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# On the intermediacy of phenyl hydrogen sulfates in the sulfonation of phenols. Sulfonation of phenol, anisole, methyl phenyl sulfate, the 2-halogenophenols, a series of phenyl methanesulfonates together with 2,6-dimethylaniline and its *N*-methylsulfonyl derivative[§,†]

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**Abstract.** The sulfonation of methyl phenyl sulfate (**4**) with concentrated aqueous sulfuric acid at 25°C yields the 4-sulfonic acid. This initial product then decomposes to give phenol-4-sulfonic acid, which is subsequently sulfonated to phenol-2,4-disulfonic acid. From the first-order-rate coefficients obtained for sulfonation of phenyl methanesulfonate (**3**) and (**4**) in 93.2% $H_2SO_4$, for which acid concentration the sulfonating entity is $H_2S_2O_7$, the $\sigma_p^+$ values of the $OSO_2Me$ and $OSO_2OMe$ substituents have been determined to be 0.40 and 0.46, respectively. The sulfonation of both 2-chlorophenyl (**10**) and 2-methylphenyl methanesulfonate (**14**) with 2.0 equiv of $SO_3$ in nitromethane at 0.0°C yields the 4-sulfonic acid as the exclusive product, whereas 2-methoxyphenyl methanesulfonate (**13**), under the same conditions, forms exclusively the 5-sulfonic acid.

2-Chloro- (**6**), 2-bromo- (**7**) and 2-iodophenol (**8**) with 1.0 and 4.0 equiv of $SO_3$ in nitromethane yield exclusively the 4-sulfonic acid, while 2-fluorophenol (**5**) with 2.0 and 5.0 equiv of $SO_3$ yields in addition the 5-sulfonic acid to the extent of 4 and 30%, respectively.

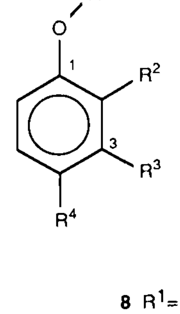
In the reactions of 2,6-dimethylphenol (**15**) and 2,6-dimethylaniline (**17**) with at least 1 equiv of $SO_3$ in nitromethane, the $3\text{-}SO_3H/4\text{-}SO_3H$ ratio was found to increase on increasing the relative amount of $SO_3$. For both **15** and **17**, the limiting $3\text{-}SO_3H/4\text{-}SO_3H$ ratio at high $SO_3$/ArOH ratios is 86/14 and this value is considered to be the ratio for the sulfonation of both 2,6-dimethylphenyl hydrogen sulfate and 2,6-dimethylaniline-*N*-sulfonic acid. This assumption is supported by the observation that the sulfonation of 2,6-dimethylphenyl methanesulfonate (**16**) and *N*-(methylsulfonyl)-2,6-dimethylaniline (**18**) with $SO_3$ leads to a similar $3\text{-}SO_3H/4\text{-}SO_3H$ ratio.

## Introduction

In the reaction of hydroxyarenes with $SO_3$ in non-protic solvents such as dioxane and nitromethane, the sulfation (at the oxygen atom) is rapid relative to the sulfonation at the ring carbon atoms[1-5]. Any sulfonation of the aryl hydrogen sulfates thus formed may lead to a sulfonic acid product distribution which is different from that obtained in the $SO_3$ sulfonation of the hydroxyarene proper, since the $OSO_3H$ substituent, although *para* (and *ortho*) directing, is in contrast to the OH substituent deactivating in nature and very substantially larger in size[1-5]. In order to gain further information about the electronically directing and steric effect of the $OSO_3H$ substituent, we have studied the sulfonation of the substrates **4–16** with $SO_3$ in nitromethane. For comparison, we have also studied the $SO_3$ sulfonation of the nitrogen analogues 2,6-dimethylaniline (**17**) and its *N*-methylsulfonyl derivative (**18**). In addition we have re-evaluated some of the previous results on the sulfonation of phenol (**1**), anisole (**2**) and phenyl methanesulfonate (**3**)[6].

## Results and discussion

The substrates **4–18** have been sulfonated with $SO_3$ in nitromethane at 0.0°C; in addition, **4** and **16** have been sulfonated with concentrated aqueous sulfuric acid at 25°C.



**1** $R^1=R^2=R^3=R^4=H$
**2** $R^1=Me$; $R^2=R^3=R^4=H$
**3** $R^1=SO_2Me$; $R^2=R^3=R^4=H$
**4** $R^1=SO_2OMe$; $R^2=R^3=R^4=H$
**5** $R^1=R^3=R^4=H$; $R^2=F$
**6** $R^1=R^3=R^4=H$; $R^2=Cl$
**7** $R^1=R^3=R^4=H$; $R^2=Br$
**8** $R^1=R^3=R^4=H$; $R^2=I$
**9** $R^1=SO_2Me$; $R^2=F$; $R^3=R^4=H$
**10** $R^1=SO_2Me$; $R^2=Cl$; $R^3=R^4=H$
**11** $R^1=SO_2Me$; $R^2=R^4=H$; $R^3=Cl$
**12** $R^1=SO_2Me$; $R^2=R^3=H$; $R^4=Cl$
**13** $R^1=SO_2Me$; $R^2=OMe$; $R^3=R^4=H$
**14** $R^1=SO_2Me$; $R^2=Me$; $R^3=R^4=H$

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[§] Aromatic Sulfonation. Part 106. For part 105, see ref. 1.

[†] For reasons of convenience, the aromatic ring positions of the sulfonic acids have been numbered as for the parent substrate.

*Table I* $^1H$ *NMR data of various sulfonic acids and methyl phenyl sulfate* (**4**) *in sulfuric acid as solvent.*

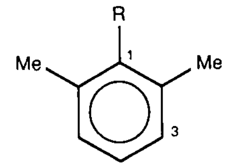
| Compound[a] | $H_2SO_4$ (wt-%) | δ (ppm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Me | $R^2$ | $H^3$ | $H^4$ | $H^5$ | $R^6$ |
| **1**-4-S | 90.4 | | 7.16 | 7.90 | | 7.90 | 7.16 |
| **1**-2,4-$S_2$ | 90.4 | | | 8.39 | | 8.13 | 7.33 |
| **4** | 98.5 | 4.17 | 7.3–7.5 | 7.2–7.3 | 7.3–7.5 | 7.2–7.3 | 7.3–7.5 |
| **4**-4-S | 98.5 | 4.27 | 7.58 | 8.07 | | 8.07 | 7.58 |
| **16**-3-S | 98.5 | 3.64 | 2.71 | | 7.97 | 7.45 | 2.53 |
| **16**-4-S | 98.5 | 3.62 | 2.53 | 7.80 | | 7.80 | 2.53 |

[a] S stands for $SO_3H$.

*Table II* $^1H$ *NMR spectral data of the sulfonic acids of* **4–18** *in* $^2H_2O$.

| Compound[a] | δ (ppm)[b,c] | | | | | |
|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $H^3$ | $H^4$ | $H^5$ | $R^6$ |
| **4**-4-S[d] | 4.32 | 7.69 | 8.16 | | 8.16 | 7.69 |
| **5**-4-S | | | 7.53 | | 7.46 | 7.05 |
| -5-S | | | 6.98 | 7.2–7.5 | | 7.69 |
| **6**-4-S[e] | | | 7.84 | | 7.63 | 7.11 |
| **7**-4-S | | | 8.03 | | 7.71 | 7.13 |
| **8**-4-S | | | 8.11 | | 7.61 | 6.93 |
| **9**-4-S | 3.51 | | 7.83 | | 7.62 | 7.6–7.8 |
| -5-S | 3.51 | | 7.46 | 7.6–7.8 | | 7.85 |
| **10**-4-S | 3.51 | | 8.04 | | 7.84 | 7.64 |
| **11**-4-S | 3.46 | 7.67 | | | 7.96 | 7.54 |
| -6-S | 3.54 | 7.65 | | 7.47 | 8.12 | |
| **12**-3-S | 3.47 | 7.94 | | | 7.55 | 7.64 |
| **13**-5-S | 3.41 | 3.97 | 7.30 | 7.78 | | 7.75 |
| **14**-4-S | 3.45 | 2.39 | 7.79 | | 7.71 | 7.47 |
| **15**-3-S | | 2.42 | | 7.31 | 6.84 | 2.02 |
| -4-S | | 2.06 | 7.34 | | 7.34 | 2.06 |
| **16**-3-S[d] | 3.46 | 2.65 | | 7.85 | 7.36 | 2.47 |
| -4-S[d] | 3.38 | 2.48 | 7.71 | | 7.71 | 2.48 |
| **17**-3-S | | 2.42 | | 7.30 | 7.08 | 2.21 |
| -4-S | | 2.21 | 7.38 | | 7.38 | 2.21 |
| **18**-3-S | 3.16 | 2.56 | | 7.68 | 7.16 | 2.31 |
| -N,3-$S_2$ | 3.52 | 2.71 | | 7.86 | 7.30 | 2.48 |
| -4-S | 3.16 | 2.31 | 7.46 | | 7.46 | 2.31 |
| -N,4-$S_2$ | 3.52 | 2.48 | 7.61 | | 7.61 | 2.48 |

[a] S stands for $SO_3^-$. [b] The *ortho* and *meta* $J_{H,H}$'s were found to be between 9 and 10 and ~1.5 Hz, respectively. [c] The *ortho*, *meta* and *para* $J_{H,F}$s were found to be between 9 and 11, 7 and 9 and ~20 Hz, respectively. [d] Solvent ($^2H_3$)nitromethane. [e] Data taken from ref. 4.



**15** R=OH
**16** R=$OSO_2Me$
**17** R=$NH_2$
**18** R=$NHSO_2Me$

The structures of the sulfonic acid products have been assigned by $^1H$ NMR and, if required, by $^{13}C$ NMR spectroscopy. The NMR data of the sulfo products and some of the substrates are collected in the Tables I-III. The sulfo.product compositions of the various reaction mixtures have been determined by $^1H$ NMR analysis[7] on the basis of the specific absorptions of the different components.

### *Reactions in concentrated aqueous sulfuric acid*

*Phenol* (**1**), *anisole* (**2**) *and phenyl methanesulfonate* (**3**). It was recently suggested that, in the sulfonation mixture of phenol (**1**) with concentrated aqueous sulfuric acid, phenyl hydrogen sulfate and/or its anion (*i.e.* the products of sulfation) may be present and that (one of) the latter two species might be the actual substrate species undergoing sulfonation[6]. An attempt to sulfonate potassium phenyl sulfate in the range of 73.5–82.8% $H_2SO_4$ failed, since its hydrolysis to phenol proved to be very fast relative to its sulfation[6].

Phenyl methanesulfonate (**3**) (which may be considered as a model compound for phenyl hydrogen sulfate) does not decompose in concentrated aqueous sulfuric acid and yields the 4-sulfonic acid as the exclusive product[6]. A comparison of the rate profiles for the conversion of **1**[6], anisole (**2**)[6], **3**[6], methyl phenyl sulfate (**4**) *(vide infra)*, benzene[9] and chloro-

*Table III* $^{13}C$ *NMR data for the sulfonic acids of* **10**, **13** *and* **14** *and some related compounds.*

| Compound[a] | δ (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2-(O)Me | $OSO_2Me$ | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 |
| $C_6H_6$[b,c] | | | 129.4 | | | | | |
| PhS[d] | | | 147.7 | 125.7 | 127.9 | 128.9 | | |
| PhCl[d] | | | 133.2 | 128.2 | 130.0 | 126.7 | | |
| **3**[d] | | 37.3 | 149.2 | 122.2 | 130.1 | 127.4 | | |
| **10**[d] | | 38.6 | 145.0 | 126.4 | 130.8 | 128.6 | 128.5 | 124.2 |
| **10**-4-S[d] | | 38.6 | 145.0 | 126.0 | 127.7 | 148.1 | 126.1 | 123.9 |
| **13**-5-S[b] | 58.4 | 39.7 | 137.3 | 155.6 | 115.6 | 128.5 | 138.8 | 123.3 |
| **14**-4-S[b] | 17.7 | 40.8 | 150.0 | 134.6 | 131.1 | 143.6 | 126.8 | 124.4 |

[a] S stands for $SO_3^-K^+$. [b] Solvent $^2H_2O$. [c] See ref. 8. [d] Solvent $(^2H_3C)_2SO$.

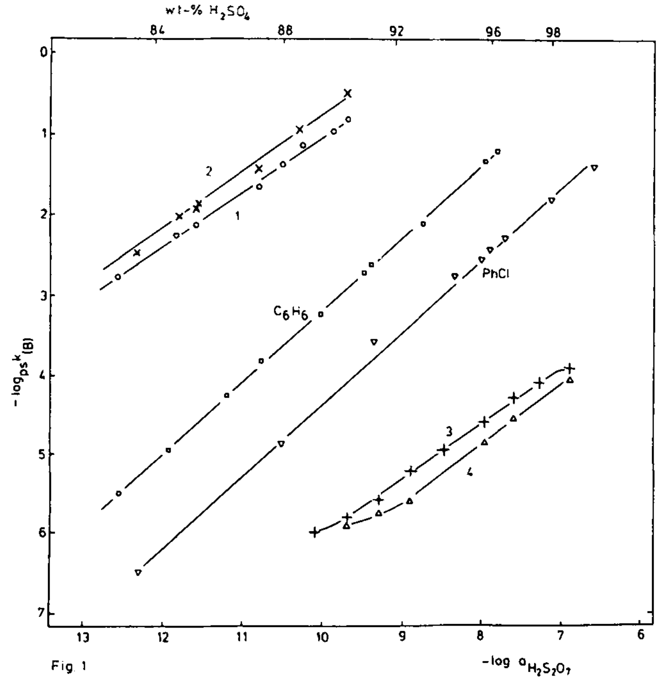


*Fig. 1. Rate profiles for the sulfonation of phenol* (**1**), *anisole* (**2**), *phenyl methanesulfonate* (**3**), *methyl phenyl sulfate* (**4**), *benzene and chlorobenzene in concentrated aqueous sulfuric acid. Correlation of* $\log_{ps}k_{(B)}$ *with* $\log a(H_2S_2O_7)$, *where* $\log_{ps}k_{(B)}$ *is the pseudo-first-order rate coefficient for the unprotonated substrate species B.*

benzene[10] in the 83–99% $H_2SO_4$ sulfuric acid range, where $H_2S_2O_7$ is considered to be the sulfonating entity[11], is shown in Fig. 1. The applied rate coefficients have been corrected for protonation of the substrate at oxygen[6], as was required for **1** and **2** for which the protonated form was presumed to be unreactive, but not for **3** and **4**, for which the degree of protonation in $\leq 98.5\%$ $H_2SO_4$ is negligibly small[12] and unknown. It is evident from Fig. 1 that the $OSO_2Me$ substituent is strongly deactivating.

The partial rate factors for the sulfonation of a series of substituted benzenes, including PhOX (X = H, Me, $SO_2Me$ and $SO_2OMe$), by the entity $H_2S_2O_7$ are collected in Table IV. For phenol (**1**) and anisole (**2**), the acid concentrations of equal rate contribution by the entities $H_3SO_4^+$ and $H_2S_2O_7$ were estimated to be 90 and 87 ± 1% $H_2SO_4$, respectively[6], thus allowing the effective contribution for the sulfonation by the entity $H_2S_2O_7$ to be calculated. On comparing the partial rate factors for 2- and 4-substitution of **1** and **2**, it appears that **1** is slightly more reactive than **2** towards $H_3SO_4^+$ as electrophile, in agreement with the reported $\sigma_p^+$ values for the OH ($-0.92$[16]) and OMe ($-0.78$[17]) substituents. However, the partial rate factors for the sulfonation of **1** and **2** by the entity $H_2S_2O_7$ show the opposite order as predicted by the substituent constants. This may be explained in terms of hydrogen bonding between the hydroxy group of the phenol and a molecule of $H_2SO_4$, the concentration of which increases very strongly with increasing acid concentration in the range of 90–100% $H_2SO_4$[11]. It may however also be explained in terms of (partial) conversion of the phenol into phenyl hydrogen sulfate which is far less reactive than phenol itself. At this point, it is important to note that both phenol-3- and phenol-4-sulfonic acid in 86–97% $H_2SO_4$ are present as the respective sulfophenyl hydrogen sulfate, the amount of which increases with increasing sulfuric acid concentration[18].

The partial rate factor for sulfonation of the 4-position of phenyl methanesulfonate (**3**) in 93.2% $H_2SO_4$ is 0.005 ± 0.001, a value which, using the $\rho^+$ value for the sulfonation by the $H_2S_2O_7$ entity of $-5.7$[11], infers $\sigma_p^+(MeSO_2O)$ to be 0.40.

*Methyl phenyl sulfate* (**4**). The sulfonation of methyl phenyl sulfate (**4**) in concentrated aqueous sulfuric acid at 25°C yields initially its 4-sulfonic acid[19] which subsequently forms phenol-4- and -2,4-di-sulfonic acid. The pseudo-first-order rate coefficients for the initial sulfonation are given in Table V and the actual compositions of the reaction mixtures in Table VI. Methyl phenyl sulfate (**4**) is slightly less reactive than phenyl methanesulfonate (**3**) (see Fig. 1) and the partial rate factor for the sulfonation of the 4-position by the entity $H_2S_2O_7$ in 93.2% $H_2SO_4$ is 0.0020 ± 0.0005, leading with $\rho^+$ $-5.7$[11] to $\sigma_p^+(MeOSO_2O)$ 0.46. As for the $OSO_3H$ group[2], the deactivating nature of the $OSO_2Me$ and $OSO_2OMe$ substituents may be explained in terms of conjugate electron release from the phenoxy oxygen to the $SO_2Me$ and $SO_2OMe$ group, respectively, thus reducing the positive mesomeric effect of that oxygen toward the phenyl group.

*Table IV Partial rate factors for the sulfonation of various substituted benzenes in concentrated aqueous sulfuric acid at 25°C by the entities* $H_3SO_4^+$ *and* $H_2S_2O_7$.

| Substrate | Position | *f* | |
|---|---|---|---|
| | | $H_3SO_4^+$ mech. | $H_2S_2O_7$ mech. |
| benzene | 1 | 1 | 1 |
| toluene | 2 | 69 ± 20[a] | 44 ± 4[a] |
| | 4 | 760 ± 200[a] | 76 ± 7[a] |
| *m*-xylene | 4 | 13000 ± 3000[b] | 260 ± 25[b] |
| | 5 | 160 ± 40[b] | 8 ± 1[b] |
| chlorobenzene | 2 | | 0.002 ± 0.001[c] |
| | 4 | | 0.48 ± 0.05[c] |
| anisole | 2 + 6 | 2000 ± 250[d,e] | 220 ± 5 |
| | 4 | 7100 ± 750[d] | 780 ± 150 |
| phenol | 2 | 3400 ± 400[d] | 80 ± 20 |
| | 4 | 7300 ± 800[d] | 180 ± 50 |
| phenyl methanesulfonate | 2 | | ≤0.0001 |
| | 4 | | 0.005 ± 0.001 |
| methyl phenyl sulfate | 2 | | ≤0.00004 |
| | 4 | | 0.0020 ± 0.0005 |

[a] Ref. 13. [b] Ref. 14. [c] Ref. 11. [d] Ref. 6. [e] *Cf.* the discussion in ref. 15.

*Table V Pseudo-first-order rate coefficients for the homogeneous sulfonation of methyl phenyl sulfate* (**4**) *in concentrated aqueous sulfuric acid at 25°C.*

| $H_2SO_4$ (wt-%, ±0.2) | $10^6 \cdot {}_{ps}k$ ($s^{-1}$, ±5%) |
|---|---|
| 90.4 | 1.3 |
| 91.5 | 1.6 |
| 92.9 | 2.6 |
| 95.9 | 13.1 |
| 96.9 | 26.7 |
| 98.5 | 93 |

*Table VI Composition of the reaction mixtures obtained on sulfonation of methyl phenyl sulfate* (**4**) *in concentrated aqueous sulfuric acid at 25°C.*

| $H_2SO_4$ (wt-%, ±0.2) | Reaction time (ks) | Reaction mixture composition (%, ±2)[a] | | | |
|---|---|---|---|---|---|
| | | **4** | **4**-4-S | **1**-4-S | **1**-2,4-$S_2$ |
| 98.5 | 0.7 | 87 | 13 | | |
| | 3.7 | 72 | 28 | | |
| | 6.5 | 64 | 36 | | |
| | 15 | 27 | 63 | | |
| | 17 | 20 | 80 | | |
| | 87 | – | 93 | | 7 |
| | 690 | | 75 | | 25 |
| | 1230 | | 66 | | 34 |
| | 2160 | | 46 | | 54 |
| 96.9 | 7.2 | 85 | 15 | | |
| | 9.9 | 74 | 22 | | 4 |
| | 21 | 55 | 40 | | 5 |
| | 90 | 20 | 70 | | 10 |
| | 105 | 8 | 79 | | 13 |
| 95.9 | 12 | 83 | 14 | | 3 |
| | 21 | 76 | 20 | | 4 |
| | 28 | 70 | 25 | | 5 |
| | 90 | 46 | 43 | <1 | 10 |
| | 115 | 33 | 55 | 1 | 11 |
| | 190 | 24 | 57 | 3 | 16 |
| 92.9 | 86 | 80 | 10 | 7 | 3 |
| | 110 | 74 | 15 | 7 | 4 |
| | 195 | 61 | 23 | 5 | 11 |
| | 435 | 44 | 27 | 7 | 12 |
| | 620 | 27 | 27 | 9 | 37 |
| 91.5 | 18 | 98 | | 2 | |
| | 85 | 85 | 5 | 2 | 8 |
| | 110 | 83 | 6 | 3 | 8 |
| | 195 | 67 | 13 | 3 | 17 |
| | 435 | 50 | 19 | 6 | 25 |
| | 620 | 33 | 20 | 7 | 40 |
| 90.4 | 15 | 96 | | 4 | |
| | 80 | 82 | 3 | 5 | 10 |
| | 255 | 71 | 6 | 6 | 17 |
| | 530 | 50 | 6 | 13 | 31 |
| | 710 | 35 | 6 | 12 | 47 |

[a] S stands for $SO_3H$.

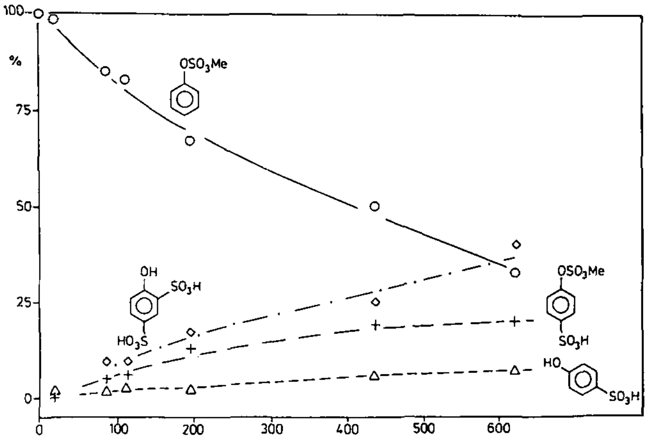


*Fig. 2. Composition of the reaction mixture of methyl phenyl sulfate* (**4**) *with 91.5%* $H_2SO_4$.

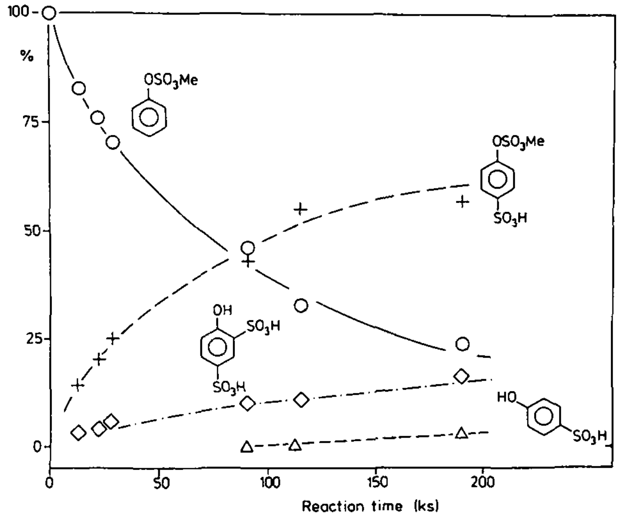
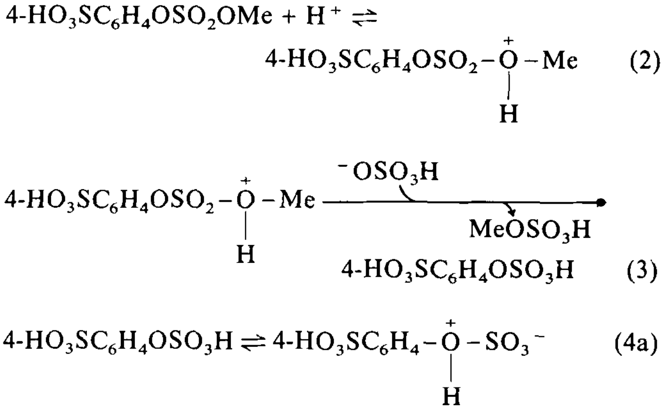


*Fig. 3. Composition of the reaction mixture of methyl phenyl sulfate* (**4**) *with 95.9%* $H_2SO_4$.

The $^1H$ NMR spectra of the reaction mixtures of **4** in 90.4–98.5% $H_2SO_4$ reveal, in addition to the **4**-4-sulfonic acid, the presence of the decomposition products phenol-4- and -4,6-di-sulfonic acid (see Table VI) and $MeOSO_3X$ ($X = H$, $SO_3^-$, $SO_3H$)[20]. The phenolsulfonic acids eventually present in the reaction mixture may be formed by initial conversion of **4** into **1** followed by sulfonation or by initial sulfonation of **4**, subsequent "sulfatolysis"[22] of **4**-4-sulfonic acid, followed by further sulfonation of the resulting **1**-4-sulfonic acid to **1**-2,4-disulfonic acid. The graphs of the composition of the reaction mixture as a function of the reaction time for 91.5 and 95.5% $H_2SO_4$ (see Figs. 2 and 3) illustrate that *(i)* the latter route is the predominant one, at least for the more concentrated sulfuric acid solutions, since the formation of **4**-4-sulfonic acid clearly preceeds that of **1**-2,4-disulfonic acid and that *(ii)* the sulfonation of **1**-4-sulfonic acid is rapid relative to its formation. The results (see Table VI) further exclude the possibility of initial sulfonation of **4**-4-sulfonic acid to the 2,4-disulfonic acid followed by conversion to phenol-2,4-disulfonic acid.

The decomposition of alkyl aryl sulfates may, in principle, proceed by alkyl–oxygen, aryl–oxygen or sulfur–oxygen scission. It was however reported that the hydrolysis of dimethyl sulfate[23] and diphenyl sulfate[24] proceeds exclusively by C–O cleavage and that the alkaline methanolysis of methyl 4-nitrophenyl sulfate proceeds by attack of the methoxide ion at the aliphatic carbon, thus exclusively by methyl–oxygen scission[25]. By analogy, the presently observed conversion of **4**-4-suifonic acid into **1**-4-sulfonic acid is proposed to proceed by methyl–oxygen scission. Nucleophilic substitution by attack of $HOSO_3^-$ at the phenyl carbon is less likely than at the methyl carbon since the former would proceed by an addition–elimination type of mechanism, whereas the latter proceeds by a simple $S_N2$ substitution process. Further, the degree of the sulfate protonation will be substantially greater for the methyl than for the 4-sulfophenyl oxygen, since the latter protonation will lead to loss of conjugation between the 4-sulfophenyl moiety and the 1-oxygen, whereas the former does not. Accordingly, the conversion of **4** into **1**-2,4-disulfonic acid is proposed to proceed by the steps 1–6. The initial reaction involves sulfonation of **4** to its 4-sulfonic acid (step 1) which is protonated in some degree at the methyl oxygen (step 2). Nucleophilic attack of a bisulfate ion on the methyl carbon of the protonated species then leads to 4-sulfophenyl hydrogen sulfate as leaving group (step 3), which decomposes to phenol-4-sulfonic acid either directly, by the steps 4a and 5a, or via initial protonation, by the steps 4b and 5b. Subsequent sulfonation than yields phenol-2,4-disulfonic acid (step 6).

$$C_6H_5OSO_2OMe + H_2S_2O_7 \rightarrow 4\text{-}HO_3SC_6H_4OSO_2OMe + H_2SO_4 \quad (1)$$



$$4\text{-}HO_3SC_6H_4OSO_2OMe + H^+ \rightleftharpoons 4\text{-}HO_3SC_6H_4OSO_2\text{-}\overset{+}{\underset{\displaystyle H}{O}}\text{-}Me \quad (2)$$

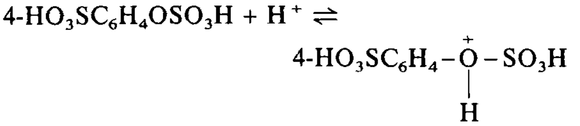
$$4\text{-}HO_3SC_6H_4OSO_2\text{-}\overset{+}{\underset{\displaystyle H}{O}}\text{-}Me \xrightarrow{^{-}OSO_3H} MeOSO_3H + 4\text{-}HO_3SC_6H_4OSO_3H \quad (3)$$

$$4\text{-}HO_3SC_6H_4OSO_3H \rightleftharpoons 4\text{-}HO_3SC_6H_4\text{-}\overset{+}{\underset{\displaystyle H}{O}}\text{-}SO_3^- \quad (4a)$$

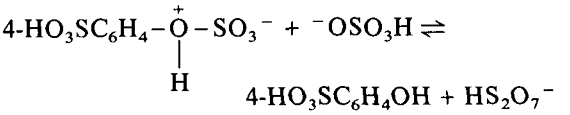
*Table VII Sulfonic acid product composition obtained on reaction of* **4–18** *with* $SO_3$ *in nitromethane at 0°C.*

| Substrate | Equiv. of $SO_3$ | Reaction time (h) | Unconverted subst. (%) | Sulfonic acid product composition (%, ±2)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 2-S | 3-S | 4-S | 5-S | 6-S | 4,6-$S_2$ |
| **4**[b,c] | 1.0 | 0.5 | 76 | | | 100 | | | |
| **5** | 2.0 | 4 | | | | 96 | 4 | | |
| | 5.0 | 4 | | | | 70 | 30 | | |
| **6** | 1.0 | 4 | | | | 100 | | | |
| | 4.0 | 4 | | | | 97 | | | 3 |
| **7** | 1.0 | 4 | | | | 100 | | | |
| | 4.0 | 4 | | | | 98 | | | 2 |
| **8** | 1.0 | 4 | | | | 100 | | | |
| | 4.0 | 4 | | | | 98 | | | 2 |
| **9** | 2.0 | 4 | | | | 33 ± 5 | 67 ± 5 | | |
| **10** | 2.0 | 4 | | | | 100 | | | |
| **11** | 4.0 | 5 | | | | 70 | | 30 | |
| **12**[d] | 4.0[e] | 0.5 | | 21 | 79 | | | | |
| **13** | 2.0 | 4 | | | | | 100 | | |
| **14** | 2.0 | 4 | | | | 100 | | | |
| **15** | 0.5 | 0.5 | | | 14 | 86 | | | |
| | 1.0 | 0.5 | | | 20 | 80 | | | |
| | 1.5 | 0.5 | | | 27 | 73 | | | |
| | 2.0 | 0.5 | | | 50 | 50 | | | |
| | 3.0 | 0.5 | | | 73 | 27 | | | |
| | 4.0 | 0.5 | | | 85 | 15 | | | |
| | 6.0 | 0.5 | | | 84 | 16 | | | |
| **16**[b] | 1.1 | 0.25 | 52 | | 86 | 14 | | | |
| **17**[c] | 1.0 | 3 | | | | 100 | | | |
| | 1.5 | 3 | | | | 100 | | | |
| | 1.75 | 3 | | | 15 | 85 | | | |
| | 2.0 | 3 | | | 41 | 59 | | | |
| | 2.5 | 3 | | | 64 | 36 | | | |
| | 3.25 | 3 | | | 72 | 27 | | | |
| | 4.0 | 3 | | | 86 | 14 | | | |
| | 5.0 | 3 | | | 83 | 17 | | | |
| | 8.0 | 3 | | | 87 | 13 | | | |
| **18** | 0.5 | 3 | | | 75 | 25 | | | |
| | 1.0 | 3 | | | 69 | 31 | | | |
| | 1.5 | 3 | | | 70 | 30 | | | |
| | 2.5 | 3 | | | 84 | 16 | | | |
| | 4.0 | 3 | | | 84 | 16 | | | |
| | 6.0[f] | 3 | | | 72 | 10 | | | |

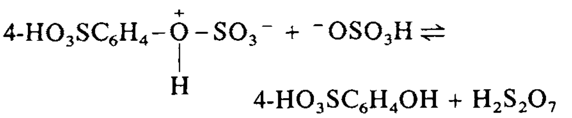
[a] S stands for $SO_3H$. [b] Solvent ($^2H_3$)nitromethane. [c] Reaction temperature 25°C. [d] Reaction in $CCl_3F$. [e] The $^1H$ NMR spectrum of the mixture obtained after alkaline work-up showed the presence of 68% of **12**-3-sulfonate, 21% of 4-chlorophenol-2- and 11% of 4-chlorophenol-3-sulfonate. Assuming the phenolsulfonates to result from the corresponding methanesulfonates, the initial **12**-2- and **12**-3-sulfonic acids are formed to the extent of 79 and 21%, respectively. [f] The $^1H$ NMR spectrum further showed the presence of 12 and 6% of **18**-$N$,3-and **18**-$N$,4-disulfonic acid, respectively.



$$4\text{-}HO_3SC_6H_4OSO_3H + H^+ \rightleftharpoons 4\text{-}HO_3SC_6H_4\text{-}\underset{\overset{|}{H}}{\overset{+}{O}}\text{-}SO_3H \quad 4b)$$



$$4\text{-}HO_3SC_6H_4\text{-}\underset{\overset{|}{H}}{\overset{+}{O}}\text{-}SO_3^- + {}^-OSO_3H \rightleftharpoons 4\text{-}HO_3SC_6H_4OH + HS_2O_7^- \quad (5a)$$



$$4\text{-}HO_3SC_6H_4\text{-}\underset{\overset{|}{H}}{\overset{+}{O}}\text{-}SO_3^- + {}^-OSO_3H \rightleftharpoons 4\text{-}HO_3SC_6H_4OH + H_2S_2O_7 \quad (5b)$$

$$4\text{-}HO_3SC_6H_4OH + H_2S_2O_7 \rightarrow 2,4\text{-}(HO_3S)_2C_6H_3OH + H_2SO_4 \quad (6)$$

*Reactions with $SO_3$ in nitromethane*

*Methyl phenyl sulfate* (**4**). The $^1H$ NMR spectrum recorded 30 min after the addition of 1.0 equiv of $SO_3$ to **4** in ($^2H_3$)nitromethane at 25°C showed the presence of 24% of 4-4-sulfonic acid, in addition to 76% of the starting substrate (Table VII).

*2-Halogenophenols (***5–8***) and ring-substituted phenylmethanesulfonates (***9–14***).* Reaction of 2-fluorophenol (**5**) with 2.0 and 5.0 equiv of $SO_3$ in nitromethane at 0°C yields, in addition to the 4-sulfonic acid, 4 and 30% of the 5-sulfonic acid, respectively, while the reactions of 2-chloro- (**6**), 2-bromo- (**7**) and 2-iodophenol (**8**) with 1.0 and 4.0 equiv of $SO_3$ all yield the 4-sulfonic acid as the exclusive monosulfonation product (Table VII).

Reaction of 2-fluorophenyl methanesulfonate (**9**) with 2.0 equiv of $SO_3$ was found to yield the 4- and 5-sulfonic acid in a *ca.* 1/2 ratio. Reaction of 2-chlorophenyl (**10**), 2-methoxyphenyl (**13**) and 2-methylphenyl methanesulfonate (**14**) with 2.0 equiv of $SO_3$ yields only one sulfonic acid product. The $^1H$ NMR spectra contained only the signals of one ABX absorption pattern which may, however, be assigned either to the 4- or to the 5-sulfonic acid. The assignment of the products has been made by means of $^{13}C$ NMR spectroscopy based on the multiplicity of the absorptions due to the $^3J_{C,H}$ coupling, the values of which are large relative to those of the $^2J_{C,H}$ and $^4J_{C,H}$ coupling[26a]. It appeared (see Experimental) that both 2-chlorophenyl (**10**) and 2-methylphenyl methanesulfonate (**14**) yield exclusively the 4-sulfonic acid, whereas 2-methoxyphenyl methanesulfonate (**13**) yields only the 5-sulfonic acid.

The formation of 2-methoxy-5-sulfophenyl methanesulfonate in the reaction of **13** with 2.0 equiv of $SO_3$ is in line with predictions based on the $\sigma_p^+$ values of the OMe ($-0.78^{17}$) and $OSO_2Me$ (0.40, *vide supra*) substituents. It is further in line with the observed increase in the ratio of the 5- to 4-substitution in the reaction of $SO_3$ with 2-methoxyphenol upon increasing the relative amount of $SO_3$ in excess to the amount of the substrate[27]. The exclusive formation of the 4-sulfonic acid (*i.e. para* to the $OSO_2Me$ substituent) in the reactions of **10** and **14** is in contrast to predictions based on a comparison of the $\sigma_p^+$ values of the chloro ($0.11^{28}$) and methyl ($-0.28^{28}$) substituents with that of the $OSO_2Me$ group (0.40). It should however be realized that the $\Delta\sigma^+$ is much larger for the couple $OSO_2Me$/OMe than for the couples $OSO_2Me$/Me and $OSO_2Me$/Cl. Considering that the (isomeric) product composition resulting in electrophilic aromatic substitution is determined by the relative conjugative stabilization of the various σ-complexes, it follows that the stabilization of the σ-complexes in the sulfonation of **10** and **14** by the $OSO_2Me$ group is the decisive factor in determining the sulfonic acid products actually obtained and thus the polarizability is significantly larger for the $OSO_2Me$ than for the Cl and Me substituents.

From the exclusive formation of the 4-sulfonic acid in the reaction of 2-chlorophenyl methanesulfonate (**10**) it follows that the formation of the 4-sulfonic acids in the reactions of 2-chloro- (**6**), 2-bromo- (**7**) and 2-iodophenol (**8**) with 4.0 equiv of $SO_3$ (*cf.* Table VII) is likely to proceed by sulfonation of the corresponding phenyl hydrogen sulfates of **6–8**. In fact, it is most likely that the reactions of **6–8** with 4.0 equiv of $SO_3$ proceed completely via the respective hydrogen sulfates, since only very small amounts of the 4,6-disulfonic acids are formed. The low yield of the 4,6-disulfonic acids may be explained assuming that the 2-halogeno substituent in the 2-X-4-sulfophenyl hydrogen sulfate (X = Cl, Br,I) forces the $OSO_3H$ group, which in view of conjugative stabilization prefers to be coplanar with the phenyl group, in the direction of 6-H, an orientation which causes a considerable amount of steric hindrance upon sulfonation of the 4-sulfoaryl hydrogen sulfate at C(6). The sulfonations of 2-fluorophenol (**5**) and 2-fluorophenyl methanesulfonate (**9**) with ≥2 equiv of $SO_3$ in nitromethane differ from the reactions of **6–8**, **10**, **11** and **14** in that they lead to sulfonation at both the 4- and 5-position (*cf.* Table VII).

The sulfonation of 3-chlorophenyl methanesulfonate (**11**) with 4.0 equiv of $SO_3$ in nitromethane yields the 4- and 6-sulfonic acids to the extent of 70 and 30%, respectively. This result is in line with the sulfonation of 3-chlorophenol with ≥2.0 equiv of $SO_3$ (yielding 74% of the 4- and 26% of the 6-sulfonic acid) which was proposed to proceed via the 3-chlorophenyl hydrogen sulfate[4]. Reaction of 4-chlorophenyl methanesulfonate (**12**) with $SO_3$ in nitromethane did not yield any sulfonic acid products. Reaction of **12** with the much more reactive reagent of $SO_3$ in $CCl_3F$ yielded, according to the $^1H$ NMR analysis of the potassium sulfonate mixture obtained after quenching of the reaction mixture with water followed by aqueous alkaline work-up, 68% of the **12**-3-sulfonate, 11% of the 4-chlorophenol-3- and 21% of the 4-chlorophenol-2-sulfonate (see Table VII)[29].

*2,6-Dimethylphenol* (**15**), *2,6-dimethylphenyl methanesulfonate* (**16**), *2,6-dimethylaniline* (**17**) *and* N-*(methylsulfonyl)-2,6-dimethylaniline* (**18**). Sulfonation of 2,6-dimethylphenol (**15**) with 1.0 equiv of $SO_3$ in nitromethane yields exclusively the 4-sulfonic acid[2]. Upon increasing the amount of $SO_3$ employed, the limiting 3- to 4-sulfonic acid isomer ratio is 84/16 which was considered to be the isomer ratio for the sulfonation of 2,6-dimethylphenyl hydrogen sulfate[2], since the degree of 4-substitution will be lower for this compound, compared with that of **15**, as a result of steric inhibition of resonance for the $OSO_3H$ group by the two adjacent methyls. To verify this assumption, the sulfonation of **15** has been restudied applying the method of "inverse addition"[30]. Again, the content of the 3-sulfonic acid was found to increase at the expense of the 4-sulfonic acid on increasing the amount of $SO_3$. With the present inverse type of addition, some 3-sulfonic acid is already found on using 0.5 and 1.0 equiv of $SO_3$ (*cf.* Table VII), but the limiting 3- to 4-sulfonic acid ratio of 84/16 is the same as previously observed[2].

Reaction of 2,6-dimethylphenyl methanesulfonate (**16**) with 1.1 equiv of $SO_3$ in ($^2H_3$)nitromethane yields 86% of the 3- and 14% of the 4-sulfonic acid, *i.e.* the same sulfonic acid isomer ratio as observed in the sulfonation of 2,6-dimethylphenyl hydrogen sulfate. On reaction with 98.5% $H_2SO_4$ at 25°C, **16** yields 93% of **16**-3- and 7% of **16**-4-sulfonic acid, whereas 2,6-dimethylphenol (**15**) is then sulfonated to the extent of 47% at the 3- and 53% at the 4-position[2], illustrating that the reacting substrate species is not 2,6-dimethylphenyl hydrogen sulfate and thus apparently the entity **15** proper.

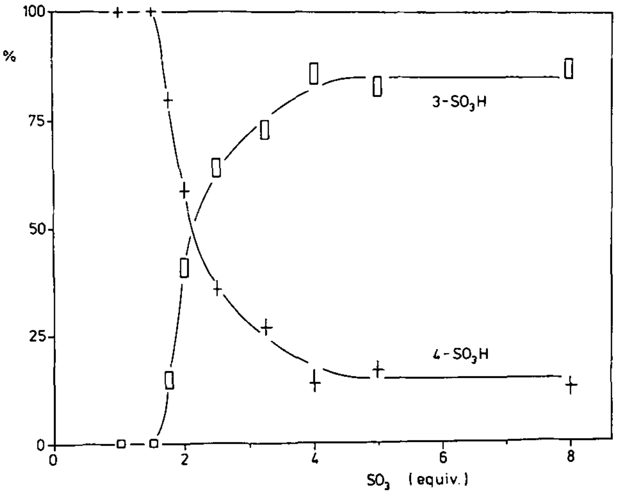


*Fig. 4. Sulfonation of 2,6-dimethylaniline* (**17**) *with* $SO_3$ *in nitromethane at 25° C.*
□ **17**-*3-sulfonic acid,* + **17**-*4-sulfonic acid.*

Whereas the sulfonic acid isomer product distribution in the sulfonation of phenols may depend on the formation of phenyl hydrogen sulfates, the product distribution in the sulfonation of anilines may be similarly influenced by the initial formation of aniline-*N*-sulfonic acids[31-33]. The (heterogeneous) reaction of 2,6-dimethylaniline (**17**) with $SO_3$ in nitromethane at 25°C (according to the normal, *i.e.* the non-inverse, method of addition) yields the 3- and 4-sulfonic acid, the ratio of which increases on increasing the amount of excess $SO_3$ employed (*cf.* Table VII and Fig. 4). The limiting 3- to 4-sulfonic acid isomer ratio for high $SO_3$ content is 84/16, which is considered to be the isomer ratio for the sulfonation of the 2,6-dimethylaniline-*N*-sulfonic acid. For the non-inverse addition, the 50/50 ratio of the 3- and 4-sulfonic acid is obtained for the phenol **15** and the aniline **17** upon using 3.6 and 2.2 equiv of $SO_3$, respectively. This difference indicates that the equilibrium constant is greater for the formation of the 2,6-dimethylaniline-*N*-sulfonic acid than for that of the 2,6-dimethylphenyl hydrogen sulfate due to a higher electron delocalization in the former as compared with the latter compound. Nitrogen is less electronegative than oxygen and accordingly the dipolar mesomeric structure **19** (*cf.* Fig. 5) will be more stable and thus will contribute to a greater extent than **20**.

Sulfonation of *N*-(methylsulfonyl)-2,6-dimethylaniline (**18**) with 1.0 and 1.5 equiv of $SO_3$ in nitromethane leads to the formation of the 3- and 4-sulfonic acid in yields of *ca.* 70 and 30%, respectively. Using larger amounts of $SO_3$, the limiting 3- to 4-sulfonic acid ratio is *ca.* 84/16, which is in fact the same as the ratio observed in the sulfonation of the corresponding aniline **17** using a large excess of $SO_3$. The $^1H$ NMR spectra recorded of the reaction mixture of **18** with 6.0 equiv of $SO_3$ after quenching with $^2H_2O$ showed, in addition to the presence of the **18**-3- and **18**-4-sulfonic acids, the presence of two other products which have been assigned (*cf.* Table II) as the **18**-*N*,3- and **18**-*N*,4-disulfonic acids, respectively.

From the results obtained with the substrates containing the $OSO_2Me$, $OSO_2OMe$ and (the *in situ* prepared) $OSO_3H$ substituents, it may be concluded that they all exhibit, as do the halogens, a dual character in electrophilic aromatic substitution in that they are *para* (and *ortho*) directing, yet also deactivating. Although the $\sigma_p{}^+$ values are significantly greater for the $OSO_2Me$ (0.40), $OSO_2OMe$ (0.46) and thus probably also for the $OSO_3H$ substituents than for the halogens (which range from −0.07 for F to 0.15 for Br[28]), the *para*-directing effect of the $OSO_2R$ (R = Me, OMe, OH) substituent appears to dominate strongly over that of the halogens in the present sulfonation studies, illustrating that the polarizability is greater for the $OSO_2R$ than for the halogeno substitutents.

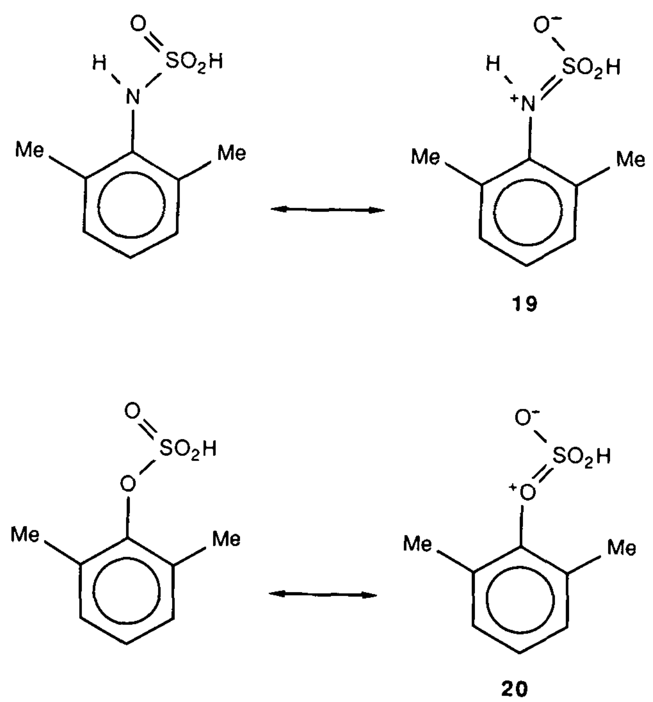


*Fig. 5. Conjugative stabilization of 2,6-dimethylphenyl hydrogen sulfate and 2,6-dimethylaniline-*N*-sulfonic acid.*

## Experimental

### *Materials*

The substrates used in this study were commercially obtained, unless stated otherwise. The phenyl methanesulfonates **1**, **9–14** and **16** were synthesized from the corresponding phenols by reaction with methanesulfonyl chloride in pyridine[34a]. Methyl phenyl sulfate (**4**) was synthesized following a reported procedure[35]. *N*-(Methylsulfonyl)-2,6-dimethylaniline (**18**) was obtained using a general method for the synthesis of sulfoanilides[34b].

### *Procedures of sulfonation, structural assignment and analysis*

The sulfonations with sulfuric acid and $SO_3$, the structural assignment of the products and the determination of the composition of the reaction mixtures were performed as previously described[2,7]. The apparent pseudo-first-order rate coefficients for the sulfonation of methyl phenyl sulfate (**4**) were determined from plots of log [**4**] against reaction time, which were found to be linear over *ca.* two half-lives.

### *Apparatus*

The $^1H$ and $^{13}C$ NMR spectra were recorded using Varian XL-100 12 FT and Bruker WM 250 and AC 200 spectrometers; the chemical shifts are relative to virtual internal TMS.

### *$^1H$-coupled $^{13}C$ NMR spectra*

The $^1H$ NMR spectra of the sulfonic acid products obtained in the reactions of 2-chlorophenyl (**10**), 2-methoxyphenyl (**13**) and 2-methylphenyl methanesulfonate (**14**) with 2.0 equiv of $SO_3$ in nitromethane all contained one ABX absorption pattern which can be assigned to either the 4- or 5-sulfonic acid. To discriminate between these two possibilities, $^1H$-coupled $^{13}C$ NMR spectra of the potassium sulfonate products were recorded, the essential data of which are compiled in Table III. The assignments of the $^{13}C$ NMR absorptions are based on the substituent shielding parameters of the Cl, $OSO_2Me$, $SO_3^-K^+$, Me and OMe groups (Table III and ref. 26b).The final structural assignment of the products was made on the basis of the observed multiplicities of the various absorptions, since the $^3J_{C,H}$ coupling constants for $6\pi$-electron aromatic systems are large (7.4 Hz) relative to the $^2J_{C,H}$ and $^4J_{C,H}$ coupling constants (being 1.2 and -1.1 Hz, respectively)[26a]. The $^1H$-coupled $^{13}C$ NMR spectrum of **10**-4-sulfonate will therefore contain two $^3J_{C,H}$ couplings for the C(1) absorption, whereas that of **10**-5-sulfonate will contain two $^3J_{C,H}$ couplings for the C(2) signal. On the basis of the substituent shielding parameters, it can be shown that C(1) of **10**-4-sulfonate will absorb at lower field than C(2) of **10**-5-sulfonate, their calculated values being 149.3 and 123.3 ppm, respectively. Furthermore, $^3J_{C,H}$ coupling will be absent for the C(6) signal of **10**-4- and the C(3) signal of **10**-5-sulfonate, for which the calculated predicted absorptions on the basis of the additivity of substituent shielding parameters are at 123.1 and 129.3 ppm, respectively. In fact, the $^1H$-coupled $^{13}C$ NMR spectrum revealed one absorption with two $^3J_{C,H}$ couplings (of 8.4 and 10.9 Hz) at 145.0 ppm and another, with no $^3J_{C,H}$ coupling, at 123.9 ppm[36], illustrating the presence of **10**-4-sulfonate.

Similarly, the sulfonate products obtained in the reaction of **13** and of **14** with 2.0 equiv of $SO_3$ were assigned as the 5- and 4-sulfonate, respectively.

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