Kinetics of Protolytic and Keto–Enol Reactions of Some 5-Monosubstituted Barbituric Acids

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We have determined the relaxation times in the millisecond range of barbituric acids with the 5-substituents H, methyl, ethyl, isopropyl, and phenyl in aqueous solution as a function of temperature. The kinetic parameters of protolysis and keto–enol interconversion have been evaluated. The influence of the substituents on these parameters can be explained more satisfactorily by the influence of the structure of solvent water rather than by the inductive effect.

WE recently determined[1] the overall dissociation constants for barbituric acid (BA) and its 5-Me (MBA), 5-Et (EBA),5-Pr^{i} (IPBA), and 5-Ph (PhBA) derivatives. We found the following unexpected series for K (pK values in parentheses): PhBA(2·54) $>$ MBA(3·39) $>$ EBA(3·69) $>$ BA(4·02) $>$ IPBA(4·91). Thus BA is a weaker acid than MBA and EBA, in contrast to the $+I$ effect of the alkyl groups and also to the statistical effect due to the possibility of double dissociation of the BA protons.

Because of keto–enol tautomerism, 1,3-dioxo-compounds with an intact hydrogen in the 2-position exist in two different undissociated forms (KH and EH). By means of the relaxation technique it has been possible to determine all kinetic constants involved and also the position of the keto–enol equilibrium. The BA system has been investigated in this way by means of the temperature-jump method.[2]

It seemed interesting to measure the influence of substituents in the 5-position on the kinetics and equilibria of these compounds. The pressure-jump method with conductimetric detection seemed more appropriate to this problem than temperature-jump with optical detection. The only ions in solution are protons and the enolate ions (E^-), both participating in the reaction, and so leading to a very favourable signal-to-noise ratio. Furthermore, there is no complication due to an added indicator. In addition, exact adjustment of temperature is necessary for the measurement of temperature dependence; this is difficult to achieve with temperature-jump.

EXPERIMENTAL

The preparation of the acids has been described elsewhere.[1] Aqueous solutions of the barbituric acids at various concentrations were placed in the pressure-jump apparatus[3] with exclusion of oxygen. At each of 10, 25, and 40°, 10—20 pressure jumps were executed and the mean value taken.

RESULTS AND DISCUSSION

The relaxation times at the three temperatures are quoted in Table 1.

The reaction process (1) applies. The attainment

$$\begin{tikzcd} \underset{(\mathrm{I})}{2\mathrm{E}^- + \mathrm{H}^+} \arrow[rr, shift left, "k_{12}"] \arrow[dr, shift left, "k_{13}"'] & & \underset{(\mathrm{II})}{\mathrm{EH} + \mathrm{E}^-} \arrow[ll, shift left, "k_{21}"] \arrow[dl, shift left, "k_{23}"'] \\ & \underset{(\mathrm{III})}{\mathrm{E}^- + \mathrm{KH}} \arrow[ul, shift left, "k_{31}"'] \arrow[ur, shift left, "k_{32}"'] & \end{tikzcd} \qquad (1)$$

of the equilibrium (II) $\rightleftharpoons$ (III) is autocatalysed by E^-. For stoicheiometric reasons, the letter E^- is added to the equilibria (I) $\rightleftharpoons$ (II) and (I) $\rightleftharpoons$ (III), though it is kinetically not relevant [this can also be seen from the rate equation (2)]. The $\mathrm{H_3O^+}$ catalysed pseudo-monomolecular keto–enol transformation is a much slower process and can be omitted here.

To derive the reciprocal relaxation time the following assumptions are made. (1) The equilibrium (I) $\rightleftharpoons$ (II) is fast and is always established ($\mathrm{d}\ln K_{\mathrm{EH}}/\mathrm{d}t = 0$). This holds because O-acids recombine faster than C-acids by some powers of ten. After that simplification, process (1) is described by only one relaxation time. (2) The activity coefficients of the charged ions H^+, E^-, and of the charged activated complexes are

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[1] H. Koffer, *J.C.S. Perkin II*, 1974, 1428.

[2] M. Eigen, G. Ilgenfritz, and W. Kruse, *Chem. Ber.*, 1965, **98**, 1623; G. Ilgenfritz, Diplomarbeit, Göttingen, 1963.

[3] W. Knoche and G. Wiese, *Chem. Instr.*, 1973—1974, **5**, 91.

TABLE 1

Experimental values of $1/\tau$

[BA]/M	τ^{-1}/s^{-1} (10°)	τ^{-1}/s^{-1} (25°)	τ^{-1}/s^{-1} (40°)
0·00040	38	104	237
0·00060	44	119	292
0·00120	58	152	384
0·00314	95	260	606
0·00350	90·5	242	601
0·0070	114	308	736
0·0078	120	336	758
0·0140	144	374	913
0·0157	148	411	949
MBA			
0·00194	32·5	88	194
0·00194	36·3	98	215
0·00204	43	107	253
0·00271	35·6	92	212
0·0050	51	132	316
0·0068	53	144	324
0·0100	60	159	368
0·0135	57	168	
0·0136	59	162	372
0·0200	75	198	465
0·0270	76	206	484
EBA			
0·0010	27	66	147
0·0013	28	73	162
0·0020	37	87	202
0·0025	37	90	209
0·0040	50	121	282
0·0050	50	123	285
0·0065	48	128	286
0·0100	67	159	372
0·0129	63	162	368
0·00153	9·1	26	66
0·00306	15	40	100
0·0063	19	52	119
0·0126	26	71	170
0·0252	35	94	222
0·0297	36	98	241
RhBS			
0·00048	86	231	449
0·000515	112	169	415
0·00078	112	237	470
0·00190	116	256	485
0·00206	122	251	513
0·0024	115	238	504
0·0039	112	255	551
0·0048	118	250	538

equal and f, the activity coefficients of uncharged particles are unity. Omitting the charges one obtains equation (2), c_i being the equilibrium concentration

$$dx_{KH}/dt = -k_{31}(c_{KH} + x_{KH}) + k_{13}(c_E + x_E)(c_H + x_H)(f^2 + x_f^2) - k_{32}(c_{KH} + x_{KH})(c_E + x_E) + k_{23}(c_{EH} + x_{EH})(c_E + x_E) \quad (2)$$

and x_j small deviations of j from the equilibrium values. Furthermore, equation (3) holds where K is the classically determinable overall dissociation constant.

$$K_{EH} = \frac{c_H c_E}{c_{EH}} f^2 = \frac{k_{21}}{k_{12}} \quad (3a)$$

$$K_{KH} = \frac{c_H c_E}{c_{KH}} f^2 = \frac{k_{31}}{k_{13}} = \frac{K \cdot K_{EH}}{K_{EH-K}} \quad (3b)$$

Neglecting the quadratic terms in x one obtains equation (4) with $\alpha = d \ln f / d \ln c_H$ and $\beta = c_{EH}(1 + 2\alpha)/c_E + c_{EH}/c_E + 1$.

$$1/\tau = k_{13}\left\{\frac{2f}{\beta}\left[c_E(2\alpha + 1) + c_H\right] + K_{KH} + \frac{k_{23}}{k_{13}}\left(\frac{K_{KH}}{K_{EH}} + \frac{\beta - 1}{\beta}\right)c_E\right\} \quad (4)$$

To calculate $c_E(=c_H)$ for each experiment we used the Davies formula[4] for the mean activity coefficient $\{-\log f = 0{\cdot}5[c_H^{\frac{1}{2}}/(1 + c_H^{\frac{1}{2}}) - 0{\cdot}3c_H]\}$ which was used also to calculate α. The value $1/\tau$ is here presented as a function of the corresponding concentrations in each experiment and of the three unknown values k_{13}, K_{EH}, and k_{23}/k_{13}. These were evaluated by the least-squares method. They are given together with the other derived constants in Table 2. The standard deviations of experimental points from the calculated curve lie between 0·035 (IPBA) and 0·11 (PhBA) and can also be taken approximately as the error in k_{13}. On varying the other constants K_{EH} and k_{23} we obtained numerically the approximate errors, *ca.* four and eight times larger than the error in k_{13}.

State (II) of process (1) is little occupied and the attainment of the equilibrium (I) $\rightleftharpoons$ (III) does not make much use of the route *via* (II). Thus our data do not contain much information on k_{23}, in contrast to the work of Eigen *et al.* who worked at pH 5·3, which is rather higher than the pK value (4·0). If we use their values for k_{23} (7000 instead of 8000 dm^3 mol^{-1} s^{-1}) our values for k_{13} and K_{EH} are not perceptibly changed.

The dissociation constant K_{KH} of the keto-form is in all cases only slightly higher than the overall dissociation constant. It is fairly sensitive to substitution in the 5-position. A more detailed discussion of the pK values is now possible by considering the rate constants k_{31} and k_{13} instead of K_{KH}. For the purpose of comparison the constants of the acids relative to BA are compiled in Table 2. To take account of the possibility of double dissociation of the BA protons we employed the experimental values divided by two for K_{KH}(BA) and k_{31}(BA). The value for k_{13}/k_{13}(BA) show that all substituents make recombination more difficult. This could be an effect of the water structure near the centre of recombination.

For k_{31}/k_{31}(BA) it is evident that the methyl and ethyl group have no great effect on the dissociation velocity. Thus the higher acidity of the methyl and ethyl derivatives is caused only by slowing down the recombination. The accelerating effect of the phenyl group and the retardation produced by the isopropyl group on the dissociation can be easily understood in terms of the inductive effect.

With *O*-acids, recombination is practically diffusion controlled and thus independent of structural effects. For this reason dissociation constants and dissociation rate constants in a series of substituted acids run parallel to one another. With *C*-acids on the contrary, the recombination is highly structure dependent and the two constants are not necessarily parallel. Moreover,

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[4] C. W. Davies, 'Ion Association,' Butterworths, London, 1962.

TABLE 2

pK Values and kinetic quantities

Acid	t/°C	pK	pK_{KH}	pK_{EH}	K_{EK}	$10^{-5}k_{13}$/ dm^3 mol^{-1} s^{-1}	k_{31}/ s^{-1}	$10^{-3}k_{23}$/ dm^3 mol^{-1} s^{-1}	E_{a13}/ kJ mol^{-1}	E_{a31}/ kJ mol^{-1}	$\frac{K_{KH}}{K_{KH}(BA)}$	$\frac{k_3}{k_{31}(BA)}$	$\frac{k_1}{k_{13}(BA)}$
BA(2b)	25	4·04		2·13	0·013	1·0	10	7					
BA	10	4·03	4·01	2·40		0·99	9·6						
	25	4·02	4·01	2·34	0·02	2·63	27	13	46·7	46·9	2	2	1
	40	4·03	4·01	2·44		2·69	65						
MBA	10	3·32	3·28	2·27		0·20	10·4						
	25	3·39	3·36	2·15	0·06	0·56	24·7	5	46·9	39·2	9·0	1·8	0·20
	40	3·44	3·42	2·18		1·42	53·9						
EBA	10	3·61	3·59	2·20		0·30	7·6						
	25	3·69	3·67	2·23	0·04	0·79	16·8	1·6	46·7	37·7	4·3	1·2	0·29
	40	3·76	3·75	2·28		1·96	35·1						
IPBA	10	4·92	4·92	2·15		0·37	0·45						
	25	4·91	4·91	2·45	0·003	1·07	1·33	21	47·9	48·9	0·25	0·10	0·39
	40	4·90	4·90	2·45		2·60	3·3						
PhBA	10	2·46	2·17	2·15		0·13	83						
	25	2·54	2·20	2·28	1·2	0·29	184	2·6	40·1	37·2	128	13·6	0·11
	40	2·63	2·33	2·43		0·59	375						

with C-acids, in contrast to O-acids, the effect of water structure seems to play a more important role and eventually exceeds the inductive effect.

The dissociation constant of the enol K_{EH} is only slightly structure dependent and the accuracy is perhaps not sufficient to discuss the trend found here. The keto–enol ratio K_{EK} is in all cases small with the exception of the phenyl compound where it is nearly unity. The k_{23} values, which can be considered only as an estimate, lie below the k_{13} values by one to two orders of magnitude, corresponding to lower acidity of the enol relative to the H_3O^+ ion. The temperature dependence of k_{13} and K_{KH} leads to the activation energies E_a quoted in Table 2.

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