was collected that readily deliquesced in air. The solid collected was believed to be the sulfonation product, 4-fluorobenzenesulfonic acid. No further analysis of the product was possible due to the nature of the product.

Attempted synthesis of benzenesulfonic anhydride by aromatic sulfonation; Study One

The reactor water jacket temperature was set to 20.0 °C. The reactor was charged with benzenesulfonic acid (12 g: 008.mol) and nitromethane (108 g: 1.77 mol) and the temperature was allowed to equilibrate. To this was added SO_3 (9.72 g: 0.12 mol) using the method outlined previously. The rate of transfer of the SO_3 was set at 24 ml/hr. No precipitate was observed to crystallise out of solution for the first 90 mins of the reaction, including the addition period. The reaction mixture was stored under an inert atmosphere of N_2 (g) for 1 week. Crystallisation was observed, and the product collected. The product was found to deliquesce readily in air. Melting point analysis carried out in a sealed tube showed the product to be recovered benzenesulfonic acid.

Melting point; Lit. Value 46 °C [29], Experimental Value 44 - 48 °C.

Preparation of sulfonic anhydrides using SO_3: General procedure – Study Two

The general procedure for the synthesis of sulfonic anhydrides using the Sulfonation Batch Reactor was revised in attempt to improve the route to the anhydrides.

Following the first series of reactions carried out at Unilever Research Port Sunlight, it was apparent that the samples of sulfonic anhydrides prepared were impure, believed to be containing the corresponding sulfonic acids. Several possible reasons could contribute to this problem, so in an attempt to improve the technique the following revisions were made to the general procedure.

1. The quantity of SO_3 used was increased from 1.6 to 2.0 mole equivalents to compensate for the loss of SO_3 as exhaust fumes.
2. The volume of nitromethane solvent was monitored throughout the duration of reactions and added to throughout the reaction to compensate for loss due to evaporation. This would help to prevent the sulfonic acid by-product crystallising out of solution due to saturation.
3. The reactor jacket temperature was set to 20 °C for all reactions to reduce evaporation.
4. The sulfonic anhydride products were recrystallised from nitromethane before analysis.

The revisions improved both the yield and purity of the sulfonic anhydride products (See Table 9, Section 5.5).

Preparation of *p*-bromobenzenesulfonic anhydride by aromatic sulfonation; Study Two

The reactor water jacket temperature was set to 20.0 °C. The reactor was charged with bromobenzene (18 g: 0.12 mol) and nitromethane (102g: 1.67 mol) and the temperature was allowed to equilibrate. To this was added SO_3 (18.34 g: 0.23 mol) using the method outlined previously. The rate of transfer of the SO_3 was set at 50ml/hr. No precipitate was observed to crystallise out of solution for the first 10 mins of the reaction, including the addition period. After 10 mins a white precipitate appeared on the top of the walls of the reactor. The reaction was allowed to continue for a further 5 mins until no further solid was observed to fall out of solution. The solid was collected as outlined in the general procedure.

Yield; 12.8 g, 49%

Melting Point: Lit. Value 182 °C [19] Experimental Value 178 – 180 °C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 7.30 (8H, m, 2-H and 3-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si). 122.1 (C-4), 128.1 (C-2), 131.1 (C-3), 147.7 (C-1).

Mass Spectrum: EI m/z 456 (^{79}Br, ^{81}Br', M^+, 10%), 458 (^{81}Br, ^{81}Br', M^+, 6%), 454 (^{79}Br, ^{79}Br', M^+, 5%), 155 (^{79}Br, $BrC_6H_4^+$, 100%), 157 (^{81}Br, $BrC_6H_4^+$, 95%).

Analysis of the molecular ion peak reveals the following isotope pattern; EI m/z 456 (^{79}Br, ^{81}Br', M^+, 100%), 458 (^{81}Br, ^{81}Br', M^+, 58%), 454 (^{79}Br, ^{79}Br', M^+, 49%).

Preparation of *p*-chlorobenzenesulfonic anhydride by aromatic sulfonation; Study Two

The reactor water jacket temperature was set to 20.0 °C. The reactor was charged with chlorobenzene (18g: 0.16 mol) and nitromethane (102 g: 1.67 mol) and the temperature was allowed to equilibrate. To this was added SO_3 (25.6 g: 0.32 mol) using the outlined method. The rate of transfer of the SO_3 was set at 50 ml/hr. No precipitate was observed to crystallise out of solution for the first 10 mins of the reaction, including the addition period. After 10 mins a white precipitate appeared on the top of the walls of the reactor. The reaction was allowed to continue for a further 5 mins until no further solid was observed to fall out of solution. The solid was collected as previously outlined.

Yield; 7.0 g, 23.9%

Melting Point: Lit. Value 141 °C [19] Experimental Value 137 – 139 °C.

NMR Data (*J* values are given in Hz).

δ_H (400 MHz; $CDCl_3$;Me_4Si) 7.38 (4H, d, $J_{2,3}$ = 8.4 Hz, 3-H), 7.63 (4H, d, $J_{3,2}$ = 8.4 Hz, 2-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 127.8 (C-2), 128.2 (C-3), 133.5 (C-4), 147.2 (C-1).

Mass Spectrum: EI m/z 366 (^{35}Cl, $^{35}Cl'$, M^+, 3%), 368 (^{35}Cl, $^{37}Cl'$, M^+, 2%), 111 (^{35}Cl, $ClC_6H_4^+$, 100%), 175 (^{35}Cl, $ClC_6H_4SO_2^+$, 70%), 113 (^{37}Cl, $ClC_6H_4^+$, 30%), 177 (^{37}Cl, $ClC_6H_4SO_2^+$, 18%).

Analysis of the molecular ion peak reveals the following isotope pattern; EI m/z 366 (^{35}Cl, $^{35}Cl'$, M^+, 100%), 368 (^{35}Cl, $^{37}Cl'$, M^+, 72%), 370 (^{37}Cl, $^{37}Cl'$, M^+, 18%).

Preparation of *p*-iodobenzenesulfonic anhydride by aromatic sulfonation; Study Two

The reactor water jacket temperature was set to 20.0 °C. The reactor was charged with iodobenzene (18 g: 0.09 mol) and nitromethane (102 g: 1.67 mol) and the temperature was allowed to equilibrate. To this was added SO_3 (14.1 g: 0.176 mol) using the outlined method. The rate of transfer of the SO_3 was set at 50 ml/hr. No precipitate was observed to crystallise out of solution for the first 10 mins of the reaction, including the addition period. After 10 mins a white precipitate appeared on the top of the walls of the reactor. The reaction was allowed to continue for a further 5 mins until no further solid was observed to fall out of solution. The solid was collected as previously outlined.

Yield; 15.3 g, 63%.

Melting Point: Lit. Value 221 °C [30] Experimental Value 217 - 219 °C.

NMR Data (J values are given in Hz).δ_H (400 MHz; $CDCl_3$;Me_4Si) 7.22 (4H, d, $J_{2,3}$ = 8.5 Hz, 2-H), 7.55 (4H, d, $J_{3,2}$ = 8.5 Hz, 3-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 95.4 (C-4), 128.1 (C-2), 136.9 (C-3), 148.2 (C-1).

Mass Spectrum: EI m/z 358 (M^+, 45%), 139 ($CH_3C_6H_4SO^+$, 100%) 251 ($IC_6H_4SO^+$, 25%)

Mass Spectrum: EI m/z 550 (M^+, 4%), 127 (I^+, 100%), 76 (C_6H_4,$^{2+}$ 70%), 267 ($IC_6H_4SO_2^+$, 20%), 203 ($IC_6H_4^+$, 29%).

Preparation of 4-iodophenyl-*p*-tolyl sulfone

To a dry flask containing *p*-toluenesulfonyl chloride (50.2 g, 266 mmol) and iodobenzene (10.8 g, 52.9 mmol) was added a solution of aluminum chloride (35.5 g, 266 mmol) in nitromethane (200 ml, 0.186 mol). The solution was added cautiously over 10 minutes whilst stirring, with dry N_2 gas passed over the reaction mixture to remove any HCl gas evolved during the addition. The reaction mixture was heated to reflux for 3 hours.

The reaction was cooled and added to an excess of iced water (2000 ml). This was basified to pH 8 / 9 using 3M NaOH (aq). The organic sulfone product was extracted into CH_2Cl_2 (4 x 200 ml). The combined organic layers were then dried over magnesium sulfate, filtered and the solvent removed by rotary evaporation. The product was then recrystallised from a minimum of hot ethanol, leaving colourless crystals.

Yield: 8.9 g, 47%.

Melting Point: Lit. Value 141°C [31], Experimental 138°C.

NMR Data (*J* values are given in Hz). δ_H (400 MHz; $CDCl_3$;Me_4Si) 2.40 (3H, s, Me), 7.30 (2H, d, $J_{2,3}$ = 8.4 Hz, 3-H), 7.50 (2H, d, $J_{3',2'}$ = 8.0 Hz, 3'-H), 7.54 (1H, m, 4'-H).

δ_C (100 MHz; $CDCl_3$; Me_4Si) 21.55 (Me), 127.48 (C-2), 127.70 (C-2'), 129.21 (C-3'), 129.91 (C-3), 132.99 (C-4'), 138.62 (C-1), 141.96 (C-1'), 144.16 (C-4).

CI (NH_3) m/z 376 (M + NH_4, 10%).

Typical competition reaction procedure:

Competition reaction between *p*-toluenesulfonic anhydride and *p*-bromobenzenesulfonic anhydride reacting with toluene, catalysed by $AlCl_3$ (5.0 mol. eq.) and carried out at 25 °C (2-nitrotoluene used as internal standard).

To dry and distilled nitromethane (100 ml), was added toluene (3.6764 g, 0.04 mol.) and 2-nitrotolune (0.1250 g, 9.11×10^{-4} mol.) to form a standard solution. A similar dry solution of $AlCl_3$ in nitromethane (0.2 M) was prepared. A third solution of *p*-toluenesulfonic anhydride (0.4 M) was prepared, along with a fourth of *p*-bromobenzenesulfonic anhydride (0.4 M). The solutions having been sealed were placed in a water bath (with the tops of the volumetric flasks above the water level) to equilibrate to 25.0 °C. It should be noted that all samples containing nitromethane were kept in the dark to avoid radical formation. This was achieved by wrapping the volumetric flasks in aluminum foil.

Having allowed the solutions to equilibrate, 2.0 ml of each of the three solutions was injected into the reaction flask, with the $AlCl_3$ catalyst added as the final component. The reaction flask was partly submerged in the water bath to keep the reaction at 25.0 °C, and contained a stirrer under an inert atmosphere of N_2 (g).

The reaction was allowed to run and was sampled after 3 hours. An aliquot (approx. 0.2 ml) was removed by dry needle and syringe, then added to ethanol (approx. 7 ml). This was then shaken thoroughly and analysed by HPLC.

Typical HPLC conditions.

Column Packing:	Excil 5μ ODS II C18
Eluent*:	67% Methanol 33% Water
Flow Rate:	1.0 ml / min
Wavelength	240 nm
Run Time:	20 mins

* The eluent composition was changed depending on the aryl substrate used.

Appendix

Calculation of response factors for 4-iodophenyl-*p*-tolyl sulfone

The response factor for 4-iodophenyl-*p*-tolyl sulfone was calculated using two standard solutions. One of the internal standard, *o*-nitrotoluene, and the other of 4-iodophenyl-*p*-tolyl sulfone. The details are shown below (See Table 1).

Table 1. Details of standard solutions used to calculate factor for di-*p*-tolyl sulfone

Soln.	Compound	F. W. (A. M. U.)	Quantity (g)	Vol. (L)	Molarity (mol dm^{-3})
A	*o*-nitrotoluene	137.14	0.0397	0.25	1.16 x 10^{-3}
B	4-iodophenyl-*p*-tolyl sulfone	358.1	0.047	0.20	0.656 x 10^{-3}

Aliquots of varying sizes of each solution were accurately measured using a Finnpipette fixed volume mechanical pipette. These were then mixed thoroughly, and analysed by HPLC using the stated conditions. Measurements were repeated to give a set of results, from which a mean value of the response factor, α could be obtained (Table 2).

Table 5. Co-injection data for calculation of response factor for 4-iodophenyl-*p*-tolyl sulfone

Vol. A* (ml)	Conc. A (mol dm^{-3})	Area A	Vol. B(ml)	Conc. B (mol dm^{-3})	Area B	Response Factor B
1	5.790 x 10^{-4}	3503	1	5.790 x 10^{-4}	9091.86	0.218276
1	5.790 x 10^{-4}	3363.7	1	5.790 x 10^{-4}	8838.5	0.215605
1	5.790 x 10^{-4}	3130.1	1	5.790 x 10^{-4}	8689.73	0.204066
1	7.720 x 10^{-4}	3184.75	1	5.790 x 10^{-4}	8926.02	0.202133
1	7.720 x 10^{-4}	1472.3	1	5.790 x 10^{-4}	4198.5	0.198665
1	7.720 x 10^{-4}	3125.4	1	5.790 x 10^{-4}	8913.16	0.198652
1	8.685 x 10^{-4}	421.4	1	5.790 x 10^{-4}	1020.5	0.233938
					Mean =	0.210191

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