Thermodynamics of Dissociation of some 5-Monosubstituted Barbituric Acids

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The influence of some 5-substituents on the acid strength and ΔH^0 and ΔS^0 of dissociation of barbituric acid in aqueous solutions has been investigated. The acid strength depends much more strongly on the substituent than is the case with carboxylic acids.

In connection with kinetic studies we determined, in the temperature range 10—40 °C, the overall dissociation constant, K, of barbituric acids with the following 5-substituents; H (BA), methyl (MBA), ethyl (EBA), isopropyl (IPBA), and phenyl (PhBA).

Because of keto–enol tautomerism we are dealing with two different acids whose dissociation constants, K_{KH} and K_{EH}, are related to the classically determinable overall dissociation constant by equation (1). The

$$K = \frac{K_{EH} \,.\, K_{KH}}{K_{EH} + K_{KH}} = \frac{K_{KH}}{1 + K_{EK}}, \text{ where } K_{EK} = \frac{K_{KH}}{K_{EH}} \quad (1)$$

values of K_{KH} and K_{EH} can be determined even at small values of K_{EK} by using kinetic measurements.[1] For barbituric acid and the analogous Meldrums' acid, values of 0·013 and 0·0045 were obtained for K_{EK}. In these cases, therefore, $K_{EK} \ll 1$ and K approaches K_K; thus one obtains the CH acidity directly.

Like MBA [2] the other derivatives autoxidize [3] so that the measurements had to take place with the exclusion of oxygen. Owing to the inevitable presence of trace amounts of oxygen, those methods which require very small concentrations, such as conductometry and u.v. spectrometry, were impracticable: we therefore used the titration method.[4]

EXPERIMENTAL

The substances which autoxidize in water were dissolved in a quasi-closed system by dropping the weighed sample into water which was flushed with nitrogen. The flow of nitrogen at constant pressure was continued during the titration. After each of the three additions of NaOH (*ca.* 35, 50, and 65% neutralization) the vessel was thermostatted at 10, 25, and 40 °C for a sufficiently long time (45 min). The value of the pH was then measured, and the sample was titrated to the end point as a check. The solutions had concentrations 0·0015—0·015 mol dm^{-3}. At least three independent experiments were performed with each substance.

The exact calibration of the glass electrodes with respect to changes in pH and temperature was of decisive importance in the experiments. Acetic and chloroacetic acids were used as calibrants, since their dissociation constants at the temperature of measurement (10—40 °C) are known very accurately.[5] These substances were measured in the same apparatus under the same conditions and at comparable concentrations (to compensate for the diffusion potential) as the test substances. The standard glass electrodes and the digital pH-meter E 500 were supplied by Metrohm.

Materials.—MBA, EBA, IPBA,[6] and PhBA [7] were prepared according to described procedures, but were recrystallized several times in an oxygen-free atmosphere in order to prevent impurities arising from oxidation products. The corrected m.p.s were higher than those in the literature: MBA, m.p. 218—220° (lit.,[6] 202—203°); EBA, m.p. 201—202° (lit.,[6] 194°); IPBA, m.p. 225° (lit.,[6] 216°); PhBA, m.p. 274—275° (lit.,[7] 263°). The equivalent weight indicated that EBA crystallizes as EBA,H_2O. For purification, chloroacetic acid (' Baker Analysed ' Reagent) was fractionally crystallized with 3% water. The acetic acid was taken from Fixanal ampoules from Riedel de Haen. The 1M-NaOH was free of carbonate. The nitrogen was freed from traces of oxygen using Oxysorb (Messer, Griesheim) and R3-11 catalyst (BASF).

RESULTS

By using equation (2) where c_0 is the overall concentration

$$\text{pH} = -\log \{f_\pm [-z + \sqrt{z^2 + K(c_0 - c_{Na})/f_\pm{}^2}]\}$$
$$\text{with } z = \frac{c_{Na} + K/f_\pm{}^2}{2} \quad (2)$$

of the substance and c_{Na} is the concentration of Na^+ ions from the NaOH added, a value for K was determined for every pH reading. The mean activity coefficient, $f_\pm$, was

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[1] M. Eigen, G. Ilgenfritz, and W. Kruse, *Chem. Ber.*, 1965, **98**, 1623.

[2] B. Doumas and H. G. Biggs, *J. Biol. Chem.*, 1962, **237**, 2306.

[3] H. Koffer, to be published.

[4] *E.g.*, A. Albert and E. P. Serjeant, ' Ionization Constants of Acids and Bases,' Wiley, New York, 1962.

[5] Handbook of Chemistry and Physics,' 50th edn., Chemical Rubber Co., Cleveland, Ohio, 1969—1970.

[6] E. Fischer and A. Dilthey, *Annalen*, 1904, **335**, 334.

[7] F. Runge and K. Koch, *Chem. Ber.*, 1958, **91**, 1217.

introduced according to equation (3),[8] by using an iterative procedure.

$$-\log f_{\pm} = 0{\cdot}5\left(\frac{\sqrt{I}}{1+\sqrt{I}} - 0{\cdot}3I\right) \qquad (3)$$

It was assumed that $K(T)$ is described by equation (4).

$$R \ln K = A + \frac{B}{T} + C \ln T \qquad (4)$$

All values of K obtained were treated using the least squares method. The standard deviation for the values pK and ΔG^0 are given in parentheses (Table).

The standard thermodynamic values are derived from equations (5)—(7), with $T = 298{\cdot}16$ K.

$$\Delta G^0 = -TA - B - (T \ln T)C \qquad (5)$$

$$\Delta H^0 = -B + TC \qquad (6)$$

$$\Delta S^0 = A + (1 + \ln T)C \qquad (7)$$

These values are summarized in the Table. The standard deviations (in parentheses) for ΔH^0 and ΔS^0 followed from those ΔH^0 and ΔS^0 values which were obtained from the three pK values at the three temperatures of every NaOH addition. All calculations were performed using a Wang 720 calculator.

Thermodynamic properties * of some barbituric and carboxylic acids

Acid	pK (at 25 °C)	ΔG^0/kJ mol^{-1}	ΔH^0/kJ mol^{-1}	ΔS^0/J K^{-1} mol^{-1}	$10^5 A$/J K^{-1} mol^{-1}	$10^{-3} B$/J mol^{-1}	C/J K^{-1} mol^{-1}
BA	4·024 (0·016)	22·96(0·09)	0·03 (0·75)	−76·9 (2·6)	−0·0339	−3·454	−11·48
MBA	3·386 (0·038)	19·32 (0·2)	−6·70 (1·7)	−87·5 (5·4)	−1·369	2·827	−13·04
EBA	3·691 (0·055)	21·06 (0·3)	−8·62 (1·7)	−99·6 (5·9)	−0·473	4·186	−14·86
IPBA	4·907 (0·020)	28·00 (0·1)	0·88 (1·0)	−90·8 (3·3)	−1·703	−4·936	−13·58
PhBA	2·544 (0·16)	14·52 (0·9)	−9·58 (2·9)	−80·8 (9·2)	−1·741	6·000	−12·08
HCO_2H	3·75						
$MeCO_2H$	4·75						
$EtCO_2H$	4·87						
Pr^iCO_2H	4·84 (at 18 °C)						
$PhCO_2H$	4·19						

* Standard deviations given in parentheses.

Values of the pK at 25 °C for the two non-autoxidizing substances BA and IPBA, which were measured using u.v. spectrometry, are given in the literature; BA 3·990 (ref. 9) and 4·035 (ref. 10), IPBA 4·940 (ref. 10). Our values agree with these very well. The temperature dependence for BA has also been investigated.[9] The values reported, $\Delta H^0 = -3{\cdot}33$ kJ mol^{-1} and $\Delta S^0 = -87{\cdot}5$ J K^{-1} mol^{-1}, are different from those which we obtained. We reinvestigated BA optically and found that the molar extinction coefficients of both the acid and the anion have a noticeable temperature dependence (−0·13% per degree in both cases). If we assume that Briggs *et al.* used an optical density value of 0·5, application of a correction for the temperature dependence to their data gives values ΔH° −1·34 kJ mol^{-1} and ΔS^0 80·8 J K^{-1} mol^{-1}, which better fit our data.

DISCUSSION

If one compares the pK values at 25 °C of barbituric acid derivatives RBA with the corresponding carboxylic acid RCO_2H (Table) one sees that the pK values for barbituric acids vary from 2·54 to 4·91 whereas those for the carboxylic acids vary only from 3·75 to 4·87: the acidity of the barbituric acids depends much more strongly on the substituents. The high acidity of the phenyl compound can be explained by mesomeric stabilization of the anion. On the other hand, it is surprising that MBA and EBA are stronger acids than BA since one would expect the opposite from statistical considerations and from the $+I$ effect. The low acidity of IPBA is also interesting. It will be shown elsewhere that the influence of substituents on acidity can be better understood from kinetic measurements.[3]

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[9] A. G. Briggs, J. E. Sawbridge, P. Tickle, and J. M. Wilson, *J. Chem. Soc.* (*B*), 1969, 802.

[10] A. I. Biggs, *J. Chem. Soc.*, 1956, 2485.