

C-H Acidity of Barbituric Acids

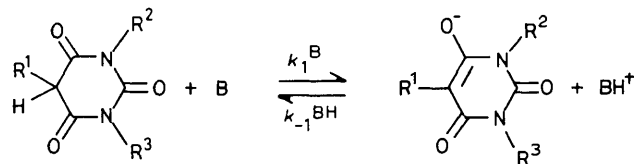
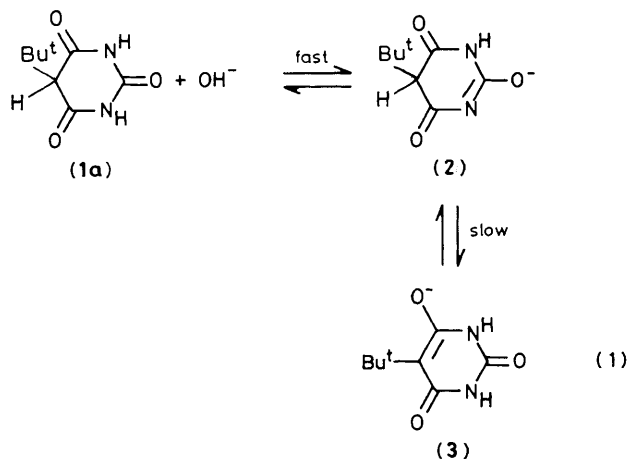
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The C-5-acidity of barbituric acids is correlated with the rates of proton transfer to and from that carbon atom.

During a recent study of the effects of alkyl substitution on the acidity of barbituric acids a slow change in the absorption spectrum of the basic form of the 5-Bu^t compound was observed. Further examination showed that this was because of slow conversion of the deprotonated amide (2) into the thermodynamically favoured enolate anion (3) [equation (1)].

This led to a more extensive study of the rates of enolization of these physiologically important compounds and the results presented here provide the basis for understanding the acidity of this type of carbon acid. Apart from the classic study by Eigen,¹ and subsequent work by Koffer,² little attention has been paid to the proton transfer reactions of these compounds.

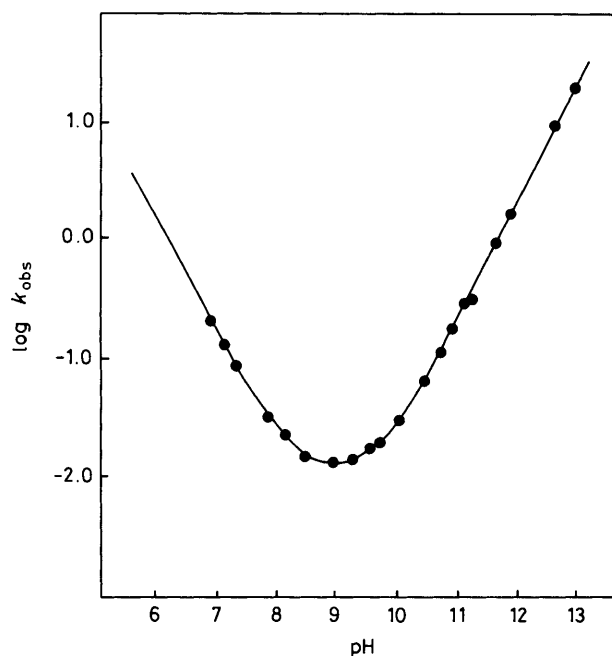


- (1) a; R¹ = Bu^t, R² = R³ = H
 b; R¹ = H, R² = R³ = Prⁱ
 c; R¹ = Prⁱ, R² = H, R³ = Prⁱ
 d; R¹ = Bu^t, R² = R³ = Me

Scheme 1

Table 1. Rate constants for proton transfer in barbituric acid derivatives at 25 °C and ionic strength, $I = 0.1 \text{ mol dm}^{-3}$ (NaCl).

Compound	pK_{CH}	$k_1^{\text{H}_2\text{O}}/\text{s}^{-1}$	$k_1^{\text{OH}^-}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{-1}^{\text{H}^+}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_{-1}^{\text{H}_2\text{O}}/\text{s}^{-1}$
(1a)	8.31	2.6×10^{-3}	8.0×10^2	3.2×10^5	1.6×10^{-3}
(1b)	5.65	4.4	—	11.7×10^5	—
(1c)	5.92	3.5×10^{-1}	—	1.8×10^5	—
(1d)	9.63	4.0×10^{-4}	1.9×10^2	11.2×10^5	8.9×10^{-3}

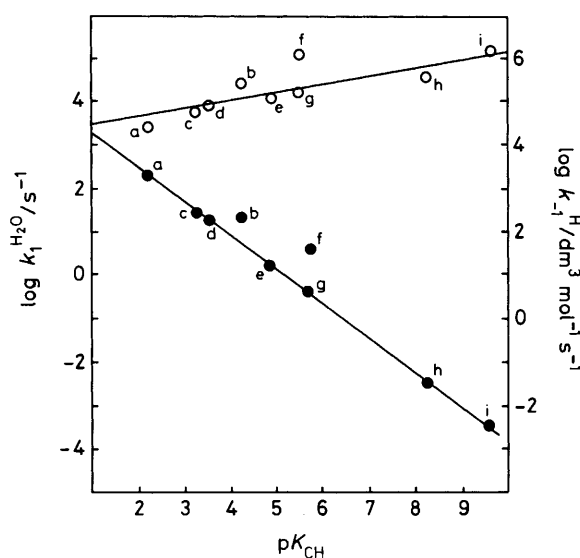
**Figure 1.** pH-Rate profile for proton transfer in 1,3-dimethyl-5-t-butylbarbituric acid (**1d**) at 25 °C and $I = 0.1 \text{ mol dm}^{-3}$ (NaCl). Points are experimental and the line is calculated using the values of the rate constants given in Table 1.

Proton transfer in most barbituric acids[†] follows the general acid-base catalysed process shown in Scheme 1, and for compounds (**1a–d**) in water this has been followed by pH perturbation methods using conventional and stopped-flow spectrophotometry. For (**1d**) the variation of the observed first order rate constant (k_{obs}) with pH is shown in Figure 1 with $k_{\text{obs}} = k_f + k_r$, and where $k_f = k_1^{\text{H}_2\text{O}} + k_1^{\text{OH}^-}[\text{OH}^-]$ and $k_r = k_{-1}^{\text{H}_2\text{O}} + k_{-1}^{\text{H}^+}[\text{H}_3\text{O}^+]$.[‡] Similar studies using compounds (**1a–c**) provide the derived rate constants in Table 1. For those barbituric acids with $pK_{\text{CH}} < 7$ [(**1b**) and (**1c**)] only H_2O and H_3O^+ are important in the proton transfer process, whereas (**1d**) ($pK_{\text{CH}} = 9.6$) is deprotonated by OH^- ca. 2×10^7 more rapidly than by H_2O . In the reprotonation reaction of (**1d**) H_3O^+ is favoured over H_2O by a factor of ca. 10^{10} .

Taken with the results of Koffer,² the data demonstrate that the rates of proton transfer closely follow substrate acidity.

[†] For barbituric acids with $pK_{\text{CH}} \approx pK_{\text{NH}}$ or $pK_{\text{CH}} > pK_{\text{NH}}$ [e.g. (**1a**)] an enolization process *via* the amide conjugate [*i.e.* (2) in equation (1) above] becomes significant.

[‡] B/BH⁺ species other than H^+ , H_2O , and OH^- also catalyse the proton transfer process. Data will be given in full elsewhere.

**Figure 2.** Dependence of the rate constants for deprotonation (●) ($k_1^{\text{H}_2\text{O}}$) and reprotonation (○) (k_{-1}^{H}) on barbituric acid (BA) acidity at 25 °C. (a) 5-PhBA, (b) BA, (c) 5-MeBA, (d) 5-EtBA, (e) 5-PrⁱBA, (f) 1,3-PrⁱBA, (g) 1,5-PrⁱBA, (h) 5-Bu^tBA, and (i) 1,3-Me₂-5-Bu^tBA. Data for a–e are taken from ref. 2, and the constants for b and f are statistically corrected.

Plots of $\log k_1^{\text{H}_2\text{O}}$ and $\log k_{-1}^{\text{H}}$ vs. pK_{CH} , Figure 2, are linear with slopes of 0.80 and 0.20 respectively. Clearly, substitution in the barbituric acid modifies C–H acidity primarily *via* the deprotonation rate $k_1^{\text{H}_2\text{O}}$, with k_{-1}^{H} varying by only a factor of ca. 50 over a 5×10^7 -fold change in K_{CH} . Similar correlations are well known for proton transfers in ‘normal’ oxygen and nitrogen acids, but in the present case the reprotonation rate never approaches the diffusion-controlled limit (ca. $10^{10} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$). This observation is not new for carbon acids, but this is one of the few sets of purely experimental data to report it over a wide range of directly measured substrate acidity.³ The results may be relevant to the understanding of the physiological action of barbituric acids since slow proton transfer could be an additional factor in determining penetration through lipid membranes.

Received, 20th July 1984; Com. 1053

References

- 1 M Eigen, G. Ilgenfritz, and W. Kruse, *Chem. Ber.*, 1965, **98**, 1623.
- 2 H. Koffer, *J. Chem. Soc., Perkin Trans. 2*, 1975, 819.
- 3 See, e.g., J. E. Crooks, ‘Proton Transfer Reactions,’ ed. E. Caldin and V. Gold, Chapman and Hall, London, 1975, ch. 6.