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The Hydrolytic Rate of Barbituric Acid and the Extrathermodynamic Relationship

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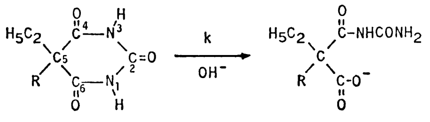
Synopsis. The enthalpy-entropy relationship of activation was subjected to discussion in connection with the alkaline hydrolysis of 10 barbituric acids. The extrathermodynamic linear equation was derived by using several parameters; the dissociation constant (pK), the ^{13}C shift value [$\delta_c(5)$] at the 5-position of the ring, and/ or the molecular connectivity index (χ).

The alkaline hydrolysis of 5-substituted 5-ethylbarbituric acids (I) were investigated. It is known that Taft-type parameters can not be used to evaluate the substituent effects in this series of compounds.[1] Therefore, as physicochemical parameters which might reflect the electronic or steric effect of the substituent, the acid-dissociation constant (pK),[2] the value of the ^{13}C chemical shift [$\delta_C(5)$] at the 5-position,[3] and the molecular connectivity index (χ) given in the literature[4] were used to discuss them.



(I)

Experimental

Materials. Ten barbituric acids (I) described previously[5] were used; they are listed in Table 1. All the other chemicals were of an analytical grade.

Hydrolysis Procedures. An appropriate quantity of (I) was weighed in a volumetric flask, dissolved, and diluted with 0.4 mol dm^{-3} NaOH to produce 1×10^{-3} mol dm^{-3}. This flask was placed in a thermostatic water bath at 30, 40, or 50 ± 0.1 °C. Samples were withdrawn periodically and diluted with 0.4 mol dm^{-3} NaOH to produce a final barbiturate concentration of about 8×10^{-5} mol dm^{-3}. Spectrophotometric readings (A) at the absorption maximum (255 nm) were taken with a Hitachi Model UV-200 spectrophotometer. Plots of $\log(A-A_\infty/A_0-A_\infty)$ *vs.* the time were reasonably linear for each compound, where A_0 or A_∞ is the initial or the final asymptotic absorbance respectively. The apparent first-order rate constant (k) was obtained from the slope.

Calculation of the Molecular Connectivity Index (χ). The χ values were calculated using the previously reported method.[4] In the case of a double-bond structure, twice the value calculated as a double bond was taken into account. These values are listed in Table 2.

Results and Discussion

Relationship between Enthalpy and Entropy of Activation. According to the absolute rate theory, the enthalpy (ΔH^*) and entropy (ΔS^*) of activation[6] may be expressed by Eq. 1:

$$\log(k/T) = -(\Delta H^*/2.303RT) + (\Delta S^*/2.303R) + \log(k_B/h), \quad (1)$$

Table 1. Rate constants, k in h^{-1}, at three different temperatures in 0.4 mol dm^{-3} NaOH, and activation parameters for the hydrolyses of barbituric acids (I)

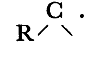
Compd No.	Substituent R	$10^3(k\pm\text{SE})^{a)}$ 30 °C	40 °C	50 °C	ΔH^* (kJ mol^{-1})	ΔS^*_{323} (J K^{-1} mol^{-1})
1	Ethyl	11.3 ±0.16	34.6 ±0.53	89.9 ±2.1	81.96	−79.75
2	Allyl	37.0 ±0.25	104.9 ±1.8	236.8 ±2.6	73.09	−99.16
3	Propyl	10.3 ±0.34	30.3 ±0.6	72.8 ±0.9	77.11	−96.52
4	3-Methylbutyl	8.72 ±0.28	26.5 ±0.22	70.0 ±0.5	82.34	−80.75
5	1-Methylbutyl	0.237 ±0.015	0.797 ±0.042	2.37 ±0.20	91.34	−81.09
6	1-Cyclohexenyl	1.30 ±0.09	3.09 ±0.29	10.1 ±0.6	80.75	−102.5
7	Cyclohexyl	0.267 ±0.018	0.877 ±0.036	2.65 ±0.17	90.92	−81.42
8	Phenyl	26.5 ±0.51	72.5 ±0.91	157.8 ±2.2	70.17	−111.5
9	Benzyl	7.80 ±0.18	23.9 ±0.41	62.8 ±0.8	82.42	−81.34
10	α-Methylbenzyl	0.304 ±0.022	1.45 ±0.17	4.93 ±0.42	93.22	−69.50

a) The rate constants were determined at least in duplicate. The values are averaged. Standard errors were calculated from a linear regression analysis of the data.

Table 2. Acid dissociation constant (pK), ^{13}C chemical shift [$\delta_C(5)$] at the 5-position, molecular connectivity index (χ), and log k at 50 °C of barbituric acids (I)

Compd No.	p$K^{a)}$	$\delta_c(5)^{b)}$	$\chi^{c)}$	log k
1	12.03	56.6	2.121	−1.046
2	11.98	55.8	2.639	−0.626
3	12.06	55.9	2.621	−1.138
4	12.13	55.8	3.477	−1.155
5	12.38	59.3	3.542	−2.625
6	11.89	61.5	4.150	−1.996
7	12.32	59.5	4.166	−2.577
8	11.60	60.0	4.177	−0.802
9	12.21	57.8	4.634	−1.202
10	12.52	60.1	5.081	−2.307

a) The apparent second acid-dissociation constants were determined by spectrophotometry at 20 °C for the ionic strength of 0.75. b) These values were reported previously.[5] c) The values are computed from the partial structure:



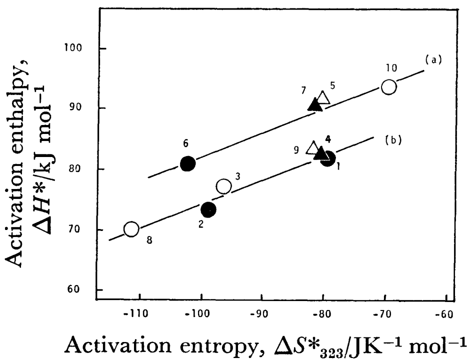


Fig. 1. Plots of the compensation effect of activation parameters.
Numbers adjacent to the marks indicate the compound numbers listed in Table 1.
Line (**a**): $\Delta H^* \times 10^3 = 122.3(\pm 5.9) \times 10^3 + 398(\pm 69) \Delta S^*$, $n=4$, $\gamma=0.971$; Line (**b**): $\Delta H^* \times 10^3 = 114.5 (\pm 3.8) \times 10^3 + 401(\pm 39) \Delta S^*$, $n=6$, $\gamma=0.981$.

where k_B is the Boltzmann constant and where h is the Planck constant. Plots of log (k/T) *vs.* T^{-1} are drawn; ΔH^* was calculated from the slope, and ΔS^* was calculated by means of Eq. 1 at 50 °C, the results being given in Table 1. The ΔH^*-ΔS^* relation is shown in Fig. 1. The linear relationship between ΔH^* and ΔS^* is well known as the isokinetic relationship or the compensation effects.[7] It is possible to draw two isokinetic lines for the plots in Fig. 1. The **a** line is applied for 4 compounds (**5**, **6**, **7**, and **10**) which have a branched substituent group at the α-position, the isokinetic temperature being 398 K. The **b** line is for the other 6 compounds (**1**, **2**, **3**, **4**, **8**, and **9**), the isokinetic temperature being 401 K.

General Structure-Hydrolytic Reactivity Correlation. The extrathermodynamic linear Eq. 2 was proposed to express the relation between the hydrolytic rate constant (k) and the parameters, pK, $\delta_C(5)$, and χ. Regression analysis was then applied to this equation.

$$\log (k/k_0) = b_1[\mathrm{p}K - \mathrm{p}K_0] + b_2[\delta_c(5) - \delta_c(5)_0] + b_3[\chi - \chi_0] \tag{2}$$

or

$$\begin{aligned}\log k &= b_0 + b_1 \mathrm{p}K + b_2 \delta_c(5) + b_3 \chi \\ &= b_0 + b_1 x_1 + b_2 x_2 + b_3 x_3,\end{aligned} \tag{3}$$

where the subscript zero refers to the values of the standard compound, where b_i ($i=0$, 1, 2, and 3) are constants, and where x_1, x_2, and x_3 are predictor variables equivalent to pK, $\delta_C(5)$, and χ respectively. The correlation matrix is shown in Table 3. The smallest correlation exists between x_1 and x_2; therefore, both the variables make nearly independent contributions to log k. The regression between log k and each of the predictor variables is given by Eqs. 4—6 (Table 4). The regression including all the variables is also given by Eq. 7; its F-value is significant at the 1% level. When the variable x_3, which has the smallest t-value for the regression coefficient, is eliminated from Eq. 7, Eq. 8 is obtained and the contribution ratio of 86% is obtained. The F-value for Eq. 8 is 21.2, which is not greatly different from that obtained for Eq. 7. Therefore, no further elimination of variables was carried out. Thus, it is found that, among the parameters which may reflect the substituent effect, the combination of pK and $\delta_C(5)$ shows a good correlation with log k in the case of the compounds examined here.

Table 3. Correlation matrix for each combination of variables

	pK	$\delta_c(5)$	χ	log k
pK	1.000			
$\delta_c(5)$	0.034	1.000		
χ	0.301	0.720*	1.000	
log k	−0.691*	−0.639*	−0.490	1.000

The asterisk indicates the significance at the 5% level.

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Table 4. Multiple regression analyses of Eq. 3[a)]

b_0	+	b_1x_1 (t value)	+	b_2x_2 (t value)	+	b_3x_3 (t value)	γ^2 Contribution ratio	V_e Variance	$F_{p,n-p-1}$[b)] Variance ratio	Eq.
22.3		−1.97 pK (2.70*)					0.478	0.333	7.31*	4
11.7				−0.228 $\delta_c(5)$ (2.35*)			0.408	0.377	5.52*	5
−0.139						−0.385 χ (1.59)	0.240	0.484	2.53	6
42.6		−2.21 pK (6.04**)		−0.317 $\delta_c(5)$ (5.03**)		0.302 χ (2.07)	0.917	0.071	21.9**	7
34.3		−1.92 pK (4.72**)		−0.218 $\delta_c(5)$ (4.33**)			0.860	0.103	21.2**	8

a) The number of observations is $n=10$, and log k at 50 °C is applied. b) p is the number of predictor variabies included in the equation. One asterisk indicates the significance at the 5% level; two asterisks, that at the 1% level.