

Experimental and molecular modelling studies on aromatic sulfonation

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The mechanism of the sulfonation of toluene has been explored both experimentally and theoretically using molecular orbital methods. Sulfonation with sulfur trioxide is proposed to proceed initially *via* the formation of a toluene-S₂O₆ π -complex (**3**) which rearranges to form a Wheland pyrosulfonate intermediate (**5**) which in turn undergoes a facile prototropic rearrangement involving the transfer of the ring hydrogen at the sp³ carbon to the sulfonate oxygen atom to form toluenepyrosulfonic acid (**7**). Once formed, this acid is thought to attack toluene to form two equivalents of toluenesulfonic acid (**6**) which preferentially react with sulfur trioxide to re-form the pyrosulfonic acid (**7**). Experimentally, sulfonation using either acetylsulfonic acid (**9**), trifluoroacetylsulfonic acid (**10**), or trimethylacetylsulfonic acid (**11**), as models for pyrosulfonic acid (**7**), appears to show second order kinetics at room temperature. The reaction with acetylsulfonic acid (**9**) shows no significant kinetic isotope effect when 4-deuterotoluene is used as the substrate, suggesting that sulfonation proceeds *via* attack of the π -electrons of the toluene ring at the sulfur atom, S8, of acetylsulfonic acid or toluenepyrosulfonic acid with simultaneous cleavage of the O7–S8 bond, where the displaced acetate or toluenesulfonate anion respectively can facilitate the removal of the ring proton at the sp³ carbon.

Introduction

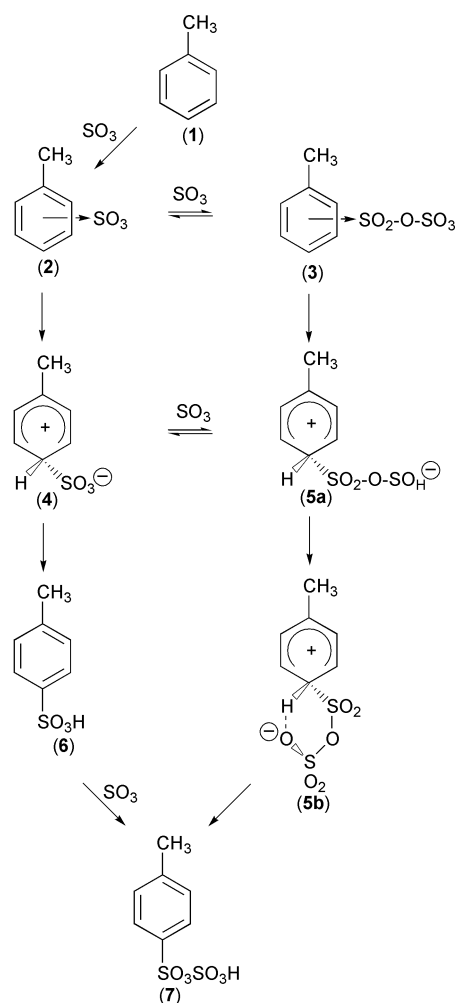
Aromatic sulfonation is an important industrial process which is used for the manufacture of detergents and surfactants from alkylbenzenes on the megaton scale.¹ The mechanism of the process is complex, reversible in many cases, and depends mainly on (1) the nature of the electrophilic species, which may be derived from sulfuric acid, pyrosulfuric acid, chlorosulfonic acid, acetylsulfonic acid or sulfur trioxide; and (2) the reactivity of the aromatic system under attack.^{1–16} At low temperatures, the reverse reaction is very slow, and the forward reaction is essentially irreversible. Several transient intermediate species are thought to be involved but few have been properly characterized. In 85% sulfuric acid the rate determining step of the reaction is the addition of the electrophile, thought to be H₃SO₄⁺, to the aromatic ring; but in stronger acid and oleum the electrophile is thought to be H₂S₂O₇, and now the loss of the ring proton becomes partially rate determining.^{15–17} The change in the attacking electrophilic species and the later transition state found with increasing acid strength are supported partly by kinetic data and also by the different *ortho/para* ratios which are obtained from the sulfonation of toluene.¹⁵

In the case of the aromatic sulfonation with sulfur trioxide, a number of intermediate structures (**4**) and (**5**) have been proposed (Scheme 1),^{9,10} but there is no direct evidence for their participation in the reaction. In fluorotrichloromethane, the reaction proceeds with the absence of a kinetic isotope effect for the ring hydrogen, and the rate limiting step is thought to involve the addition of the reagent to the aromatic ring to give the Wheland intermediate (**4**). In contrast, the corresponding rate limiting step for the same reaction in nitromethane is thought to involve the addition of sulfur trioxide to intermediate (**4**) to give the pyrosulfonate intermediate (**5**).^{8–12} The abstraction of a proton from either intermediate (**4**) or (**5**) then gives aryl sulfonic acid (**6**) or aryl pyrosulfonic acid (**7**)

respectively. In the latter case, once the pyrosulfonic acid (**7**) has been formed it would be expected to behave as a highly reactive sulfonating agent which will attack the aromatic substrate to form two equivalents of the aryl sulfonic acid (**6**). None of this acid (**7**) has been detected in the reaction products, however, even early on in the sulfonation process.

In contrast to the extensive experimental studies, there have been very few theoretical studies on aromatic sulfonation. Recently we attempted to model the sulfonation of toluene¹⁸ initially using semi-empirical MO methods such as the MNDO,¹⁹ AM1²⁰ and PM3²¹ methods of the MOPAC program,²² but none of these treatments gave satisfactory results,¹⁸ probably because the binding energy of the sulfur atom is represented by the valence 3s and 3p orbitals only (despite a sulfur parameterization²³ that has been adapted to represent the vacant 3d orbitals). Much better results were obtained at the *ab initio* level (see later) where the reaction of sulfur trioxide with toluene is predicted to proceed initially *via* the formation of a π -complex (**2**) which can rearrange to form the Wheland intermediate (**4**). This structure readily reacts with a further molecule of sulfur trioxide to give a pyrosulfonate intermediate (**5a**) which rearranges to form conformer (**5b**) where the ring proton at the sp³ carbon is initially hydrogen bonded to an adjacent sulfonate oxygen atom (Scheme 1), and then transfers completely to form the corresponding pyrosulfonic acid (**7**). The overall calculated thermodynamic change in moving from the reaction of one molecule of sulfur trioxide with toluene to the sulfonic acid (**6**) was found to be fully consistent with an estimated experimental value of -33.5 kcal mol⁻¹ for the same reaction using simple alkylbenzenes.

However, while the formation of the π -complex (**2**) from toluene and sulfur trioxide, and the pyrosulfonic acid (**7**) from intermediate (**5**), were calculated to be exothermic processes, the formation of the simple Wheland intermediate (**4**) was found to be endothermic by around 24.1 kcal mol⁻¹. In practice,



Scheme 1 Primary mechanism of aromatic sulfonation with sulfur trioxide.

because the sulfonation of toluene with sulfur trioxide takes place readily at room temperature and in very high yield (97%), our results suggested that the Wheland intermediate (4), which has been proposed as the key intermediate in many textbooks, is unlikely to be formed and it follows that the sulfonation process must follow some other path.

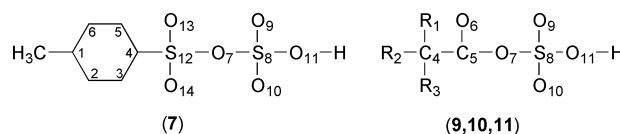
The present studies have been carried out to further explore the sulfonation of toluene using a combination of experimental methods to probe the kinetics of the process, and molecular modelling techniques to explore the structures, electronic properties, and energies of some of these unstable species in an overall attempt to gain a greater understanding of the fundamental reactions which occur during sulfonation. No quantitative account has been taken of the entropy changes involved in the sulfonation reaction which would be expected to be significantly negative for the formation of intermediates (4) and (5), though smaller and less important for the formation of toluenesulfonic acid (6) from the pyrosulfonic acid (7).

Methods of calculation

The 4-31G basis set²⁴ of the GAMESS program²⁵ with polarisation functions present for sulfur (subsequently referred to as 4-31G/S*) was used for all calculations. Although potentially more accurate basis sets are available with configuration interaction treatments, we do not believe that better results would have ensued because the reactions described here occur initially in the presence of an excess of reactants and end in the presence of an excess of product(s). The dielectric field experienced by the individual molecules during the course of the reaction will therefore vary and will have an influence on their geometry and

properties, and the energetics of the reaction. For example, at the beginning of the reaction, the reactants only experience a small dielectric field as the relative permittivities and dipole moments of toluene and sulfur trioxide are very small with values of 2.38 and 0.36 D for the former and 3.31 and 0.0 D respectively for the latter²⁶ and the reaction resembles a gas phase process. However, as the reaction proceeds, the dielectric field experienced by the reactants increases with increasing conversion to products, and although there are no dielectric data available for the products, related compounds such as toluene-*p*-sulfonyl chloride, *p*-methoxybenzenesulfonyl chloride, and methyl phenyl sulfone have relative permittivities of 22.6, 27.2, and 37.9 respectively.²⁶ The calculated dipole moment of 11.2 D for the pyrosulfonic acid¹⁸ is also indicative of the expected change in the reaction medium with increasing conversion.

The 4-31G/S* basis set was selected primarily because the vacant d orbitals present on the sulfur atom alone gave almost identical C–S bond lengths and C–S–C angles to the 6-31G** basis set in our recent studies on aryl sulfides,²⁷ and the calculated structures of diphenyl sulfide,²⁷ benisothiazolone²⁸ and 5-phenyl-(*E*)-2-styryl-3-isothiazolone²⁸ all show a close fit with crystallographic data. Attempts to locate and characterize transition states between toluene and the appropriate sulfonating species were carried out using the SADDLE and FORCE directives in the GAMESS program.²⁵ Other attempts to locate the transition states using the MNDO, AM1, or PM3 methods were generally unsuccessful because none of these methods include ‘d’ orbitals on the sulfur atom, with the result that the key carbon–sulfur and sulfur–oxygen bond lengths obtained were extremely unreliable. The atom numbering conventions used for these studies are shown below (Scheme 2).



Scheme 2 Numbering convention adopted for toluenepyrosulfonic acid (7, left) and the acetylsulfonic acids (9, 10, and 11, right).

All the structures were prepared and analysed before and after optimisation using the SYBYL molecular modelling program,²⁹ and calculations were performed on a cluster of networked Silicon Graphics workstations.

Discussion

Cerfontain has argued that the mechanism of aromatic sulfonation of substrates such as toluene proceeds by two distinct steps which involve (i) a primary sulfonation step by sulfur trioxide on toluene to generate the pyrosulfonic acid (7); (ii) a secondary or main sulfonation step by the pyrosulfonic acid formed in step (i) on toluene to generate two molar equivalents of toluenesulfonic acid (6), each of which then reacts with sulfur trioxide as a third step (iii) to regenerate the toluenepyrosulfonic acid as the main sulfonating species.^{8–12}

- (i) $\text{ArH} + 2\text{SO}_3 = \text{ArS}_2\text{O}_6\text{H}$ primary sulfonation step
- (ii) $\text{ArH} + \text{ArS}_2\text{O}_6\text{H} = 2\text{ArSO}_3\text{H}$ secondary or main sulfonation step
- (iii) $\text{ArSO}_3\text{H} + \text{SO}_3 = \text{ArS}_2\text{O}_6\text{H}$ re-generation step for process (i)

This mechanism is supported by the observation that early in the reaction, two molar equivalents of sulfur trioxide are consumed per mole of substrate, whereas later in the reaction, only one molar equivalent is consumed. In Cerfontain's proposed mechanism for step (i), the Wheland intermediate (4) formed

Table 1 Molecular energies of the reactants, intermediates and products (1–14) involved in the sulfonation of toluene calculated at the *ab initio* 4-31G/S* level

Structure	Molecular energy ^a	Reaction ^b	Relative energy ^c
SO ₃	-621.260830		
1	-269.358158	1 + SO ₃ → 2	-4.09
2	-890.625507	1 + SO ₃ → 3	-12.53
3	-1511.899784	2 → 4	24.13
4	-890.587056	3 → 5b	1.79
5b	-1511.896934	5b → 7b	-46.27
6	-890.671708	6 + SO ₃ → 7	-23.93
7b	-1511.970674	1 + 7b → 6 + 6	-9.15
9	-848.772792		
13	-227.470337	9 + 6 → 7b + 13	-2.19
10	-1144.939034		
14	-523.648289	10 + 6 → 7b + 14	-5.16
11	-965.710735		
15	-344.406414	11 + 6 → 7b + 15	-3.36

^a In hartrees. ^b See Schemes 1, 3 and 4. ^c In kcal mol⁻¹ (1 hartree = 627.46 kcal mol⁻¹).

initially, reacts with a further molecule of sulfur trioxide to form the pyrosulfonate intermediate (5). The overall rate determining step of the reaction is the formation of either (4) or (5) depending on the solvent used.^{8–12}

Molecular modelling studies

In our recent modelling studies,¹⁸ we found that a simple π -complex (2) between toluene and sulfur trioxide is initially formed, which is 4.09 kcal mol⁻¹ more stable than the reactants, but its conversion to the Wheland intermediate (4) was unlikely to occur under mild sulfonation conditions because of the large thermodynamic change of 24.1 kcal mol⁻¹ required (Table 1). In these studies, we have explored an alternative pathway for the sulfonation which involves the formation of a toluene–S₂O₆ π -complex (3) from a reaction between the initial π -complex (2) and a further molecule of sulfur trioxide. This step is calculated to be an exothermic process (Scheme 1), though there are a number of possible stable conformations for the resulting toluene–S₂O₆ π -complex. However, the most stable conformation appears to be one where the sulfur of the first sulfur trioxide molecule is positioned over C4 of the aromatic ring, at a calculated distance of 3.17 Å, with the three oxygens positioned over C5, C3, and H4 in an eclipsed fashion. The second sulfur trioxide molecule is orientated so the S8–O11 bond lies in the same plane as the C4, S12, and O7 atoms (see Scheme 2 for numbering) to give a torsion angle S12–O7–S8–O11 of 0° and a bond angle S12–O7–S8 of 167.7°. The O7–S8 distance of 2.52 Å is considerably longer than the covalent S12–O7 bonding distance of 1.41 Å. There is a net transfer of charge from the aromatic ring to the S₂O₆ moiety of 0.028 electrons and a resulting dipole moment of 2.43 D for the π -complex. While the calculations indicate that the S₂O₆- π -complex lies 12.5 kcal mol⁻¹ below the reactants (Table 1), in practice, the overall free energy change is likely to be much smaller because of the large negative entropy associated with the process.

Unlike the large endothermic change predicted for the conversion of the π -complex (2) to the Wheland intermediate (4), the conversion of the S₂O₆- π -complex (3) to the pyrosulfonate intermediate (5) is predicted to be energetically more facile with an enthalpy change of only 1.79 kcal mol⁻¹, but we were unable to locate a definite transition state for this gas phase rearrangement to estimate the barrier height. Similar results have been reported for other reactions, *e.g.*, between pyridine and methyl chloride, where the lack of a transition state has been attributed to the absence of solvent in the calculation.³⁰ Repeated attempts to resolve this problem by modelling the transition state in a solvent of low relative permittivity using the Polarizable Continuum Model (PCM) of the Tomasi method³¹ coded in the

GAMESS program, where the solute molecule is surrounded by a dielectric continuum of permittivity ϵ and embedded in a cavity constructed from intersecting van der Waals spheres of the component atoms, were unsuccessful due to persistent convergence problems. However, there seems little doubt from the molecular modelling studies (Fig. 1), that the pyrosulfonate

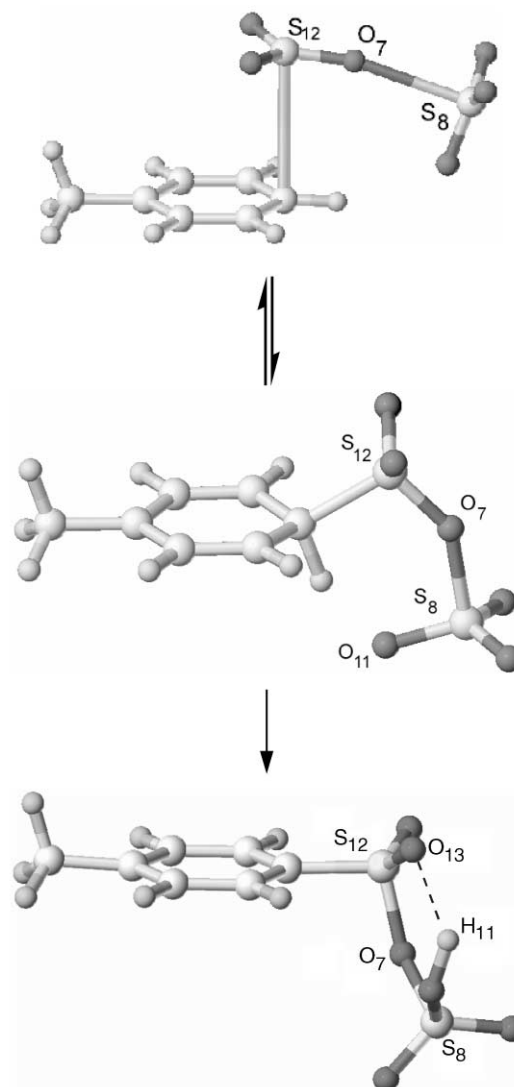


Fig. 1 Conformations of the toluene–S₂O₆ π -complex (3, top), the cyclic toluenepyrosulfonate Wheland intermediate (5b, centre); and the hydrogen bonded conformer of toluenepyrosulfonic acid (7b, bottom).

intermediate (**5a**) can rearrange easily to form the hydrogen bonded conformer (**5b**) and that abstraction of the ring proton, H4, by the terminal sulfonate oxygen, O11, to form the pyrosulfonic acid (**7**) is highly exothermic. On the basis of these calculations, therefore, the primary sulfonation step (i) to form the pyrosulfonic acid (**7**) is predicted to be a facile process, which we believe proceeds *via* the formation of a initial S_2O_6 - π -complex (**3**) rather than the originally proposed Wheland intermediate (**4**).

In the second step of the sulfonation reaction, it has been proposed that the transient pyrosulfonic acid (**7**), reacts with the substrate to form two molar equivalents of toluenesulfonic acid (**6**). In sulfuric acid, the sulfonating species involved in the electrophilic substitution of toluene³² shows a high substrate selectivity by comparison with benzene ($k_{\text{toluene}}/k_{\text{benzene}} = 31.0$), but a poor positional selectivity as reflected by the *ortho* : *meta* : *para* ratio of 36 : 4.5 : 59. The sulfonation of toluene with sulfur trioxide in fluorotrichloromethane¹⁰ shows a higher substrate selectivity by comparison with benzene with an average $k_{\text{toluene}}/k_{\text{benzene}}$ ratio of 34.4 over the temperature range -18 to 21 °C, and a slightly better positional selectivity with an approximate *ortho*(*ortho* : *meta* : *para*) ratio here of 0.33. For the related sulfonation in nitromethane,¹⁰ the substrate selectivity increases sharply to give an average $k_{\text{toluene}}/k_{\text{benzene}}$ ratio of 146.2 over the same temperature range, with an approximate *ortho*(*ortho* : *meta* : *para*) ratio here of 0.25. However, in the direct sulfur trioxide sulfonation of toluene in the absence of solvent, at low conversions of the substrate into toluenesulfonic acid, similar high *ortho*(*ortho* : *meta* : *para*) ratios are found early in the reaction. Thus at a 0.4% conversion of the substrate into product an *ortho*(*ortho* : *meta* : *para*) ratio of 0.28 is found which falls with increasing conversion to give ratios of 0.20 at 2.4%, 0.17 at 8.7%, and 0.14 at 60.6% conversion.¹¹ These data are consistent with the initial attack by the sulfur trioxide molecule, which would be expected to attack at both *ortho* and *para* positions in a similar way to sulfur trioxide in fluorotrichloromethane or nitromethane,¹⁰ and subsequent attack by the larger pyrosulfonic acid electrophile which would be more sterically impeded at the *ortho* position by the adjacent methyl group. As the reaction progresses therefore, sulfonation by toluenepyrosulfonic acid becomes the dominating process.

Structurally, we calculate that a cyclic conformation for toluenepyrosulfonic acid (**7b**) is favoured over the open chain conformation (**7a**), which we have previously described,¹⁸ by 7.52 kcal mol⁻¹, where the acidic hydrogen, H11, is strongly hydrogen bonded to one of the adjacent oxygens O13 or O14 (Scheme 2) at a distance of 1.99 Å. An examination of the atomic charges suggests that the terminal sulfonate group of the pyrosulfonic acid (**7b**) is likely to act as a better electrophile than sulfur trioxide because the positive charge at the sulfur atom, S8, in the former is significantly greater than that in the latter with values of 1.692 and 1.467 respectively. The mechanism of the reaction of this transient molecule (**7b**) with toluene is not known, but in one suggested mechanism (Scheme 3, A), the π -electrons at the 4'-position of the toluene ring (primed to distinguish it from the acid **7b**) initially attack the pyramidal electropositive sulfur atom, S8, of toluenepyrosulfonic acid, to form a hypothetical σ -bonded Wheland intermediate (**8**), originally proposed by Cerfontain, which can be orientated in a similar way to the pyrosulfonate intermediate (**5b**), so that one oxygen, O9 or O10, is hydrogen bonded to the ring proton, H4'. The simultaneous cleavage of the S8–O7 bond and proton abstraction from the C4' position of the intermediate (**8**) would be expected to be facile to yield two toluenesulfonic acid molecules as shown (Scheme 3, A). Thermodynamically, the overall reaction is predicted to be favoured by 9.15 kcal mol⁻¹ (Table 1), but attempts to optimise the structure of the postulated intermediate (**8**) were unsuccessful with the starting template either reverting back to toluene (**1**) and the toluenepyrosulfonic acid (**7**) or breaking to form two molecules of

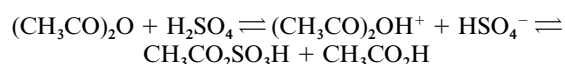
toluenesulfonic acid (**6**). While our theoretical results are not conclusive, they suggest that this process is unlikely to occur. An alternative mechanism which involves the same attack by the π -electrons at the 4-position of the toluene ring at the sulfur atom, S8, of toluenepyrosulfonic acid with simultaneous cleavage of the S8–O7 bond seems more likely (Scheme 3, B). Here the displaced toluenesulfonate anion can associate with the ring proton, H4', and facilitate its removal. The possibility that a third mechanism operates, C, where the cleavage of the S8–O7 bond and the C4'–H4' bond occur simultaneously in a concerted process which does not involve a discrete intermediate, however, cannot be discounted. In this case a substantial kinetic isotope effect would be expected, whereas no significant effect would be expected if the rate controlling step of this reaction involves the formation of a C4'–S8 bond.

Once toluenesulfonic acid (**6**) is formed by one of these mechanisms, it can react exothermically with sulfur trioxide to give toluenepyrosulfonic acid (**7**) by -23.9 kcal mol⁻¹ (Table 1). This reaction therefore, is favoured over the competing reaction of sulfur trioxide with toluene to give either a toluene–SO₃ π -complex or a toluene–S₂O₆ π -complex, and will dominate with increasing conversion of reactants to product.

Experimental studies

An experimental investigation of the reaction mechanisms discussed above is not possible because toluenepyrosulfonic acid (**7**), formed *in situ* from the reaction of toluenesulfonic acid and sulfur trioxide, immediately reacts with itself to form toluenedisulfonic acid, toluenesulfonic acid, toluenesulfonic anhydride, and sulfuric acid.¹¹ Alternative model electrophiles such as methanepyrosulfonic acid also break down in a similar way to toluenepyrosulfonic acid to give an equilibrium mixture consisting of the unchanged acid, methanesulfonic acid, methanesulfonic anhydride, and sulfuric acid in approximately equal amounts.³³ It follows that the intrinsic instability of all alkyl and aryl pyrosulfonic acids effectively rules them out as potential sulfonating probes.

However, there are other sulfonating species which are related to the pyrosulfonic acids such as acetylsulfonic acid (**9**) which could be used to model the reaction of toluenepyrosulfonic acid. Acetylsulfonic acid^{34–37} is stable, shows similarities to methanesulfonic acid, and is easily prepared from the reaction of sulfuric acid with an excess of acetic anhydride:



The reagent readily sulfonates aromatics such as anthracene³⁸ though the precise mechanism has not been explored. In toluene sulfonation, it would be expected to behave in a similar way to the pyrosulfonic acid, with the π -electrons at the 4-position of the ring initially attacking the pyramidal electropositive sulfur atom of acetylsulfonic acid (**9**), with the subsequent direct or indirect displacement of the acetate group as shown (Scheme 4, A, B, or C). However, because the rate of this reaction is partly dependent on the strength of the S8–O7 bond of acetylsulfonic acid (Scheme 4), which may differ considerably from that of the corresponding bond in the pyrosulfonic acid, we have attempted to vary the strength of this bond by using trifluoroacetylsulfonic acid (**10**) and trimethylacetylsulfonic acid (**11**) as additional model reagents. Support for using reagents (**9**), (**10**), and (**11**) as model sulfonating agent in place of toluenepyrosulfonic acid is provided by the results of our calculations which show that the sulfur atom, S8, has a similar large positive charge in these three cases with values of 1.667 , 1.673 , 1.666 respectively, *versus* 1.692 for S8 in toluenepyrosulfonic acid (**7**), and 1.467 for the sulfur atom in sulfur trioxide. It follows that each acetylsulfonic acid would be expected to behave as a powerful electrophilic reagent.

Experimentally, the sulfonation of toluene proceeds readily with all of these reagents over a range of temperatures from 22 to 60 °C, and the reactions can be conveniently followed by ^1H NMR spectroscopy by monitoring the decrease in the intensity of the five aromatic protons of toluene which appear as multiplets resonating between 7.28 and 7.36 ppm relative to tetramethylsilane, and the appearance of two well resolved doublets resonating at 7.51 and 7.93 ppm arising from the protons at the 2- and 3-positions of toluene-4-sulfonic acid respectively. These shifts vary slightly depending on the temperature of reaction and the conversion. At the lowest temperature explored of 22 °C, these reactions appear to be first order with respect to toluene (initial concentration, a) and the acetyl-

sulfonic acids (initial concentration, b), as linear correlations are found between $\ln [b(a - x)]/[a(b - x)]$ and time (Fig. 2), if the initial first few minutes of the reaction are ignored when a small exotherm is produced on mixing the toluene with the sulfonating reagent. The rate determining step of the process shows second order kinetics where the rate constants for the three reagents at this temperature vary from 0.90 to 0.86, and then to $1.88 \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for sulfonic acids (9), (10), and (11) respectively (Table 2). In an attempt to distinguish among the three possible mechanistic pathways for the sulfonation (Scheme 4), kinetic isotope effects were explored by using 4-deuteriotoluene in place of toluene in the sulfonation reaction with acetylsulfonic acid (9). The former was prepared

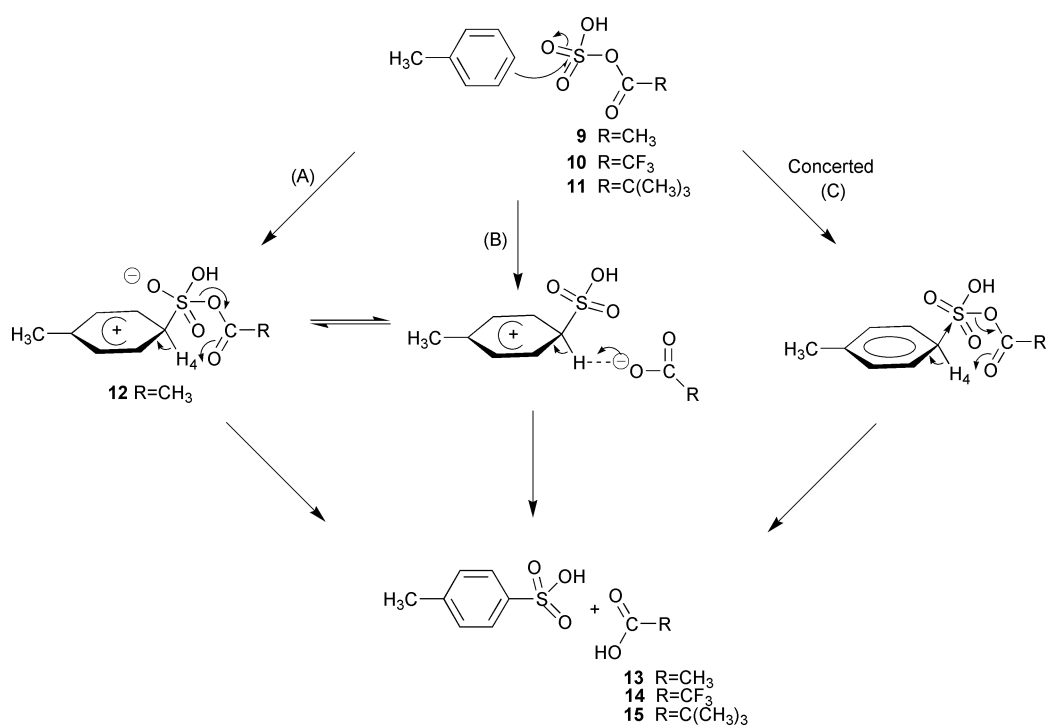
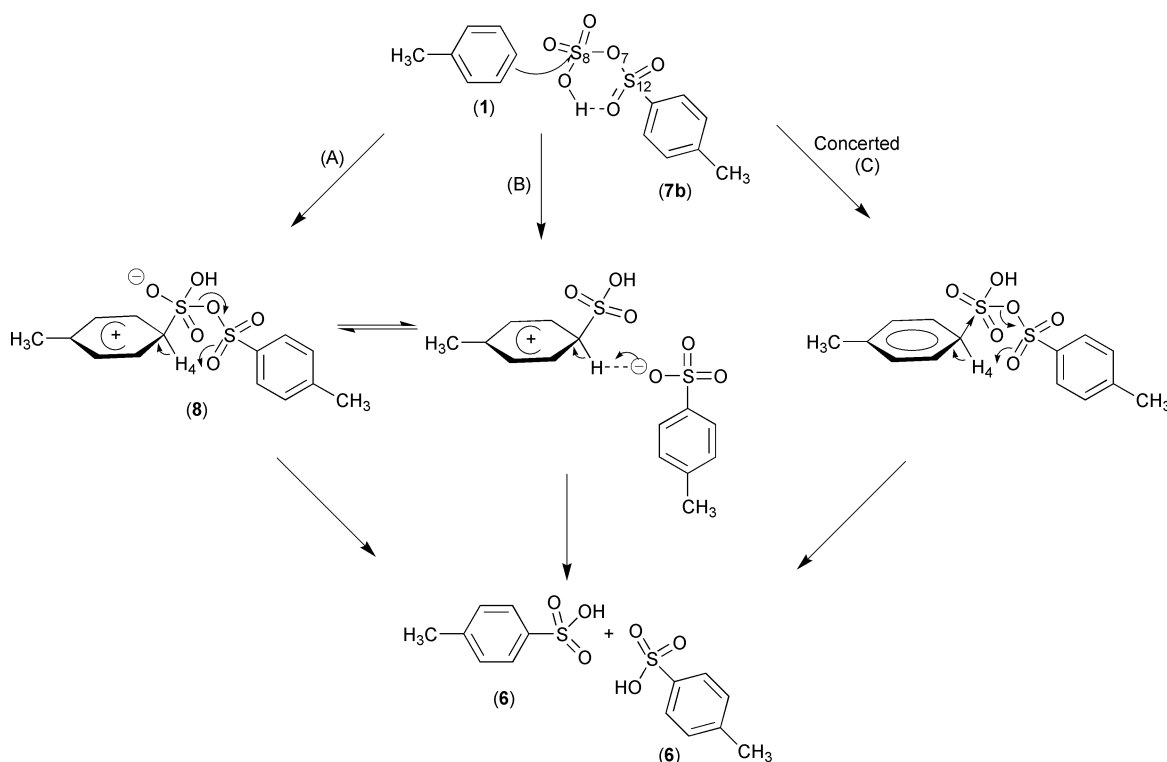
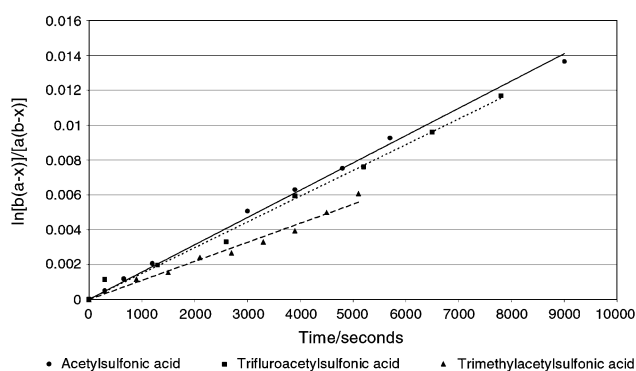


Table 2 Rate constants and activation energies obtained for the sulfonation of toluene (**1**) using the acetylsulfonic acids (**9**), (**10**) and (**11**)

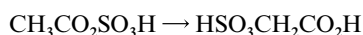
	Temperature/°C	(9)	(9) ^c	(10)	(11)
k^a	22	0.897	0.550	0.860	1.879
	40	5.451	3.000		3.98
	50	10.06 ^d			
	60				11.24
E_{act}^b		16.64 ^e			9.193

^a Rate constants in $10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. ^b Activation energies in kcal mol^{-1} . ^c Using 4-²H-toluene in place of toluene. ^d Estimated from the initial 35% of the reaction. ^e Estimated from the temperature range 22–50 °C.

**Fig. 2** Graph of $\ln [b(a-x)]/[a(b-x)]$ versus time for the reaction between toluene (**1**; initial concentration, a) and the acetylsulfonic acids (**9**, **10**, and **11**; initial concentration, b) at 22 °C.

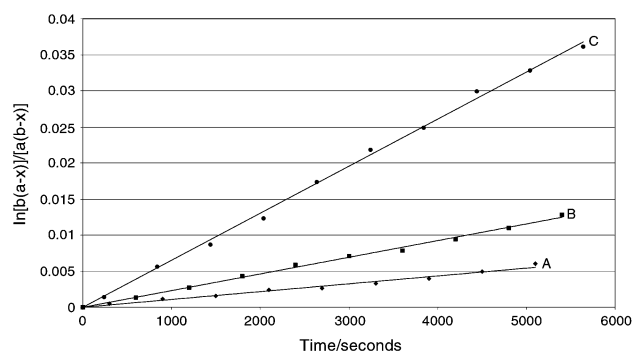
by reacting 4-bromotoluene with *n*-butyllithium, followed by hydrolysis of the resulting reagent with deuterium oxide. The results obtained with 4-deuteriotoluene, however, only show small differences to those obtained with toluene with rate constants of 0.55 versus $0.90 \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ respectively at 22 °C and 3.00 versus $5.45 \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ respectively at 40 °C (Table 2). The average kinetic isotope effect, $k_{\text{H}}/k_{\text{D}}$, of 1.72 is essentially a secondary isotope effect which is possibly caused by steric factors arising during the formation of the transition state. The value obtained is similar, therefore, to the kinetic isotope effects found for the sulfonation of toluene with sulfur trioxide in both fluorotrichloromethane and in nitromethane where $k_{\text{H}}/k_{\text{D}} = 1.23$ and 1.34 respectively,¹⁰ and clearly shows that the loss of the ring proton is not the rate controlling step of the sulfonation process.

With increasing temperatures of 50 to 60 °C, the kinetics of the sulfonation of toluene with acetylsulfonic acid (**9**) become more complex and are no longer simple second order processes, possibly because the known rearrangement³⁸ of the acid to sulfoacetic acid, which occurs very slowly at room temperature, becomes a competing reaction at the higher temperatures, *i.e.*



However, this rearrangement does not occur with trimethylacetylsulfonic acid (**11**) and here the sulfonation of toluene appears to show consistent second order kinetics over the temperature range of 22 to 60 °C (Fig. 3) with a calculated activation energy of 9.19 kcal mol^{-1} (Table 2).

While the three acetylsulfonic acids (**9**), (**10**), and (**11**) show a high positional selectivity for the 4-position of toluene with only small amounts of the 2-sulfonic acid detected in these experiments, the selectivity of these reagents for different substrates is unknown. Accordingly, we have explored the rate of the sulfonation of both anisole and benzene using acetylsulfonic acid as an example, where the former would be expected to be much more reactive to electrophilic attack than toluene, and the latter less reactive than toluene. The results obtained by ¹H NMR spectroscopy clearly show that the sulfonation of

**Fig. 3** Graph of $\ln [b(a-x)]/[a(b-x)]$ versus time for the reaction between toluene (**1**; initial concentration, a) and trimethylacetylsulfonic acid (**11**; initial concentration, b) at 22 °C (A); 40 °C (B); and 60 °C (C).

anisole proceeds extremely rapidly with acetylsulfonic acid at 22 °C, with the resonances of the five aromatic protons at 6.95 to 7.35 ppm, relative to tetramethylsilane, disappearing almost immediately to be replaced by two well resolved doublets resonating at 8.10 and 7.25 ppm arising from the protons at the 2- and 3-positions of 4-methoxybenzenesulfonic acid respectively with the reaction complete in less than 1 minute. In contrast, there is no reaction with benzene even after 48 hours, suggesting that the substrate selectivity here expressed as $k_{\text{toluene}}/k_{\text{benzene}}$ is even greater than the value of 146.2 found for sulfonation with sulfur trioxide in nitromethane.¹⁰ This electrophilic reagent, therefore, is highly discriminating and shows both a high positional and substrate selectivity.

The results for toluene effectively eliminate the possibility of a concerted mechanism, **C**, for the sulfonation as a substantial kinetic isotope effect would be expected because the rate controlling step of this reaction directly involves the cleavage of the C4'–H4' bond (Scheme 4). It seems likely therefore that the sulfonation reaction proceeds *via* the stepwise mechanisms **A** or **B** (Scheme 4) but as theoretical calculations on a template for the postulated intermediate (**12**) failed to locate a stationary point on the potential energy surface, with the molecule either dissociating back to toluene (**1**) and acetylsulfonic acid (**9**) or breaking to produce toluenesulfonic acid (**6**) and acetic acid (**13**), in a similar way to toluenepyrrosulfonate intermediate (**8**), mechanism **B** appears to be favoured. This is supported by the significant increase in sulfonation rate observed for the trimethylacetylsulfonic acid (**10**) versus the two other sulfonic acid (**9**) and (**11**), which can be attributed to steric effects with the former containing the trimethylacetyl group which behaves as a much better leaving group.

Thermodynamically, the overall processes in moving from the reactants of the acetylsulfonic acids (**9**), (**10**), and (**11**) and toluene to the products of toluenesulfonic acid and the carboxylic acids (**13**), (**14**), and (**15**), are calculated to be exothermic by -2.19 , -5.16 , and $-3.36 \text{ kcal mol}^{-1}$ respectively (Table 1) and are of the same magnitude as the exotherm of $-9.15 \text{ kcal mol}^{-1}$ calculated for the reaction of toluenepyrrosulfonic acid with toluene to give two equivalents of toluenesulfonic acid (Table 1). This suggests that the analogy between the sulfonation reactions involving the acetylsulfonic acids (**9**), (**10**), and (**11**), and toluenepyrrosulfonic acid is valid and that a similar mechanism (**B**) operates also in the latter case.

Conclusions

The results of the calculations suggest that the sulfonation of toluene proceeds *via* the formation of a toluene–S₂O₆ π-complex (**3**) which rearranges to form a Wheland pyrosulfonate intermediate (**5**) which undergoes a facile prototropic rearrangement to form toluenepyrrosulfonic acid (**7**). Once formed, this acid reacts with toluene to form toluenesulfonic acid (**6**) which preferentially reacts with excess sulfur trioxide to

generate more toluenepyrosulfonic acid (7). Experimentally, the related reaction of toluene with acetylsulfonic acid (9) appears to follow second order kinetics and shows no significant kinetic isotope effect when 4-deuteriotoluene is used as the substrate, and implies that sulfonation proceeds *via* attack of the toluene ring at the sulfur atom, S8, of acetylsulfonic acid or toluenepyrosulfonic acid with simultaneous cleavage of the S8–O7 bond, where the displaced acetate or toluenesulfonate anion respectively can facilitate the removal of the ring proton, H4'.

Experimental

NMR spectra were measured using a Bruker AC400 spectrometer, and analysed using the Bruker Xwinnmr software. Diethyl ether used in the deuteration of 4-²H-toluene was dried over calcium chloride and distilled before use.

4-²H-toluene

A solution of *n*-butyllithium (7.69 g, 120 mmol) in pentane (60 mL) was slowly added to a stirred solution of 4-bromotoluene (10.2 g, 59.6 mmol) in diethyl ether (150 mL) maintained at approximately –78 °C during addition using an acetone–dry ice bath. After addition was completed the reaction mixture was allowed to warm to room temperature and stirred for 3 h, then cooled again to –78 °C and deuterium oxide (2.17 mL, 120 mmol) slowly added. The solution was allowed to warm to room temperature and stirred for a further 3 h. Dilute hydrochloric acid (30 mL, 2 M, 60 mmol) was added, and the solution stirred until there was no remaining precipitate. The organic layer was separated, washed with distilled water (30 mL), dried (MgSO₄) and the excess solvent removed by rotary evaporation to give 4-²H-toluene (4.05 g, 43.5 mmol) after distillation (bp 110–111 °C). ¹H NMR (neat) 7.25 (d, H2, H6), 7.17 (d, H3, H5) ppm; *J*_{2,3} = 7.56 Hz.

Acetylsulfonic acid (9)

Sulfuric acid (4.41 g, 45 mmol) was slowly added to a mixture of acetic anhydride (9.58 g, 94 mmol) and glacial acetic acid (5.64 g, 94 mmol) maintained below 25 °C during the addition (ice-bath). The reagent was used without any further work-up.

Trifluoroacetylsulfonic (10) and trimethylacetylsulfonic acids (11)

These were prepared in a similar way by adding sulfuric acid (4.41 g, 45 mmol) either to a mixture of trifluoroacetic anhydride (19.8 g, 94 mmol) and trifluoroacetic acid (10.7 g, 94 mmol), or to a mixture of trimethylacetic anhydride (17.48 g, 94 mmol) and trimethylacetic acid (9.58 g, 94 mmol).

Kinetic experiments

An aliquot (0.30 mL) of the acetic acid–acetic anhydride solution containing acetylsulfonic acid (0.11 g, 0.82 mmol) prepared as described above, was injected into an NMR tube which was placed in a thermostated NMR probe and allowed to warm to the specified temperature. The tube was then removed from the probe, toluene (0.069 g, 0.75 mmol) was quickly injected into the mixture, and the tube shaken vigorously and placed back into the probe. The mixture was allowed to equilibrate to the appropriate temperature for 2–3 minutes, and spectra were then recorded every 10 minutes. The reactions were investigated at temperatures of 22, 40, 50, 60 and 70 °C (± 0.5 °C). The rate of reaction was monitored by integrating the ¹H NMR resonances at 7.36 (m, H2, H4, H6) and 7.28 ppm (m, H3, H5) for toluene, and at 7.51 (d, H2, H6), and 7.93 ppm (d, H3, H5) for toluene-4-sulfonic acid. These resonances, however, were found to vary slightly depending on both temperature and the % conversion into product. A similar procedure was adopted for monitoring the reactions of the other

sulfonic acids using in these cases toluene (0.048 g, 0.53 mmol) and either an aliquot (0.30 mL) of trifluoroacetic acid–trifluoroacetic anhydride solution containing trifluoroacetylsulfonic acid (0.12 g, 0.59 mmol), or an aliquot (0.31 mL) of trimethylacetic acid–trimethylacetic anhydride solution containing trimethylacetylsulfonic acid (0.097 g, 0.52 mmol).

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