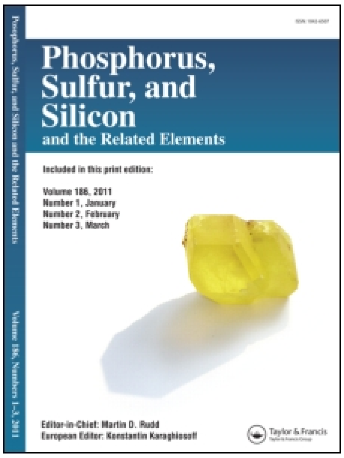

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REVERSIBILITY IN THE SULFONATION OF 3,5-DIMETHOXYPHENOL AND ITS METHANESULFONATE ESTER[1,2]

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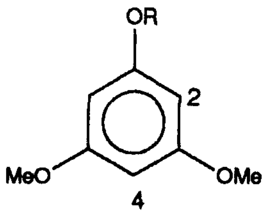
The reactions of 3,5-dimethoxyphenol (**1**) and its methanesulfonate ester (**3**) with sulfur trioxide have been studied. On reaction with 0.9 equiv of SO_3 in nitromethane, **1** gives a 65:35 mixture of its 2-sulfonic acid (**1**-2-S) and **1**-4-S, whereas with 4.0 equiv of SO_3, exclusively **1**-2,6-S_2 is formed. **1**-2,6-S_2 is subsequently converted into its hydrogen sulfate (**2**-2,6-S_2), which in turn rearranges to give the intramolecular anhydride 5,7-dimethoxy-8-sulfobenzo-1,3,2,4-dioxadithiin 2,2,4,4-tetraoxide (**4**). Reaction of **3** with SO_3 in nitromethane leads to a 85:15 mixture of **3**-2-S and **3**-4-S which, upon further reaction, yields initially **3**-2,6-S_2 and eventually **4**. Temperature dependent ^1H NMR evidence suggests that there exist for both **1** and **3** equilibria between the two monosulfonic acids and the substrate.

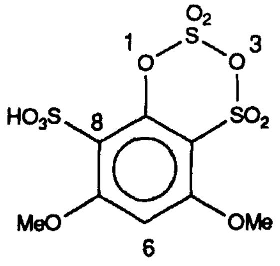
Key words: Sulfur trioxide sulfonation; reversibility in sulfonation; sulfation; 3,5-dimethoxyphenol; 3,5-dimethoxyphenyl methanesulfonate; temperature dependent ^1H NMR; benzo-1,3,2,4-dioxadithiin 2,2,4,4-tetraoxide.

INTRODUCTION

The effects of steric hindrance and of initial hydrogen sulfate formation on the substitution pattern in the sulfonation of phenols with sulfur trioxide have been the objective of recent studies.[3,4] We now report on the SO_3 sulfonation reaction of 3,5-dimethoxyphenol (**1**) of which all the three substituents are activating the substitution at the three hydrogen containing positions, but of which the steric overcrowding in the resulting sulfonic acid products will be substantial. Substrate **1** may undergo initial sulfation with formation of 3,5-dimethoxyphenyl hydrogen sulfate (**2**), which may lead to a variation in the sulfonation product distribution



1 R = H
2 R = SO_3H
3 R = SO_2Me



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upon changing the SO_3 to substrate ratio. In that light, the sulfonation of 3,5-dimethoxyphenyl methanesulfonate (**3**), which could serve as a model compound for **2**, was studied as well.

RESULTS AND DISCUSSION

Upon reaction of 3,5-dimethoxyphenol (**1**) with $\leq$1.0 equiv of SO_3 in nitromethane at either 0 or 25°C and subsequent quenching with an aqueous KOH solution, a mixture of its potassium 2-sulfonate (**1**-2-SO_3^-) and **1**-4-SO_3^- in a (65 ± 2):(35 ± 2) ratio is obtained, whereas upon reaction with $\geq$2.0 equiv of SO_3, **1**-2,6-$(SO_3^-)_2$ is formed as the only disulfonate, even when adding $\geq$2.0 equiv of SO_3 to the reaction mixture obtained on using 0.9 equiv of SO_3. Eventually, as appeared from direct ^1H NMR studies using $C^2H_3NO_2$ as solvent, the **1**-2,6-disulfonic acid (**1**-2,6-S_2) formed is slowly converted into the intramolecular anhydride 5,7-dimethoxy-8-sulfobenzo-1,3,2,4-dioxadithiin 2,2,4,4-tetraoxide (**4**),[5] *via* **2**-2,6-S_2 as intermediate.

There is an apparent discrepancy between the results of the reaction of **1** with 0.9 equiv and with an excess of SO_3 in that the initially formed **1**-4-S cannot lead directly to **1**-2,6-S_2, *i.e.* the only disulfonic acid product formed. Obviously, some kind of isomerization has taken place. This explanation is based on the ^1H NMR observations that, when reacting **1** with 0.8 equiv of SO_3 at −20°C in $C^2H_3NO_2$, the reaction mixture contains a 34:33:33 mixture of **1**, **1**-2-S and **1**-4-S as is apparent from the clearly resolved NMR patterns, while the signals of this mixture at 0°C start to coincide to give, at 25°C, a different pattern (see Figure). These observations lead us to conclude that in the reaction mixture there exist equilibria between **1**-2-S, **1**, **1**-4-S and the two respective intermediary sulfonation σ-complexes of which the various interconverting steps are fast on the ^1H NMR time scale. Upon raising the temperature of the reaction mixture from −20 to 25°C, leaving it there for 22 h, and subsequently rapidly lowering the temperature to −30°C, the mixture was found to contain 24% of **1**, 50% of **1**-2-S and 26% of **1**-4-S, which is thought to be the "frozen" composition of the equilibrium at 25°C.[7] When, on the other hand, the reaction mixture of 25°C is warmed up, the aromatic signals start to coincide again to give, at 90°C, one broad singlet with a high field shoulder (see Figure).

Upon mixing, at −60°C, homogeneous solutions of both **1** and 0.9 equiv of SO_3 in $C^2H_2Cl_2$, a precipitate is formed of most probably the hydrogen sulfate **2**, since this compound according to ^1H NMR is present in the homogeneous reaction mixture at −40 and −20°C for 25 and 20% in addition to **1**, **1**-2-S and **1**-4-S; at temperatures ≥ 0°C, **2** is not present beyond the limit of detection which is 2%. The patterns present in the ^1H NMR spectra of the reaction mixture of **1** with 0.9 equiv of SO_3 in the temperature range of 0 to 25°C are very similar to those for nitromethane as solvent. Upon heating the reaction mixture in $C^2H_2Cl_2$ from −60 to 25°C and lowering the temperature of the resulting homogeneous mixture again to −60°C, the precipitate is formed again. Upon heating from −60 to −40°C, the specific ^1H NMR signals of the hydrogen sulfate **2** reappear. These observations illustrate the reversibility of both the sulfonation and the sulfation. Apparently, the sulfonic acids **1**-2-S and **1**-4-S desulfonate to yield **1** and SO_3, which react together to yield, in part, the hydrogen sulfate **2** in an equilibrium reaction.

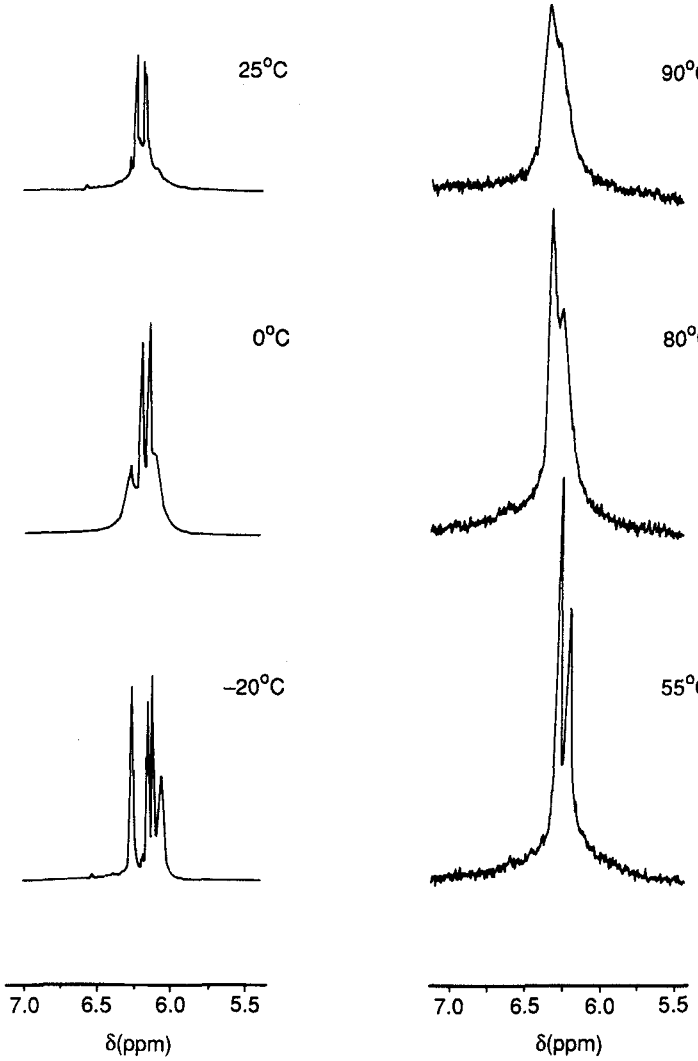

FIGURE Aromatic part of the ^1H NMR spectra of the reaction mixture of 3,5-dimethoxyphenol (**1**) with 0.8 equiv of SO_3 in $C^2H_3NO_2$ at 25°C, recorded at various temperatures.

Related evidence for the reversibility of the sulfonation of **1** comes from the addition of 1-octene (0.4 equiv relative to the substrate) to a matured reaction mixture of **1** with 0.9 equiv of SO_3 in $C^2H_3NO_2$ at 25°C. In an irreversible reaction 2-octene-1-sulfonic acid is formed, illustrating that SO_3 is transferred from the sulfonic acids of **1** to 1-octene to produce the unsaturated sulfonic acid *via* 1,2-octanesultone as intermediate.[8]

The main driving forces for the conversion of **2**-2,6-S_2 into the corresponding intramolecular anhydride benzo-1,3,2,4-dioxadithiin 2,2,4,4-tetraoxide **4** and sulfuric acid are (i) relief of steric strain between the hydrogen sulfate group and one of the sulfonic acid groups of **2**-2,6-S_2 and (ii) the more planar orientation of the

O(1)-SO_2 moiety of the 1,3,2,4-dioxadithiin 2,2,4,4-tetraoxide fragment relative to the benzo moiety of **4**, as compared with the O—SO_3H moiety relative to the phenyl group of **2**-2,6-S_2, leading to an enhanced degree of conjugation between the carbon bonded oxygen and the 8-SO_3H group of **4**, as compared with the 6-SO_3H of **2**-2,6-S_2.

On reaction of 3,5-dimethoxyphenyl methanesulfonate (**3**) with 0.6–2.0 equiv of SO_3 in nitromethane at 0°C, a mixture of **3**-2-S and **3**-4-S is formed in a ratio of (85 ± 2):(15 ± 2); upon reaction with 5.0 equiv of SO_3, **3**-2,6-S_2 is formed as the only product. The ^1H NMR spectra of the reaction mixture obtained on reacting **3** with 0.8 equiv of SO_3 using $C^2H_3NO_2$ at 25°C contain only clearly resolved signals. Apparently, the interconversion of the 2- and 4-sulfonic acids, which is required to explain the formation of **3**-2,6-S_2 as the only disulfonic acid, is slower for **3** than for **1**. As to the product composition, the result of the disulfonation of **3** resembles that of **1**. Upon reaction of **3** with 4.0 equiv of SO_3 at 25°C, the initially formed **3**-2,6-S_2 is also slowly converted into **4**.

TABLE

^1H NMR data of **1**, **3** and their sulfoproducts at 25°C

		δ(ppm, ±0.03)[c,d]					
Compound[a]	Solvent[b]	1	2	3	4	5	6
1	N		6.13	3.86	6.13	3.86	6.13
	W		6.08	3.74	6.08	3.74	6.08
	C[e]			3.60		3.60	
1-2-S	N[f]			3.93	6.21	3.93	6.21
	N[e]			3.88	6.18	3.87	6.14
	C[e]			3.75	5.96	3.68	6.02
	W			3.92	6.27	3.86	6.21
1-4-S	N[f]		6.21	3.93		3.93	6.21
	N[e]		6.28	4.06		4.06	6.28
	C[e]			3.73		3.73	
	W		6.14	3.80		3.80	6.14
1-2,6-S_2	N			4.18	6.60	4.18	
	W			3.99	6.38	3.99	
2	C[e]		6.21	3.91	5.99	3.91	6.21
3	N	3.29	6.58	3.90	6.58	3.90	6.58
3-2-S	N	3.42		4.14	6.75	4.02	6.83
	W	3.44		3.97	6.67	3.92	6.76
3-4-S	N	3.37	6.89	4.10		4.10	6.89
	W	3.43	6.82	3.94		3.94	6.82
3-2,6-S_2	N	3.51		4.27	7.09	4.27	
	W			4.07	6.89	4.07	
4	N			4.32	7.11	4.29	

[a] S stands for SO_3H when $C^2H_3NO_2$ or $C^2H_2Cl_2$ are used as solvent and for SO_3^- when ^2H_2O is used. [b] N, C and W stand for $C^2H_3NO_2$, $C^2H_2Cl_2$ and ^2H_2O, respectively. [c] All values are relative to virtual internal TMS. [d] All the doublets resulting from ortho- and meta-hydrogen couplings have J values of 8–9 and 1.5–2.5, respectively. [e] Values at −20°C. [f] Mean values of the unresolved pattern at 25°C.

From the results of this study the following interesting conclusions may be drawn. First, due to steric overcrowding in the sulfonic acid products of **1** in combination with the high reactivity of the substrate itself, a fast sulfonation-desulfonation equilibrium *via* the sterically less hindered σ-complexes[9] is set up in the reaction of **1** with a slightly deficient amount of SO_3. The overcrowding in the 2,6-disulfonic acid products of **1** and **3** is apparent from the formation of the intramolecular anhydride **4** enforced by relief of steric strain and enhanced conjugation. Second, substitution in between the two methoxy substituents is favoured far less than at the other two, equivalent, positions both for **1** and **3**, probably as a result of larger steric effects. Whether **3** is a satisfactory model compound for **2** remains as yet undecided, as hardly any hydrogen sulfate appears to be formed in the initial stages of the reaction of **1** at 25°C even with 4.0 equiv of SO_3; only at temperatures ≤ -20°C in dichloromethane, **2** appears to be formed.

Our present findings that disulfonic acids are formed in the reaction of **1** and **3** with SO_3 denounce an earlier tentative report on the sulfonation of **1** and **3**.[4]

EXPERIMENTAL

3,5-Dimethoxyphenol (**1**) was obtained commercially and used without further purification. The methanesulfonate **3** was synthesized from **1** and methanesulfonyl chloride.[11]

Sulfonation procedures and analysis. Sulfonation reactions were carried out either in nitromethane as solvent with subsequent aqueous alkaline work-up to determine the sulfonate product composition or, when monitoring the reactions with ^1H NMR, in perdeuterated solvents; both methods have been described elsewhere.[4] The ^1H NMR spectra were recorded on Bruker AC-200 and WM-250 spectrometers. The assignments of the sulfoproducts, based a.o. on the principle of additivity of the —OH, —OMe, —SO_3H, —SO_3^-, —OSO_3H and —OSO_2OSO_2— substituent shifts,[6] are compiled in the Table.

REFERENCES

1. Aromatic sulfonation part 112. For part 111, see ref. 4.
2. For reasons of convenience, the sulfonic acid products have all been numbered as for the starting substrate, except for **4**.
3. H. Cerfontain, A. Koeberg-Telder, H. J. A. Lambrechts and P. de Wit, *J. Org. Chem.*, **49**, 4917 (1984).
4. H. Cerfontain, H. R. W. Ansink, N. J. Coenjaarts, E. J. de Graaf and A. Koeberg-Telder, *Recl. Trav. Chim. Pays-Bas*, **108**, 445 (1989).
5. This type of cyclic sulfonate sulfate anhydride is known to hydrolyse under aqueous conditions to afford the corresponding phenolsulfonic acid quantitatively.[6]
6. H. Cerfontain, N. J. Coenjaarts and A. Koeberg-Telder, *Recl. Trav. Chim. Pays-Bas*, **108**, 7 (1989).
7. Note that the ratio **1**-2-S:**1**-4-S is the same as after aqueous work-up!
8. B. H. Bakker and H. Cerfontain, *Tetrahedron Lett.*, 5451 (1989).
9. It has been outlined that the proton abstraction from sulfonation σ-complexes which lead to overcrowded arenesulfonic acid products is the rate-limiting step.[10]
10. K. Lammertsma and H. Cerfontain, *J. Chem. Soc. Perkin Trans. 2*, 28 (1980); H. Cerfontain, *Recl. Trav. Chim. Pays-Bas*, **104**, 153 (1985).
11. A. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co. Ltd., London, 1970, p. 684.