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A ^{13}C NMR Study of the Protonation of 3,5-Dihydroxybenzoic Acid in Aqueous Sulfuric Acid

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The protonation parameters in the Cox–Yates treatment pK_{BH^+} = 3.45 ± 0.28 and m^*=0.34 ± 0.06 have been determined by ^{13}C NMR spectroscopy for 3,5-dihydroxybenzoic acid in sulfuric acid–water mixtures.†

Quantitative data on the basicity of phenolic compounds are rather limited.[1] This is due probably to two factors: (i), many phenolic compounds are rapidly sulfonated in aqueous sulfuric acid solutions;[2,3] and (ii), the solubility of substituted phenolic compounds is, as a rule, insufficient for protonation studies by NMR spectroscopy.

The ^{13}C chemical shifts (δ) of 3,5-dihydroxybenzoic acid (3,5-DBA) in water–sulfuric acid mixtures are presented in Table 1. It is evident that the chemical shifts of all the carbon atoms present are changed when 3,5-DBA becomes protonated in concentrated sulfuric acid solutions. In this case the chemical shifts of C–O, C–4 and C–2,6 are moved to lower field by 7.4, 4.4 and 3.2 ppm, respectively. The case is opposite for C–1, C–3 and C–5: the protonation of 3,5-DBA causes the chemical shifts to move

Table 1 Chemical shifts (δ) of 3,5-dihydroxybenzoic acid in aqueous sulfuric acid.

%H_2SO_4	δ (ppm)				
(w/w)	C–O	C–1	C–2,C–6	C–3,C–5	C–4
O^a_{cal}	173.5[b]	132.5[a]	110.4[a]	157.2[a]	108.4[a]
O_{exp}	171.5	133.9	109.8	158.1	108.6
51.2	171.5	132.5	110.9	157.5	109.9
56.0	171.5	132.4	111.1	157.3	110.0
60.4	171.8	132.2	111.1	157.1	110.1
64.4	172.0	132.0	111.4	156.9	110.4
69.5	172.5	131.8	111.7	156.6	110.5
70.2	172.6	131.7	111.8	156.5	110.7
75.3	173.2	131.3	112.3	156.3	111.3
80.5	174.4	131.3	113.2	155.8	112.2
83.6	175.2	130.1	113.4	155.9	112.6
84.9	175.0	130.1	113.3	155.8	112.4
86.3	175.9	129.7	113.6	156.2	113.0
87.8	176.1	129.6	113.8	155.9	113.0
90.2	177.0	128.9	113.8	155.4	–
92.2	176.8	—	113.7	156.3	—
93.7	178.3	128.0	—	—	–
96.6	178.8	—	—	—	–
98.4	178.8	—	—	—	–

[a] The assignment of chemical shifts to the carbon atoms: the calculated chemical shifts, based on the equation and increments given by D. F. Ewing in ref. 10. [b] The chemical shift for ^{13}C in the -COOH groups of benzoic acid, refs. 11 and 12.

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† *General experimental details. Materials.* 3,5-DBA from MERCK was used as supplied. Sulfuric acid (Sojuzreaktiv, Moscow), analytically pure grade, was used as supplied. The sulfuric acid concentration was determined by titration with Na_2CO_3. All the solutions were prepared by diluting the concentrated sulfuric acid with distilled water (the weight method was used).

Solutions of 3,5-DBA were prepared by dissolving it in aqueous sulfuric acid. The concentrations of 3,5-DBA were 0.1–1.5% (w/w) due to its solubility.

The ^{13}C NMR spectra were run on a Bruker AC-200 spectrometer operating in the pulsed Fourier transform mode. The spectra were taken with broad-band proton decoupling. Due to the poor solubility and line broadening we needed *ca.* 20000 scans (a 12 h spectrometer time) in order to obtain a good spectrum. 3,5-DBA with a natural abundance of ^{13}C was used. The chemical shifts presented in Table 1 were measured relative to the tetraethylammonium ion (TEA^+). The chemical shifts of the α-carbon (δ = 53.1 ppm) of TEA^+ does not change more than 0.2 ppm with increasing acid concentration up to 64% H_2SO_4.[9] The chemical shifts of 3,5-DBA as well as that of TEA^+ in water were measured relative to dioxane (δ = 67.8 ppm).

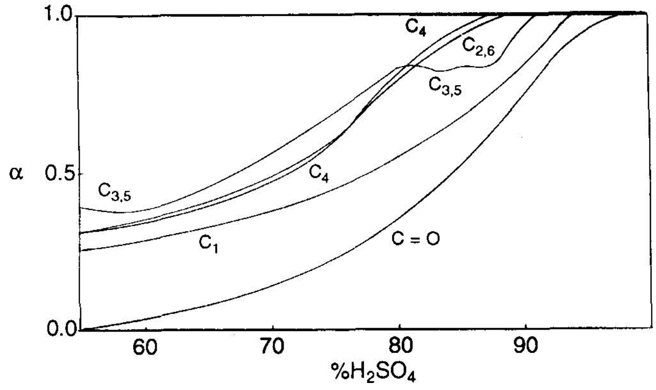

Fig. 1 Protonation degree α for different carbon atoms in 3,5-dihydroxybenzoic acid *vs.* %H_2SO_4 (w/w). In water α is set to be equal to 0.0.

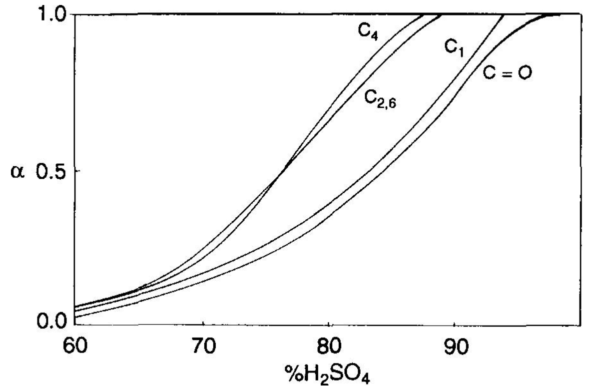

Fig. 2 Protonation degree α for different carbon atoms in 3,5-dihydroxybenzoic acid *vs.* %H_2SO_4 (w/w). α is set to be α = 0.0 in 56%H_2SO_4, *i.e.* the strong H-bond formation in the region of 0–56%H_2SO_4 has been eliminated.

towards higher field by 5.9 and 2.7 ppm, respectively. A remarkably small change in δ(C–3, C–5), 2.7 ppm, allows us to conclude that 3,5-DBA is probably not protonated on the hydroxy groups present at C–3 and C–5 carbon atoms. On the other hand, the relatively large change in δ (C–O), 7.4 ppm, indicates that 3,5–DBA is most probably protonated on the carboxy group (–COOH).

Provided that all the dependencies δ on the sulfuric acid concentration reflect the same process, the protonation of 3,5-DBA, they should be compared among themselves. For this purpose the protonation degree $\alpha = C_{BH^+}/(C_B + C_{BH^+})$ was calculated by applying the standard procedure, ref. 4.

The α values were calculated for all six ring carbons and also for the C–O carbon atom, see Fig. 1. Instead of a single sigmoid dependence α *vs.* %H_2SO_4 a number of relationships α *vs.* %H_2SO_4 were obtained (Fig. 1). First of all we decided to avoid further treatment of α(C–3, C–5) because of its rather unsmooth shape. This seems to be due to a narrow range of changes (2.7 ppm) for C–3, C–5 compared to the estimated probable error in our experiment (±0.1–0.2 ppm). After neglecting α(C–3, C–5) there remain three relationships: α *vs.* %H_2SO_4:α(C–O), α(C–1) and almost a common relationship for α(C–4, C–2 , C–6). Similar to the traditional pattern is the behaviour of α(C–O) *vs.* %H_2SO_4: α(C–O) is almost unchanged from water to 60.4%H_2SO_4 and only after that does a smooth increase in α begin. Quite a different behaviour was observed for α(C–2, C–4, C–6): in the range 0–56%H_2SO_4 *ca.* 30% of the change due to protonation has already occurred. It seems that these changes in the range 0–56%H_2SO_4 are not related to an early appearance of the protonated form of the base (BH^+) but they reflect the formation of strong H-bonds to the B-form of the base studied. A similar situation has also been encountered in some other papers[4–7] where the NMR technique has been applied to basicity constant estimations.

Table 2 The pK_{BH^+} and m^* values calculated by the excess acidity method.[8]

Initial data used	Carbon atom	pK_{BH^+}	m^*
α for the whole range from water to conc. sulfuric acid	C–O	−3.52±0.18	0.36±0.02
	C–1	−2.06±0.19	0.18±0.02
	C–2,C–6	−2.50±0.33	0.32±0.06
	C–4	−2.30±0.49	0.27±0.10
α values taking α = 0 in 56%H_2SO_4	C–O	−3.49±0.15	0.35±0.03
	C–1	−3.37±0.17	0.33±0.02
	the mean from α(C–2,C–6) and α(C–4)	−3.76±0.48	0.48±0.08
Weighted mean		−3.45±0.28	0.34±0.06

If we assume that in 56%H_2SO_4 we still have to deal with an unionized form of the base studied (B-form), we can recalculate α values by applying the δ values in 56% H_2SO_4 instead of δ values in water. After doing this we obtained the relationship presented in Fig. 2, in which we can see only two relationships α *vs.*%H_2SO_4: the first for atoms C–2, C–6, C–4 and the second for C–O, C–1. The last relationship seems to be more reliable because it reflects the changes at carbon atoms closer to the basicity centre of the base studied.

The relationship α *vs.*%H_2SO_4 may be used to estimate the pK_{BH^+} and m^* values of 3,5-DBA by the Cox–Yates excess acidity method.[8] The values of the indicator ratio $I = C_{BH^+}/C_B$ were calculated by $I = \alpha/(1-\alpha)$. Applying the Cox–Yates excess acidity method the pK_{BH^+} and m^* values listed in Table 2 were obtained. In this treatment only the log I values within ± 1.0 were used. It should be noted that the pK_{BH^+} values obtained are generally not equal to the H_0 values at half-protonation ($I = 1$).[8]

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