482. *Thermodynamic Ionization Constants of Barbituric Acid and Some of its Derivatives.*

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The thermodynamic ionization constants of barbituric acid and some of its 1 : 5-, 1 : 3-, 5 : 5-, and 1 : 5 : 5-derivatives have been measured at 25° by spectrophotometric means, and the relation between these values and the possibilities of enolization has been discussed.

ROBINSON and BIGGS [1] have shown that the determination of the ionization constant of a weak acid by spectrophotometric methods can be much improved in accuracy if use is made of a number of buffer solutions whose pH values have been determined with precision by workers at the National Bureau of Standards. If D_1 and D_2 are the optical densities of a solution of a weak acid in very acid and in very alkaline solution respectively, then the optical density of a solution of the same stoicheiometric concentration in a buffer of known pH is given by $D = (1 - \alpha)D_1 + \alpha D_2$, where α is the degree of ionization. The thermodynamic ionization constant of a weak acid, HA, is :

$$K = \gamma_{\mathrm{H}} m_{\mathrm{H}} \gamma_{\mathrm{A}} m_{\mathrm{A}} / (\gamma_{\mathrm{HA}} m_{\mathrm{HA}}) = \gamma_{\mathrm{H}} \gamma_{\mathrm{A}} m_{\mathrm{H}} \alpha / (1 - \alpha)$$

since γ_{HA} approximates closely to unity in dilute solutions; the pH values in question are $(-\log \gamma_{\mathrm{H}} m_{\mathrm{H}})$ and therefore these, combined with measurements of optical density,

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[1] Robinson and Biggs, *Trans. Faraday Soc.*, 1955, **51**, 901.

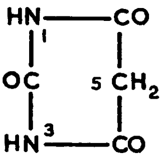
suffice to give K provided that γ_A can be estimated. It has been found[1] that a slight modification of Davies's equation :[2]

$$-\log\gamma = 0{\cdot}5092I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0{\cdot}2I$$

suffices for dilute solutions at 25°

The buffers used in this work were (1) succinic acid–sodium hydrogen succinate mixtures, (2) sodium hydrogen succinate itself,[3] (3) primary and secondary sodium phosphate mixtures,[4] or (4) borax,[5] the data quoted in the papers cited being sufficient to enable the pH to be calculated.

We have recently had need for accurate values of the ionization constants of barbituric acid and a number of its derivatives as part of a programme of analytical work and we now report a number of measurements which are of interest in relation to the position of enolization.[6] Erlenmeyer, Epprecht, Lobeck, and Gärtner[7] have shown that replacement of all four hydrogen atoms by deuterium occurs in a solution of barbituric acid (I) in heavy water : it follows that enolization must occur in at least two of the 1 : 2-, 1 : 6-, and 5 : 6-positions (or the equivalent 2 : 3-, 3 : 4-, and 4 : 5-positions) and may occur in all three. We have found by potentiometric titration that, as might be expected, 5 : 5-diethyl-1 : 3-dimethylbarbituric acid is devoid of acid properties and possesses no absorption at wavelengths of 241 mμ or longer, *i.e.*, there is no absorption in the region where less fully substituted barbituric acids absorb freely.



(I)

A trisubstituted acid, 5-*cyclo*hexenyl-1 : 5-dimethylbarbituric acid in which enolization can occur only in the 2 : 3- or 3 : 4-positions, shows only weak acidity (pK 8·37) but, if there is a hydrogen atom in the 1-position, then, with increased possibility of enolization, the acidity is increased. Thus seven 5 : 5-disubstituted acids were found to have pK values ranging from 7·73 to 7·99 (the 5-benzyl-5-ethyl acid having pK 7·45), *i.e.*, they are about three times stronger. In 1 : 3-dimethylbarbituric acid enolization can occur in the 4 : 5- and 5 : 6-positions and this leads to acidity of a much higher order (pK 4·68). Barbituric acid, the 1-methyl acid, and the 1 : 3-dimethyl acid have spectra of the *same type* (markedly different from that of the 5 : 5-disubstituted acids) and it is therefore probable that they are structurally similar and enolization, which might be expected in the first two of these acids at the 2 : 3- and 3 : 4-positions, does not occur to any marked extent here. The decreasing acidity of barbituric acid (pK 4·04), the 1-methyl acid (pK 4·35), and the 1 : 3-dimethyl acid (pK 4·68) may therefore be ascribed to the introduction of methyl groups. Finally, if enolization is reduced by substitution in the 5-position, as in the 5-*iso*propyl acid (pK 4·94), then, as would be expected, the acidity is also decreased.

The value found for the 5 : 5-diethyl acid, pK $7{\cdot}97_1$, is in good agreement with that found by Manov, Schuette, and Kirk,[8] *viz.*, 7·980, thus providing a cross-check on the reliability of our method and the accuracy of the buffer solution.

Table 1 gives the detailed results from which the pK's of barbituric acid and five of its derivatives have been calculated. The experimental pK values for eight 5 : 5-disubstituted derivatives of barbituric acid are reported in the Experimental section, together with the values found by Krahl.[9] With the exception of 5 : 5-diallylbarbituric acid, the pK values obtained for 5 : 5-disubstituted derivatives of barbituric acid are greater by about 0·06 pK unit than those obtained by Krahl; the e.m.f. method used by him involved, however, liquid-junction potentials and this may well account for the difference.

[2] Davies, *J.*, 1938, 2093.
[3] Pinching and Bates, *J. Res. Nat. Bur. Stand.*, 1950, **45**, 322, 444.
[4] Bates and Acree, *ibid.*, 1943, **30**, 129.
[5] Manov, DeLollis, Lindvall, and Acree, *ibid.*, 1944, **33**, 543.
[6] Stuckey, *Quart. J. Pharm. Pharmacol.*, (*a*) 1940, **13**, 312; (*b*) 1941, **14**, 224; (*c*) 1942, **15**, 370.
[7] Erlenmeyer, Epprecht, Lobeck, and Gärtner, *Helv. Chim. Acta*, 1936, **19**, 354.
[8] Manov, Schuette, and Kirk, *J. Res. Nat. Bur. Stand.*, 1952, **48**, 84.
[9] Krahl, *J. Phys. Chem.*, 1940, **44**, 449.
[10] Robinson and Kiang, *Trans. Faraday Soc.*, 1955, **51**, 1398.

TABLE 1. *Ionization constants of barbituric acid and some derivatives.*

		D	α	pH	− log γ	p*K*
	781×10^{-7}M-Barbituric acid (λ = 258 mμ)					
	pH 10·0	1·640	—	—	—	—
Buffer (1)	$C_4H_6O_4$, 0·04730M	0·696	0·411	3·787	0·093	$4{\cdot}03_6$
	,, 0·03786M	0·702	0·415	3·797	0·087	$4{\cdot}03_3$
	,, 0·01893M	0·709	0·419	3·826	0·068	$4{\cdot}03_6$
	0·1N-HCl	0·038	—	—	—	—
	$703{\cdot}7 \times 10^{-7}$M-1-Methylbarbituric acid (λ = 258 mμ)					
	pH 10·0	1·386	—	—	—	—
Buffer (1)	$C_4H_6O_4$, 0·04730M	0·369	0·255	3·787	0·093	$4{\cdot}34_6$
	,, 0·03786M	0·368	0·255	3·797	0·087	$4{\cdot}35_0$
	,, 0·01893M	0·376	0·260	3·826	0·068	$4{\cdot}34_8$
	0·1N-HCl	0·019	—	—	—	—
	64×10^{-6}M-1 : 3-Dimethylbarbituric acid (λ = 258 mμ)					
	pH 10·0	1·154	—	—	—	—
Buffer (1)	$C_4H_6O_4$, 0·04730M	0·168	0·138	3·787	0·093	$4{\cdot}67_4$
	,, 0·03786M	0·168	0·138	3·797	0·087	$4{\cdot}68_0$
	,, 0·01893M	0·172	0·141	3·826	0·068	$4{\cdot}68_0$
	0·1N-HCl	0·011	—	—	—	—
	588×10^{-7}M-5-*iso*Propylbarbituric acid (λ = 269 mμ)					
	pH 10·0	1·132	—	—	—	—
Buffer (2)	$C_4H_5O_4Na$, 0·05M	0·489	0·435	0·724	0·102	$4{\cdot}94_0$
	,, 0·04M	0·491	0·437	0·736	0·096	$4{\cdot}94_2$
	,, 0·03M	0·497	0·442	4·753	0·088	$4{\cdot}94_3$
	,, 0·02M	0·509	0·453	4·777	0·077	$4{\cdot}93_6$
	0·01N-HCl	0·004	—	—	—	—
	272×10^{-6}M-5 : 5-Diethylbarbituric acid (λ = 241 mμ)					
	pH 11·0	2·800	—	—	—	—
Buffer (3)	NaH_2PO_4, 0·01M	0·456	0·138	7·085	0·089	$7{\cdot}96_6$
	,, 0·005M	0·488	0·150	7·155	0·070	$7{\cdot}97_1$
	,, 0·0025M	0·511	0·158	7·211	0·052	$7{\cdot}97_6$
	0·001N-HCl	0·081	—	—	—	—
	106×10^{-6}M-5-*cyclo*Hexenyl-1 : 5-dimethylbarbituric acid (λ = 241 mμ)					
	pH 11·0	0·418	—	—	—	—
Buffer (4)	Borax, 0·025M	0·378	0·884	9·172	0·081	$8{\cdot}36_7$
	,, 0·010M	0·376	0·878	9·177	0·058	$8{\cdot}37_5$
	0·1N-HCl	0·073	—	—	—	—

Summary of p*K* values :

Barbituric acid	$4{\cdot}03_5$	5-*iso*Propylbarbituric acid	$4{\cdot}94_0$
1-Methylbarbituric acid	$4{\cdot}34_8$	5 : 5-Diethylbarbituric acid	$7{\cdot}97_1$
1 : 3-Dimethylbarbituric acid	$4{\cdot}67_8$	5-*cyclo*Hexenyl-1 : 5-dimethylbarbituric acid	8·37

Notes to Table 1.—*Buffers.* (1) Succinic acid, sodium hydrogen succinate, and sodium chloride in molar ratio 1 : 0·5 : 1 : the succinic acid concentration is listed. (2) Sodium hydrogen succinate (of stated molarity) and sodium chloride in equimolar quantities. (3) Sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride in molar ratio 1 : 1·529 : 1. (4) Aqueous sodium tetraborate without sodium chloride.

A small correction may have to be made because the introduction of the weak acid at low concentration compared with that of the buffer has a slight disturbing effect on the pH : this correction has been discussed by Robinson and Kiang.[10] Only for the last two acids is this correction significant and it has been included in the computation of p*K*.

EXPERIMENTAL

The following four compounds were prepared by Messrs. May and Baker Ltd., and were found by them to have the stated properties : 1-Methylbarbituric acid, m. p. 132—133° (Found : N, 19·7. Calc. for $C_5H_6O_3N_2$: N, 19·7%), 1 : 3-dimethylbarbituric acid, m. p. 123° (Found : N, 18·0. Calc. for $C_6H_8O_3N_2$: N, 18·0%), and 5 : 5-diethyl-1 : 3-dimethylbarbituric acid, m. p. 38—38·5° (Found : C, 56·6; H, 7·7; N, 13·2. Calc. for $C_{10}H_{16}O_3N_2$: C, 56·6; H, 7·6; N, 13·2%), were all prepared by Stuckey's method.[6a] 5-*iso*Propylbarbituric acid, m. p. 218°, was prepared by a method which precluded the possibility of contamination by the isomeric

5-*n*-propyl isomer. 5-*cyclo*Hexenyl-1 : 5-dimethylbarbituric acid, m. p. 144°, was a recrystallized commercial specimen. Our p*K* value of 8·37 compares with that of 8·34 found by Krahl.[9]

5 : 5-*Disubstituted barbituric acids.* The acids were commercial specimens purified by recrystallization and the p*K* values given in Table 2 were found, those of Krahl [9] being listed for comparison. All measurements were made in phosphate buffers at a wavelength of 241 mμ.

TABLE 2.

Barbituric acid	M. p.	p*K* (found)	p*K* (Krahl)	Barbituric acid	(M. p.	p*K* (found)	p*K* (Krahl)
5-Allyl-5-*iso*propyl ...	140°	7·99	7·91	5-Ethyl-5-*iso*pentyl ...	155°	7·96	7·94
5 : 5-Diallyl	171	7·77	7·79	5-Allyl-5-*iso*butyl	137	7·79	7·68
5-Ethyl-5-phenyl	174	7·45	7·41	5-Butyl-5-ethyl	124	7·98	7·92
5-Methyl-5-phenyl	221	7·73	—	5 : 5-Diethyl	188	$7{\cdot}97_1$	7·91

For the last acid Manov *et al.*[8] found p*K* 7·980.

The buffer solutions were prepared as described by the various authors;[3,4,5] all chemicals used were of analytical quality. Spectrophotometric measurements were made on a " Uvispek " spectrophotometer in an air-conditioned room at 25° ± 1°.

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