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Sulfonation of 2- and 3-Methylphenol

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The product composition in the sulfonation of 2- and 3-methylphenol was studied by means of HPLC. The sulfonating reagents were sulfuric acid and chlorosulfonic acid. In the synthesis procedures the ion-pair technique was used for separation of the isomers. A chemical shift factor for the $-OSO_3^-$ group in ^{13}C NMR calculations is given.

The sulfonation of phenolic compounds has been studied by several authors and by several methods.[1,2] The main problem in these studies was the separation and analysis of the reaction mixture. A common method of analysis was spectrophotometric measurements of the mixture of sulfonic acids, while the phenyl hydrogen sulfates and the phenol were studied separately.[2a] One investigator [3] used an indirect method to elucidate a complex mixture, bromodesulfonation and analysis of the brominated products. Others [4] separated the compounds in the mixture by paper chromatography, but selective measurements of each component were difficult to obtain by these methods.

RESULTS AND DISCUSSIONS

A more convenient method for the analysis of the reaction mixture is reversed phase HPLC.[5] With this technique each component can be measured selectively and a rather complex reaction mixture can be studied in the same solution without partial work-up procedures for different classes of compounds. The high sensitivity of the method makes it possible to study even very low concentrations of by-products.

Since some of the results from earlier studies [6,7] on the sulfonation of 2-methylphenol were confusing and incomplete, we were interested in studying these reactions and therefore repeated the sulfonations and analysed the reaction mixtures by HPLC. Our results are given in Table 1.

We wish to draw special attention to the following points: Tatibouet *et al.*[7] presented a method in which they claimed 87 % sulfonation in the 5-position of 2-methylphenol giving *2* in a one-hour reaction at 150 °C. We found only 9.0 % of the isomer (*2*) but 66.8 % of the disulfonic acid (*4*), which seems more plausible under these conditions.

In another experiment they reported 90—100 % sulfonation in the 4-position and no substitution in the 6-position at −10 °C, 24 h. Our results do not agree with these findings. To ascertain a complete conversion of the 2-methylphenol to sulfonic acids, we extended the reaction time to 140 h. In agreement with our expectations we found a rather high degree of sulfonation in the 6-position. This must have been formed initially, because a rearrangement of the 4-sulfonated isomer seems very improbable under these conditions.

Muramoto [8] obtained results more similar to ours in some cases, but his reaction conditions were much too different from ours ($HgCl_2$-catalyst and less than equivalent amount of sulfuric acid) to be discussed in connection with this work.

As a complement to sulfonation in sulfuric acid, we wish to present the product formation from a method similar to Spryskov's, [2b] *viz.* sulfonation with chlorosulfonic acid in dichloromethane at low temperature. This gives an almost 1:1 ratio of products sulfonated in the 4- and 6-positions and practically none in the 3- and 5-positions. In this reaction 2-methylphenyl hydrogen sulfate is the main product

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Table 1. The product composition[a] in the sulfonation of 2-methylphenol.

Comp. No.	R in R–Ph	93 % H_2SO_4 100 °C, 4 h		100 % H_2SO_4 150 °C, 1 h		20 to 60 °C, 12 h		−10 to −20 °C, 140 h[b]		$ClSO_3H$ −20 °C, 6 h
		Publ.[6]	Found	Publ.[7]	Found	Publ.[7]	Found	Publ.[7]	Found	Found
1	1-SO_3H-2-OH-3-CH_3	–	3.0	–	0.1	–	4.2	–	25.3	32.5
2	1-SO_3H-3-OH-4-CH_3	–	0.5	87	9.0	25	0.7	–	1.0	<0.1
3	1-SO_3H-3-CH_3-4-OH	85	83.1	18	20.0	75	57.2	>90	61.7	35.4
4	1,3-di-SO_3H-4-OH-5-CH_3	0.5	9.1	–	66.8	–	36.3	–	7.9	0.9
5	1-OSO_3H-2-CH_3	–	<0.1	–	0.7	–	0.1	–	1.0	17.4
6	1-SO_3H-3-CH_3-4-OSO_3H	–	–	–	1.5	–	1.0	–	1.0	5.0
7	1-OH-2-CH_3	–	2.8	–	<0.1	–	<0.1	–	1.5	8.3
	Unidentified products[c]	–	≤1.5	–	≤2.0	–	≤0.5	–	≤0.5	≤0.5

[a] Products in per cent. [b] Published 24 h. [c] There are 1–3 unidentified products and the most abundant is probably the sulfuric acid ester of *4*.

initially formed. It is slowly converted to the products sulfonated in the 4- and 6-positions. The content of the ester is thus a function of the reaction time and conditions and can be brought to a very low value if the reaction time is increased or the temperature raised at the end of the reaction. From other work on alkylphenols [9] sulfonated in the same way, we know that such variations in the conditions will not appreciably change the *ortho*:*para* ratio. Of the methods presented, the sulfonation with chlorosulfonic acid thus gives the highest proportion of the 6-sulfonated isomer.

Another remarkable fact is that the disulfonic acid (*4*) was present in only 0.9 %, while the ester (*6*) occurred in 5 %, which is in direct contrast to the results from sulfonation in sulfuric acid at −10 °C. This difference can be explained in a way similar to that given above, since we know that the ester (*6*) can be transformed to *4*.[9] With an extended reaction time, one could thus expect that the ratio of these products should approach that observed in the reaction with sulfuric acid.

The earlier studies [8b,10] on the sulfonation of 3-methylphenol were also incomplete. We therefore reinvestigated the reaction of 3-methylphenol with chlorosulfonic acid and our results are given in Table 2. In this case the two products sulfonated in the 2- and 6-positions *8* and *9*, occurred in a 3:1 ratio. As far as we know, compound *9* has not been reported previously except in Ref. 11. Comparing the sulfonation procedures in Table 1

Table 2. Product composition[a] in the sulfonation of 3-methylphenol with chlorosulfonic acid.

Comp. No.	R in R–Ph	$ClSO_3H$ −15 °C in CS_2 Publ.[10]	−20 °C in CH_2Cl_2 Found
8	1-SO_3H-2-OH-4-CH_3	0	30.9
9	1-SO_3H-2-OH-6-CH_3		11.0
10	1-SO_3H-2-CH_3-4-OH	15	40.4
11	1,3-di-SO_3H-4-OH-6-CH_3		1.4
12	1-OSO_3H-3-CH_3	50	6.4
13	1-SO_3H-2-CH_3-4-OSO_3H		6.5
14	1-OH-3-CH_3		2.5
	Unidentified products[b]		≤1

[a] Products in per cent. [b] There are 3 unidentified products and the most adundant is probably the 1,3-di-SO_3H-4-OH-2-CH_3 compound.

Table 3. NMR data.

Compound *1*

^1H δ 7.54 (1 H, d, J 7.6 Hz), 7.29 (1 H, d, J 7.2 Hz,), 6.91 (1 H, dd, J 7.6 Hz), 2.20 (3 H, s). ^{13}C δ 151.3 (C2), 135.2 (C4), 127.8 and 127.4 (C1,C3), 125.5 (C6), 120.7 (C5), 16.0 (Cα).

Compound *2*

^1H δ 7.29 (3 H, s), 2.25 (3 H, s). In (CD_3) CO 7.66 (1 H, d, J 1.4 Hz), 7.15 (1 H, dd, J 7.6 and 1.4 Hz) 6.94 (1 H, d, J 7.7 Hz). ^{13}C δ 154.6 (C3), 141.8 (C1), 132.1 (C5), 129.7 (C4), 118.1 (C6), 112.6 (C2), 16.0 (Cα).

Compound *3*

^1H δ 7.54, 7.44, 7.40 (2 H, m), 6.79 (1 H, d, J 8 Hz), 2.24 (3 H, s). ^{13}C δ 157.2 (C4), 135.0 (C1), 129.0 (C2), 126.2 (C3), 125.5 (C6), 115.5 (C5), 16.1 (Cα).

Compound *4*

^1H δ 7.87 (1 H, d, J 2.8 Hz), 7.53 (1 H, d, J 2.8 Hz), 2.14 (3 H, s). ^{13}C δ 168.7 (C4), 131.9 and 128.7 (C1,C3), 130.2 (C6), 124.8 (C2), 124.1 (C5), 17.8 (Cα).

Compound *5*

^1H δ 7.23 (3 H, m), 2.30 (3 H, s). ^{13}C δ 150.4 (C1), 132.2 (C2 and C3), 127.8 and 127.0 (C4,C5), 122.2 (C6), 16.3 (Cα).

Compound *6*

^1H δ 7.74, 7.64, 7.62, 7.53, 7.42 (3H), 2.37 (3H, s). ^{13}C δ 152.5 (C4), 140.8 (C1), 133.1 (C3), 129.3 (C2), 125.2 and 122.3 (C5,C6), 16.5 (Cα).

Compound *8*

^1H δ 7.58 (1 H, d, J 8.4 Hz), 6.82 (2 H, m), 2.28 (3 H, m). ^{13}C δ 153.5 (C2), 145.5 (C4), 128.2 (C6), 125.5 (C1), 121.7 and 118.9 (C3,C5), 21.2 (Cα).

Compound *9*

^1H δ 7.25 (1 H, dd, J 8.1, 7.9 Hz), 6.87–6.73 (2 H, m), 2.55 (3 H, s). ^{13}C δ 153.9 (C2), 139.0 (C6), 133.2 (C4), 125.6 (C1), 124.2 (C5), 116.0 (C3), 20.9 (Cα).

Compound *10*

^1H δ 7.71 (1 H, d, J 8.3 Hz), 6.79, 6.68, 6.64 (2 H, m), 2.54 (3H, s). ^{13}C δ 158.8 (C4), 139.4 and 133.7 (C1,C2), 129.8 (C6), 119.2 (C3), 112.9 (C5), 20.4 (Cα).

Compound *11*

^1H δ 8.15 (1 H, s), 6.96 (1 H, s), 2.57 (3 H, s). ^{13}C δ 156.0 (C6), 143.2 (C4), 133.4 (C3), 127.9 (C2), 125.6 (C2), 121.0 (C6), 20.3 (Cα).

Table 3. Continued.

Compound *12*

^1H δ 7.33–7.09 (3 H, m), 2.35 (3 H, s). ^{13}C δ 151.2 (C1), 140.5 (C3), 129.7 and 127.0 (C4,C5), 122.2 (C2), 118.9 (C6), 21.6 (Cα).

Compound *13*

^1H δ 7.91 (1 H, d, J 7.8 Hz), 7.29, 7.20, 7.17 (2 H, m), 2.62 (3H, s). ^{13}C δ 153.8 (C4), 139.4 and 139.1 (C1,C2), 129.4 (C6), 125.1 (C3), 118.9 (C5), 20.4 (Cα).

and 2, one can see that the two phenols follow the same reaction pattern. In the case of 2-methylphenol the degree of conversion was lower, probably due to experimental differences since the reactions were not performed on the same day and the reagent is very sensitive towards humidity.

EXPERIMENTAL

The starting materials in the experiments were purified by distillation and the dichloromethane was dried over molecular sieves. The reference compounds *1*–*6* and *8*–*13*, used in the HPLC analysis, were tested for water content by the Karl Fischer method and the absence of sulfate and chloride ions was established by precipitation tests with $BaCl_2$ and $AgNO_3$. The structure of the reference compounds was established by ^1H and ^{13}C NMR analysis.

The NMR measurements. ^1H NMR (79.54 MHz) and ^{13}C NMR (20 MHz) were recorded on a Varian CFT 20 instrument using D_2O as solvent and sodium 3-trimethylsilyltetradeuteriopropionate and dioxane, respectively, as internal standards (Table 3).

The assignments in the ^{13}C spectra were based on comparison with calculated shift-values,[13] together with the fact that carbon atoms carrying a substituent give peaks with strongly reduced intensities. The found and calculated values were coincident and had a standard deviation of 1.92 ppm. One value (C4 in *4*) was excluded, however, because it deviated as much as 11 ppm from the calculated value. In this case there was no problem with the assignment, because the distance to the nearest peak was 36.8 ppm. Chemical shift factors for $-OSO_3^-$ group were not available and they were therefore calculated from measurements on compounds *8*, *12*, phenyl hydrogen sulfate and 2-isopropylphenyl hydrogen sulfate giving $Z_1 = 22.8$, $Z_2 = -6.5$, $Z_3 = 2.0$ and $Z_4 = -1.6$.

The HPLC analysis. A portion of the reaction mixture, buffered to pH 6.5 and diluted with mobile phase, was separated on a 150 × 4.5 mm column using LiChrosorb RP8, d_p 5 or 10 μm, as stationary phase. The mobile phase was 0.01 M tetraethylammonium hydrogen sulfate in water-methanol 9:1, pH 6.5. A Cecil 212 UV-spectrophotometer was used as detector at 212 nm. Quantitation was based on peak height measurements and comparisons with each reference compound *1–14*. (A detailed description of the procedure will be published [5]).

Sulfonation of 2- and 3-methylphenol with chlorosulfonic acid. Of the appropriate methylphenol 3.6 g, 33 mmol, were dissolved in 20 ml of dichloromethane in a three-necked flask and the solution was cooled to −20 °C. Under magnetic stirring, 4.3 g, 36.7 mmol, of chlorosulfonic acid, dissolved in 5 ml of dichloromethane, was added dropwise. The temperature was kept at −20 °C during the addition and then the reaction flask was placed in a cryostat for 6 h. After that time, the reaction mixture was poured into a chilled solution of 4.7 g, 72 mmol, of potassium hydroxide in 20 ml of water and the pH was rapidly adjusted to 7. The organic layer was separated and the aqueous phase extracted twice with dichloromethane. The combined organic layers were washed once with water to compensate for incomplete separation and then dried over sodium sulfate, diluted to 100 ml and analysed for methylphenol content by means of GLC. The combined aqueous phases were diluted to 50 ml and analysed by HPLC.

Preparation of reference compounds 1, 3, 8, 9 *and* 10. The sulfonic acids were prepared by the same procedure as above, but the work-up procedure was selected to separate the desired isomers. To obtain the isomers sulfonated *ortho* to the OH-group we used the ion-pair extraction method given in Ref. 11. The potassium salts of compound *8* and *9* were separated by crystallization from water and ethanol, respectively.

When the 2- and 6-sulfonated isomers had been completely extracted from the reaction mixture, it was possible to obtain a salt of the appropriate 4-sulfonated products by conventional methods, *viz.* neutralization of the aqueous phase with potassium hydroxide and recrystallization from methanol until no sulfate or chloride ions could be detected.

Preparation of disulfonic acids 4 *and* 11. The method given in Ref. 7 with 100 % sulfuric acid at 150 °C was used. The reaction mixture was poured into ice water, neutralized with potassium hydroxide and purified by crystallization from a water–ethanol mixture.

Preparation of sulfonic acid 2. From the nitration of 4-methylbenzenesulfonic acid and catalytic hydrogenation of the nitro compound, the potassium salt of 3-amino-4-methylbenzenesulfonic acid was obtained. This salt, 6.75 g, 30 mmol, was suspended in 65 ml of 1 M sulfuric acid and the suspension was diazotizated at 10–15 °C with 2.2 g, 34 mmol, of sodium nitrite dissolved in 10 ml of water. After 30 min, when the sulfonate had dissolved, the mixture was poured into a solution of 2.5 ml of conc. sulfuric acid in 15 ml of water at 95 °C. After another 30 min at 50 °C the mixture was cooled and 9 g, 60 mmol, of *N,N*-diethylaniline was added. Extraction with 3 × 50 ml of 1,1,2,2-tetrachloroethane was then performed in order to extract the product as an ion pair from the sulfuric acid phase. To the organic layer, 20 ml of water was added and the pH was adjusted to 6.5 with 1 M potassium hydroxide. The aqueous phase was separated and washed twice with dichloromethane and then evaporated, yielding 6 g of the crude potassium salt. This was recrystallized three times from the methanol:ethanol mixture giving 1.8 g pure product.

Preparation of sulfuric acid esters 5, 6, 12, 13. A general procedure is given in Ref. 12.

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