Sulfonation and sulfation of 1,3-dihydroxybenzene and its methyl ethers in concentrated sulfuric $acid^{\$,\dagger}$

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Abstract. The homogeneous sulfonations of 1,3-dihydroxybenzene (1), its monomethyl (2) and dimethyl ether (3) in concentrated aqueous sulfuric acid at 25°C have been studied and isomer distributions and rate coefficients for the sulfonation of 1-3 and their monosulfonic acids are reported. The initial process, upon dissolution of the reactants, is protonation at C(4) and C(6). The subsequent sulfonation of the symmetrical reactants 1 and 3 yields the 4-sulfonic acids and that of 2 the 4- and 6-sulfonic acids, the ratio of which is 0.8 ± 0.1 at 73.5% H₂SO₄. The sulfonation of the 4-sulfonic acids of 1 (1-4-S) yields a mixture of 2,4- and 4,6-disulfonic acids, that of 2-4-S and 3-4-S yields the 4,6-S₂ and that of 2-6-S gives a mixture of 2,6- and 4,6-S₂. The disulfonic acids 1-2,4-S₂ and 2-2,6-S₂ both slowly isomerize to yield the 4,6-disulfonic acid isomers. At acid concentrations $\geq 82.8\%$ H₂SO₄, the disulfonic acids of 1 slowly yield 1-2,4,6-S₃, whereas those of 2 and 3 are not further sulfonated. The absence of 2-2,4-S₂ from 2-4-S and of 2-2,4,6-S₃ and 3-2,4,6-S₃ is discussed in terms of conformer populations of the precursory sulfonic acid substrates.

Introduction

Following our studies on the sulfonation of 1,2-dihydroxybenzene (catechol) and its methyl ethers in concentrated sulfuric acid¹, we now report on the reactions of 1,3-dihydrobenzene (resorcinol) (1) and its methyl ethers (2 and 3) in the same solvent system. The sulfonation of 1-3 has already been reviewed in ref. 1.

Results

1,3-Dihydroxybenzene (1), its mono- (2) and dimethyl ether (3) have been reacted in a large excess of concentrated aqueous sulfuric acid at 25° C in order to study their sulfonation and sulfation. The product compositions, as a function of the sulfuric acid concentration and reaction time for the three substrates, are collected in Table I. Hydrogen OR^{1} OR^{2} $R^{1} = R^{2} = H$ $R^{1} = H ; R^{2} = Me$ $R^{1} = R^{2} = Me$

sulfates were not found to be present in the reaction mixtures above the limits of the ¹H NMR detection which is thought to be 2%.

The 1,3-disubstituted substrates, upon dissolution in concentrated sulfuric acid, are very rapidly protonated at the 4and 6-positions to yield the corresponding benzenonium ions², the amount of which increases with increasing sulfuric acid concentration^{3,4}. Subsequently, ring sulfonation occurs very predominantly – if not exclusively – t the 4- and

[§] Aromatic sulfonation 104. For part 103, see ref. 1.

[†] For reasons of convenience, the aromatic ring positions of the sulfonic acids, the hydrogen sulfates and the benzenonium ions have been numbered as for the parent substrate. 1,3-Dihydroxy-benzene is called 1,3-benzenediol by *Chem. Abstr.*; 1,3-dihydroxybenzene-4-sulfonic acid is numbered 2,4-1.

Substrate	H_2SO_4 (%, ± 0.5)	Reaction time (ks)	Reaction mixture composition $(\%, \pm 2)^a$							
			Substrate ^b	4-S	6-S	2,4-S ₂	2,6-S ₂	4,6-S ₂	2,4,6-S ₃	
1 ^b	73.5 82.8	2.4 9.6 22.5 86.4 173 1.6 3.1 6.1 9.6	89 69 46 10 	11 31 51 76 69 38 49 47 40 25		1 4 8 4 10 17 18		2 10 23 3 10 26 37 55	1 2	
	88.5	18.0 24.7 1.0 4.5 7.2	50 13 6	19 9 5 1		13 13 16 10		65 28 55 65	3 11 18	
	95.5	1.3 2.7 4.7	27 9 2			10 6 4		50 64 70	13 21 24	
	98.5	0.8 6.5	18			5 -		63 75	14 25	
2 ^ь	73.5	5.4 14.4 21.1 87	79 68 53	9 13 20 30	11 17 21 38		1 2 3 5	3		
	82.8	1.4 4.8 14.2 21.2	81° 45° 16°	16 18 14	9 20 20 18		7 9 9	12 37 49		
	88.5	0.9 2.3 8.8	79 58 18				6 8 12 10	15 34 70 82		
	95.5	1.0 2.2 6.3 8.6	$\begin{array}{cccccccccccccccccccccccccccccccccccc$				6 10 11 9 7	19 36 60 77 86		
	98.5	0.8 6.5 17.6 23.6	24 35 4 7				9 8 6 ≤2	32 81 94 ≥98		
3°	73.5	16.8 ^f 23.2 ^f 87	73 62 22	27 38 67				11		
	82.8	1.0 5.5	91 66	9 24				10		
	88.5	20.8 1.6 5.9	25 87 63	26				49 13 37 78		
	95.5	23.5 1.2 6.6 22.4	91 67 34					9 33 66		
	98.5	0.9 6.7 25.2	80 51 13					20 49 87		

Table I Sulfonation of 1,3-dihydroxybenzene (1), its methyl (2) and dimethyl ether (3) in concentrated sulfuric acid at 25°C.

^a S stands for SO₃H. ^b The unconverted starting materials 1 and 3 were present predominantly as the C(4)-protonated species² and 2 as the C(4)- and C(6)-protonated species. ^c Present for 30% as the C(4)- and C(6)-protonated species. ^{d-e} Substrate species protonated at C(4) and C(6), respectively. ^f Some undissolved starting material was still present.

6-positions. The ratio of formation of the 4- and 6-sulfonic acids from 3-methoxyphenol (2) in 73.5% H₂SO₄ is 0.8 ± 0.1 .

1,3-Dihydroxybenzene-4-sulfonic acid (1-4-S) yields the 2,4and 4,6-disulfonic acids, of which the former slowly isomerizes to yield the latter. At the higher sulfuric acid concentrations, some 2,4,6-trisulfonic acid is eventually formed. 3-Methoxyphenol-4-sulfonic acid (2-4-S) yields 2-2,4-S₂ and 2-4,6-S₂, whereas 2-6-S only yields 2-4,6-S₂. No further ring sulfonation of 2-2,4- and 2-4,6-disulfonic acid is observed, but again, as appears from the decrease in the $2,4-S_2/4,6-S_2$ ratio with increasing reaction time, the 2-2,4-S₂ isomerizes to yield the 4,6-isomer.

1,3-Dimethoxybenzene-4-sulfonic acid (3-4-S) yields only 3-4,6-S₂ and no further sulfonation was observed.

The results obtained with the methoxy-containing reactants 2 and 3 clearly show that (i) no sulfonic acid products are formed which have two sulfo groups ortho to the same methoxy substituent and (ii) no sulfonic acids are formed in which a given sulfo group has two ortho methoxy groups. The sulfonation reactions were found to follow first-order kinetics with respect to the aromatic substrates. The (pseudo)-stoichiometric first-order rate coefficients $_{ps}k_{stoich}$ are given in Table II. For a given reactant, the rate coefficients increase with increasing sulfuric acid concentration and, for a given sulfuric acid concentration, they decrease in the order 1 > 2 > 3.

Table II First-order rate coefficients for the homogeneous sulfonation of 1-3 and 1-4-sulfonic acid in sulfuric acid at 25° C.

$[\begin{array}{c} H_2 SO_4 \\ (\%, \pm 0.5) \end{array}]$	$10^6 \cdot {}_{ps}k_{stoich} (s^{-1})$							
	1	2	3	1-4-S ^a				
73.5 82.8 88.5 95.5 98.5	$\begin{array}{r} 36 \pm 2 \\ 380 \pm 10 \\ 630 \pm 130 \\ 1000 \pm 200 \\ 2300 \pm 800 \end{array}$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	51 ± 10				

^a S stands for SO₃H.

Discussion

Monosulfonation of 1-3

The initial process, upon dissolving the reactants 1-3 in concentrated aqueous sulfuric acid, is protonation at C(4) and C(6). With 3-methoxyphenol (2), the degree of protonation is significantly less at C(4) than at C(6). This ob-



Scheme 1. Planar conformations of 3-methoxyphenol (2).

servation is opposite to that which would be predicted on the basis of the *para* σ^+ values of the OH (-0.92) and OMe (-0.78) substituents⁵. The ratio of protonation at the 4- and 6-position, is apparently determined mainly by the *ortho* substituents. There is no evidence for phenyl hydrogen sulfate formation with 1 and 2.

The subsequently observed process is ring sulfonation. 1,3-Dihydroxybenzene (1) yields very predominantly the 4-sulfonic acid, the degree of 2-substitution being 4% at most⁶. 3-Methoxyphenol (2) yields very predominantly the 4- and 6-sulfonic acids, the degree of 2-substitution being <5%. The sulfonation of 3 yields only the 4-sulfonic acid⁶. The degree of 2-substitution for 1-3 is far less than expected on the basis of additivity of the substituent effects⁷. For 2, the observed ratio of 4- to 6-sulfonic acid of 0.8 \pm 0.1 for 73.5% H₂SO₄ compares with the calculated ratio of 0.6. The very low degree of 2-substitution with 1-3 may be explained by specific solvation of the hydroxy and possibly of the methoxy groups.

Important are the differences in reactivity of the various conformers of 1-3 (see Scheme 1) towards sulfonation. In view of the stabilizing conjugative effects of the OH and OMe substituents, only the planar conformations are considered. For steric reasons, the most reactive conformer of 1-3 for sulfonation at position 2 will be a and the least reactive c. The absence of any 3- (and 6-)substitution in both the sulfuric acid¹ and sulfur trioxide⁹ monosulfonation of 1,2-dimethoxybenzene and the absence of any disulfonic acid products having two sulfo groups ortho to one and the same methoxy group in the present study infers that 3a, for example, may only be sulfonated at the 2-position, 3b only at C(6), 3c at both C(4) and C(6) and 3d at C(4). Since the steric hindrance by the hydroxy hydrogen is far less than that caused by the methoxy methyl, 2a and 2b may, in principle, be sulfonated at C(2) and C(6), and the conformers 2c and 2d at C(4) and C(6). For 1 there is no steric prevention of substitution at C(2), C(4) and C(6) for any of the four conformers.

Sulfonation of the sulfonic acids of 1-3

1,3-Dihydroxybenzene-4-sulfonic acid (1-4-S), upon further sulfonation, yields the 2,4- and 4,6-disulfonic acids. From the dependence of the product composition on the reaction time (Fig. 1), it appears that the 1-2,4-S₂ isomerizes slowly to 1-4,6-S₂. The latter acid is eventually slowly sulfonated to yield 1-2,4,6-S₃.

The initial ratio of sulfonation at the 2- and 6-positions of 1-4-S increases from 0.5 to ≈ 1.0 upon varying the sulfuric acid concentration from 73.5 to 82.8% H₂SO₄ (cf. Fig. 1). The variation in f_2/f_6 is ascribed to the change-over in sulfonation entity from H₃SO₄⁺, at the lower sulfuric acid concentrations, to H₂S₂O₇ at the higher ones^{8,10}. A similar variation in the isomer ratio with the sulfuric acid concentration is observed with 4-methoxyphenol¹¹.

The formation of the monosulfonic acids of 3-methoxyphenol (2) together with their sulfonation are shown in Scheme 2. Of the disulfonic acids, only the 2,6- and 4,6-isomers are present and not the 2-2,4-isomer. However, 1,3-dihydroxybenzene (1) yields 1-2,4-S₂ as one of the reaction products (vide supra). The absence of 2-2,4-S₂ is therefore ascribed to the presence of the methoxy methyl in 2-4-S. This sulfonic acid, due to the large steric requirements of the SO₃H group, has only two stable conformations, viz. 2c-4-S and 2d-4-S (cf. Scheme 1), the torsion angle around the C-OMe bond in the less stable 2a-4-S and 2b-4-S conformers being ca. 60°, as estimated from Catalin Stuart space-filling molecular models. Sulfonation of the two stable conformers 2c-4-S and 2d-4-S both yield 546



Fig. 1. Sulfonation of 1,3-dihydroxybenzene (1) in 82.8% H₂SO₄ at $25^{\circ}C$.

only the 4,6-disulfonic acid, the formation of which – even with 2d-4-S – will not encounter much steric hindrance, since the sulfonation at the 2-position is very severely hindered by the 3-methoxy methyl which is in the plane of the benzene ring. The absence of any 2-2,4,6-trisulfonic acid is now understandable since (*i*) the stable conformers of the 4,6-disulfonic acid are 2c-4,6-S₂ and 2d-4,6-S₂, which refute sulfonation at the 2-position because of steric hindrance by the 3-OMe methyl, and (*ii*) the stable conformers of the 2,6-disulfonic acid will be 2a-2,6-S₂ and 2b-2,6-S₂, of which the 4-position is blocked for sulfonation by the 3-OMe methyl.

The 3-methoxyphenol-2,6-disulfonic acid is unstable and gradually isomerizes to the 4,6-disulfonic acid, as appears from the decrease in the $2,6-S_2/4,6-S_2$ ratio with increasing reaction time. In view of the conformational explanation given for the non-formation of the 2,4,6-trisulfonic acid, the isomerization of the 2,6- into the 2,4-disulfonic acid is thought to proceed by initial desulfonation to the 6-sulfonic acid and subsequent sulfonation to the 4,6-disulfonic acid. Sulfonation of 1,3-dimethoxybenzene (3) yields only the 4-sulfonic acid. This acid, as with 2-4-S, yields, upon further sulfonation, exclusively 3-4,6-S₂ due to sulfonation of the



Scheme 2. Sulfonation of 3-methoxyphenol (2) and its sulfonic acids.

conformer 3c-4-S, which only allows sulfonation at the nonsterically hindered position. Further sulfonation of the 4,6-disulfonic acid does not occur, since the sulfonation of the only occurring conformer $3c-4,6-S_2$ (cf. Scheme 1) at C(2) is sterically hindered by the two methyl groups.

Species undergoing sulfonation

The general aspects of the sulfonation of 1-3 and their sulfonic acids are in essence very similar to those of the 1,2-isomers¹ and the halogenated phenols and anisoles¹² which were discussed previously. In contrast to the corresponding 1,2-isomers – which are in part protonated on oxygen – the presently reported 1,3-isomers 1-3 were found to be ring-protonated at C(4) and C(6) in the sulfuric acid reagent. However, no ring protonation was observed for the sulfonic acids of 1-3, probably as a result of the strong electron-withdrawing effect of the additional sulfo group, the effect of which is both inductive and mesomeric in nature^{13,14}.

The oxygen- and carbon-protonated species, as well as the sulfated species, will be far less reactive than the corresponding substrate species $C_6H_4OR^1OR^2$ and $C_6H_3OR^1OR^2SO_3^-$ (R¹ = H, Me; R² = H, Me) proper^{7,15}. The latter species are therefore the ones in fact being sulfonated.

The differences between the apparent sulfonation rates of 1-3 on the one hand and of their monosulfonic acids on the other are far less (cf. Table II and ref. 16) than would be expected on the basis of the strong deactivating effect of the SO_3H substituent, the latter being estimated to be 3×10^{-8} ¹³. This may be explained by presuming that the degree of C protonation is far less for the sulfonic acids than for the starting substrates. In fact, for the sulfonic acids of 1-3, there is no direct ¹H NMR evidence for C protonation.

Experimental

The substrates were commercial, high-quality compounds which were used as such. The reaction procedures and the method of analyses of the sulfuric acid reaction mixtures were as previously described¹. In concentrated aqueous sulfuric acid, the presently

Substrate	H ₂ SO ₄ (%)	Protonation site	δ (ppm) at C(x)						
			1	2	3	4	5	6	
1	74 95 98	4 4 4		6.60 6.55 6.52		4.03 3.99	7.36 7.65 7.62	6.5–7.1 6.96 6.94	
2	74 95	4 6 4		6.57 6.57 6.57	3.99 3.99 4.33	6.1-7.2 3.99	7.37 7.37 7.53	6.1–7.2 6.91	
	98	6 4 6		6.52 6.55 6.57	4.21 4.32 4.20	6.97 3.97 6.95	7.68 7.50 7.65	3.99 6.90 3.97	
3	74 89 98	4 4 4	4.10 4.35 4.25	6.70 6.57 6.49	4.10 4.44 4.37	4.06 3.96	7.45 7.64 7.53	6.3-6.9 6.99 6.91	

Table III ¹H NMR data of the cations formed from 1,3-dihydroxybenzene (1) and its mono- (2) and dimethyl ether (3) in sulfuric acid as solvent.

Table IV ¹H NMR data of the sulfo products of 1,3-dihydroxybenzene and its methyl ethers in sulfuric acid as solvent.

Benzene	H ₂ SO ₄ (%)	δ (ppm, ± 0.05) ^b at C(x)						
substituents ^a		1	2	3	4	5	6	
1,3-(HO) ₂ -4-S	74		6.66			7.73	6.70	
1,3-(HO) ₂ -2,4-S ₂	74					7.91	6.76	
1,3-(HO) ₂ -4,6-S ₂	74		6.79 6.86			8.21 8.35		
1,3-(HO) ₂ -2,4,6-S ₃	83 95-98					8.46 8.56		
1-HO-3-MeO-4-S	74		6.70 6.71	4.01		7.72	6.70 6.71	
1-HO-3-MeO-6-S	74		6.53 6.71	3.93 4.03	6.53 6.71	7.75		
1-HO-3-MeO-2,6-S ₂	74 89–98			3.88 4.12	6.90	8.17		
1-HO-3-MeO-4,6-S ₂	74 83–98		6.84 6.92	4.06 4.15		8.25 8.33		
1,3-(MeO) ₂ -4-S	74	4.01	6.69 6.79	4.05 4.10		7.82 7.87	6.72 6.85	
$1,3-(MeO)_2-4,6-S_2$	83-98	4.22	6.91	4.22	ļ	8.35	0.00	

^a S and SO stand for SO₃H and OSO₃H, respectively. ^b All the doublets resulting from *ortho-* and *meta-*hydrogen coupling have J values of 7.5-9.5 and 1.5-2.5 Hz, respectively.

studied *meta*-disubstituted reactants are protonated at the benzene ring prior to being sulfonated. The relevant ¹H NMR data of the benzenonium ions and the sulfo products are collected in Tables III and IV, respectively.

References and Notes

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- ⁶ The upper limits of the degree of 2-substitution of 1-3 have been determined presuming that the initial amount of 1-2.4- S_2 ,

2-2,6-S₂ and 3-2,4-S₂ is formed solely from 1-2-S, 2-2-S and 3-2-S, respectively. In actual fact, part of the 1-2,4-S₂ and 2-2,6-S₂ will result from 1-4-S and 2-6-S, respectively, whereas 3-2,4-S₂ is not formed above the limits of detection which is thought to be 2%.

- ⁷ The ratio of 2- to 4-substitution of 1 and 3 was calculated, on the basis of the principle of additivity of the substituent effects, using the equations f_2/f_4 (1) = ${}^{\rm HO}f_o/2 \cdot {}^{\rm HO}f_p$ and f_2/f_4 (3) = ${}^{\rm MeO}f_o/2 \cdot {}^{\rm MeO}f_p$ and the reported OH and OMe partial rate factors⁸, to be 0.23 and 0.14, respectively. Similarly, the ratio of 2-/4-/6-substitution for 2 was calculated using the equation $f_2/f_4/f_6 = ({}^{\rm HO}f_o \cdot {}^{\rm MeO}f_o)/({}^{\rm HO}f_p \cdot {}^{\rm MeO}f_o)/({}^{\rm HO}f_o \cdot {}^{\rm MeO}f_p)$ to be 15:32:53.
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- ¹⁶ The ¹H NMR spectra of the reaction mixtures of 1-3 in sulfuric acid containing more than 88.5% H₂SO₄ only show the presence of the protonated substrate species and disulfonic acids, illustrating that the apparent rates of sulfonation of the monosulfonic acids far exceed those of the protonated substrates species.