Notes

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Substituent Effects on the Alkaline Hydrolysis of 1-Methylbarbituric Acid Derivatives

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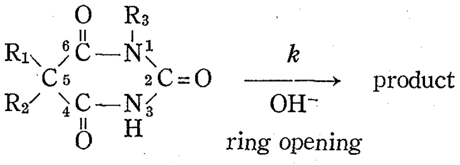
Hydrolytic reactions of 5,5-disubstituted 1-methylbarbituric acid derivatives at 30°, 40°, and 50° in alkaline solutions of various concentrations were investigated, and the rate constants and thermodynamic parameters of all of the compounds tested were determined. As physico-chemical parameters which might reflect the substituent effect on the hydrolytic rate, the acid dissociation constant (pK_a), the value of ^{13}C chemical shift (δ_C) at the 5-position, the "six number" (Six No.), and the molecular connectivity index (χ) were selected. An extrathermodynamic linear equation was then derived using these parameters. The correlation between log k'_{OH} and the combined parameters pK_a and $\delta_C(5)$ was largest, as determined by multiple regression analyses.

Keywords——alkaline hydrolysis of 1-methylbarbiturates; substituent effect; extrathermodynamic relationship; carbon-13 chemical shift; dissociation constant of 1-methylbarbituric acid; Newman's rule of six; molecular connectivity index; multiple regression analysis

Many kinetic investigations on the stability of medicinal agents have been published.[2] In the case of the hydrolyses of barbituric acid derivatives (I), nonkinetic data[3] have been used as a basis for a qualitative appreciation of substituent effects, and systematic kinetic studies have been undertaken in a few instances.[4-7] The hydrolytic rate of I is considered to be influenced by electronic and steric effects of the substituents attached to the carbon atom at the 5-position.



I

Ia: $R_3=H$
Ib: $R_3=CH_3$

The rates of chemical reactions of organic compounds and their chemical structures have been correlated theoretically by means of thermodynamics. The effects of molecular structures which modify the increment of free energy required to attain the activated state may be expressed, in many cases, as the sum of components contributing to the total effect, such as the polar, steric or resonance effects of the substituent. This makes a quantitative treatment possible; for instance, the linear free energy relationship of Taft[8] is very well known. In some cases, however, a linear relationship may be demon-

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1) Location: *Motoyamakita-machi, Higashinada-ku, Kobe, 658, Japan.*
2) E.R. Garrett, "Advances in Pharmaceutical Sciences," Vol. 2, ed. by H.S. Bean, A.H. Beckett, and J.E. Carless, Academic Press, Inc., New York, 1967, p. 2.
3) F. Fretwurst, *Arzneimit. Forsch.*, **8**, 44 (1958); M. Freifelder, A.O. Geiszler, and G.R. Stone, *J. Org. Chem.*, **26**, 203 (1961).
4) F. Tishler, J.E. Sinsheimer, and J.E. Goyan, *J. Pharm. Sci.*, **51**, 214 (1962).
5) J.T. Carstensen, E.G. Serenson, and J.J. Vance, *J. Pharm. Sci.*, **53**, 1547 (1964).
6) S.O. Eriksson and A. Holmgren, *Acta Pharm. Suec.*, **2**, 293 (1965); S.O. Eriksson, *ibid.*, **2**, 305 (1965).
7) E.R. Garrett, J.T. Bojarski, and G.J. Yakatan, *J. Pharm. Sci.*, **60**, 1145 (1971).
8) R.W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. by M.S. Newman, John Wiley and Sons, Inc., New York, 1956, Chapt. 13.

strated experimentally, but not be proven theoretically. Such a relationship has been designated by Leffler as an extrathermodynamic relationship.[9]

Eriksson *et al.*,[6] who studied the hydrolyses of 1-methylbarbituric acid derivatives (Ib) with various substituents, pointed out the importance of the steric effect of the substituent, and stated that Taft's parameters were not useful for explaining the effects of substituents in this series of compounds. To obtain further information as to the structure-reactivity relationship, the hydrolyses of a series of compounds Ib having substituents different from those examined by Eriksson were investigated in the present study. As physico-chemical parameters which might reflect the polar or steric effect of the substituents the acid dissociation constant (pK_a),[5] the value of ^{13}C chemical shift at the 5-position ($\delta_c(5)$),[10] the "six number" in the Newman's rule of six (Six No.),[7,11] and the molecular connectivity index (χ)[12] given in the literature were used. The extrathermodynamic linear equation (1) was postulated to express the relation between hydrolytic rate constant and the parameters, and was used for regression analysis.

$$\begin{aligned}\log(k/k_0) &= f[\Delta pK_a,\ \Delta\delta_c(5),\ \Delta \text{Six No.},\ \Delta\chi] \\ &= b_1[pK_a - pK_{a0}] + b_2[\delta_c(5) - \delta_c(5)_0] \\ &\quad + b_3[(\text{Six No.}) - (\text{Six No.})_0] + b_4[\chi - \chi_0]^{13)} \qquad \text{Eq. (1)}\end{aligned}$$

Experimental

Materials——Fourteen 5,5-disubstituted 1-methylbarbituric acid derivatives (Ib) were used. The compounds are listed in Table I. Compounds **1** to **12** were prepared by the method described previously.[14] Compounds **13** and **14** were prepared according to the following general method. Disubstituted malonic acid esters were prepared from diethylmalonate and appropriate alkyl bromides; the disubstituted diethylmalonates were condensed with methylurea in the presence of sodium ethoxide. 5,5-Dibenzyl-1-methylbarbituric acid (**13**) was recrystallized from acetone, mp 212° and pK_a 7.85. 5-Benzyl-1-methyl-5-(α-methyl)-benzylbarbituric acid (**14**) was recrystallized from acetone, mp 183—186° and pK_a 7.90. All other chemicals used in this study were of analytical grade.

Hydrolysis Procedures——An appropriate quantity of Ib to produce a final concentration of 2×10^{-3} M was weighed in a volumetric flask, dissolved and diluted to the final volume with standardized NaOH solution of an appropriate concentration. The reaction flask was placed in a thermostated water bath at 30°, 40°, or 50°±0.1°. Samples were withdrawn periodically and diluted with 0.1 M $Na_2B_4O_7$ solution to produce a final barbiturate concentration of about 1.6×10^{-4} M. Spectrophotometric readings at the absorption maximum (244—248 nm) were taken with a Hitachi UV-200 spectrophotometer.

Calculation of the Molecular Connectivity Index (χ)——The structure of Ib is drawn out in skeletal form, ignoring the hydrogens. A number, δ_i, is assigned to each atom in the molecule which is equal to the number of bonds connected to that atom. The connectivity index is the sum of connectivities, C_m, computed from each pair of bonded atoms as follows: $C_m = (\delta_i \times \delta_{i'})_m^{-1/2}$. Bond m consists of two atoms, i and i':

$$\chi = \sum_{m=1}^{N} C_m = \sum_{m=1}^{N} 1/(\sqrt{\delta_i \times \delta_{i'}})_m \qquad \text{Eq. (2)}$$

where N is the total number of bonds. In the case of a double bond structure, the value calculated as a double bond is doubled.[12] Values of χ are listed in Table II, where the value of the common ring skeletal moiety is subtracted to arrive at χ.

Calculation of "Six Number" (Six No.)——The "Six number" is obtained by summation of the total number of atoms in the 6-position taking the carbonyl oxygen as number "one."[11] These numbers are listed in Table II.

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9) J.E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, 1963.

10) J. Okada and T. Esaki, *Chem. Pharm. Bull.* (Tokyo), **22**, 1580 (1974).

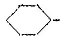
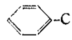
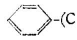
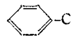
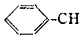
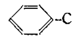
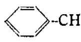
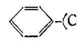
11) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Holt Rinehart and Winston, New York, 1959, p. 323.

12) W.J. Murray, L.B. Kier, and L.H. Hall, *J. Med. Chem.*, **19**, 573 (1976); L.B. Kier and L.H. Hall, "Molecular Connectivity in Chemistry and Drug Research," Academic Press, Inc., New York, 1976.

13) Values of the standard compound are indicated by subscript zero.

14) S. Asada, A. Kashimoto, and T. Yamada, *Yakugaku Zasshi*, **96**, 1169 (1976).

Table I. Rate Constants, k (hr^{-1}) and k'_{OH} (l·mol^{-1}·hr^{-1}), at Three Temperatures, and the Activation Parameters at 50° for the Hydrolysis of 5,5-Disubstituted 1-Methylbarbiturate Ions

Compound No.	Substituent		Conc. of NaOH mol/l	30°		40°		50°		log A	ΔH^*[b] kcal/mol	ΔS^*[b] cal/mol degree
	R_1	R_2		10^2k	k'_{OH}[a] (mean ± SD)	10^2k	k'_{OH}[a] (mean ± SD)	10^2k	k'_{OH}[a] (mean ± SD)			
1	C_2H_5	C_2H_5	0.05	1.94	0.422 ±0.037	2.94	0.712 ±0.048	7.19	1.43 ±0.26	8.20	11.26 (14.7)	−41.31 (−29.7)[c]
			0.1	3.21		5.96		10.8				
			0.2	5.63		9.54		16.6				
2	C_2H_5	$CH_2{=}CHCH_2$	0.05	2.97	0.728 ±0.022	5.35	1.36 ±0.08	10.9	2.71 ±0.11	9.09	12.17	−37.20
			0.1	5.91		11.5		22.1				
			0.2	10.4		19.1		37.9				
3	C_2H_5	$CH_3CH_2CH_2$	0.05	0.702	0.174 ±0.006	1.73	0.424 ±0.012	4.54	1.08 ±0.04	12.03	17.11	−23.74
			0.1	1.42		3.41		8.44				
			0.2	2.48		6.02		14.9				
4	C_2H_5	$(CH_3)_2CHCH_2CH_2$	0.05	0.484	0.111 ±0.006	1.53	0.317 ±0.039	3.03	0.668 ±0.072	11.69	16.87	−25.32
			0.1	0.873		2.31		5.33				
			0.2	1.51		4.13		8.30				
5	C_2H_5	$CH_3CH_2CH_2(CH_3)CH$	0.05	0.044	0.0108 ±0.0001	0.126	0.027 ±0.003	0.307	0.068 ±0.007	10.94	17.26	−28.74
			0.1	0.085		0.210		0.537				
			0.2	0.161		0.336		0.855				
6	C_2H_5	-	0.05	0.273	0.070 ±0.004	0.750	0.171 ±0.009	1.28	0.317 ±0.008	9.49	14.09 (13.4)	−35.39 (−35.6)[c]
			0.1	0.585		1.31		2.53				
			0.2	1.00		2.34		4.49				
7	C_2H_5	-	0.05	0.063	0.014 ±0.001	0.156	0.033 ±0.004	0.271	0.058 ±0.007	8.28	13.39 (14.3)	−40.94 (−36.5)[c]
			0.1	0.110		0.247		0.447				
			0.2	0.177		0.432		0.730				
8	C_2H_5	-	0.05	7.40	1.77 ±0.02	13.9	3.07 ±0.23	22.9	5.87 ±0.40	8.64	11.01 (12.1)	−39.28 (−34.2)[c]
			0.1	13.8		22.2		42.8				
			0.2	25.8		43.5		93.7				
9	C_2H_5	$-CH_2$	0.05	0.660	0.139 ±0.019	1.46	0.312 ±0.042	2.55	0.577 ±0.061	9.16	13.24	−36.87
			0.1	1.13		2.52		4.74				
			0.2	1.66		3.74		7.14				
10	C_2H_5	$-(CH_3)CH$	0.05	0.039	0.010 ±0.001	0.119	0.023 ±0.004	0.151	0.037 ±0.001	7.31	12.24	−45.34
			0.1	0.091		0.166		0.302				
			0.2	0.132		0.258		0.524				
11	C_2H_5	$-CH_2CH_2CH_2$	0.05	0.860	0.208 ±0.028	1.50	0.423 ±0.052	3.68	0.891 ±0.085	9.53	13.52	−35.21
			0.1	1.88		3.20		7.64				
			0.2	2.54		7.21		11.4				
12	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	0.05	8.51	2.11 ±0.13	14.9	3.56 ±0.07	32.3	7.66 ±0.19	9.36	11.91 (12.0)	−35.99 (−34.2)[c]
			0.1	15.4		27.8		57.4				
			0.2	33.6		50.9		111				
13	$-CH_2$	$-CH_2$	0.05	0.235	0.057 ±0.0006	0.539	0.128 ±0.003	1.14	0.287 ±0.026	10.08	15.07	−32.67
			0.1	0.452		0.958		2.01				
			0.2	0.834		1.89		4.69				
14	$-CH_2$	$-(CH_3)CH$	0.05	0.047	0.0093 ±0.0015	0.076	0.016 ±0.002	0.140	0.031 ±0.003	6.32	10.95	−49.88
			0.1	0.073		0.129		0.235				
			0.2	0.106		0.204		0.391				

a) $k=k'_{OH}\cdot(OH^-)$, and $(OH^-)=\gamma_{\pm}\cdot[NaOH]$ where $\gamma_{\pm}$ is the mean activity coefficient of sodium hydroxide solution, obtained from Ref. 15: 0.820, 0.817, and 0.813 in 0.05 N NaOH; 0.780, 0.776, and 0.772 in 0.1 N NaOH; 0.738, 0.733, and 0.728 in 0.2 N NaOH at 30°, 40°, and 50°, respectively.

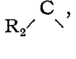
b) $\log k'_{OH}=\log A-Ea/2.303\,RT$: $\Delta H^*=Ea-RT$ and $\Delta S^*=2.303\,R\,[\log A-\log(kT/h)+\log(OH^-)]$ where $T=273+50°$ and $(OH^-)=0.142$ at 50° in 0.2 N NaOH.

c) The parenthesized values are taken from Ref. 6, and were obtained in experiments at 25°.

Table II. Acid Dissociation Constant (pK_a), Carbon-13 Chemical Shift [$\delta_c(5)$] at the 5-position, "Six Number" (Six No.), Molecular Connectivity Index (χ), and log k'_{OH} at 50° of 5,5-Disubstituted 1-Methylbarbituric Acid Derivatives

Compound No.	pK_a	δ_c (5)[a]	Six No.	χ[b]	log k'_{OH}[c]
1	8.01	56.86	6	2.121	0.157
2	7.88	56.20	5	2.639	0.434
3	7.83	56.20	6	2.621	0.033
4	7.94	56.11	6	3.477	−0.175
5	8.17	59.74	9	3.542	−1.168
6	7.60	61.73	8	4.150	−0.499
7	8.21	60.31	9	4.166	−1.236
8	7.41	60.27	7	4.177	0.769
9	7.87	58.32	5	4.634	−0.239
10	8.09	61.04	8	5.081	−1.427
11	7.99	56.33	6	5.634	−0.050
12	7.69	55.40	4	3.157	0.885
13	7.85	59.73	4	7.146	−0.542
14	7.90	61.81	7	7.594	−1.516

a) Value in ppm downfield from TMS.

b) Computed from the partial structure; 

, $\delta_i=4$ at C-5.

c) Calculated using the value at 50°.

Measurement of Acid Dissociation Constants and Carbon-13 NMR Spectra of 1-Methylbarbituric Acid Derivatives——The apparent acid dissociation constant (pK_a) was determined by spectrophotometry at 20° at an ionic strength of $\mu=0.75$.[14] ^{13}C NMR spectra were measured in a completely proton-decoupled state on a Nichiden-Varian NV-21 (22.6 MHz) spectrometer. All the samples were dissolved in $(CD_3)_2SO$ to give 1 M concentration. ^{13}C chemical shifts at the 5-position, which have been observed at about 56—62 ppm,[10] from tetramethylsilane (TMS), are listed in Table II.

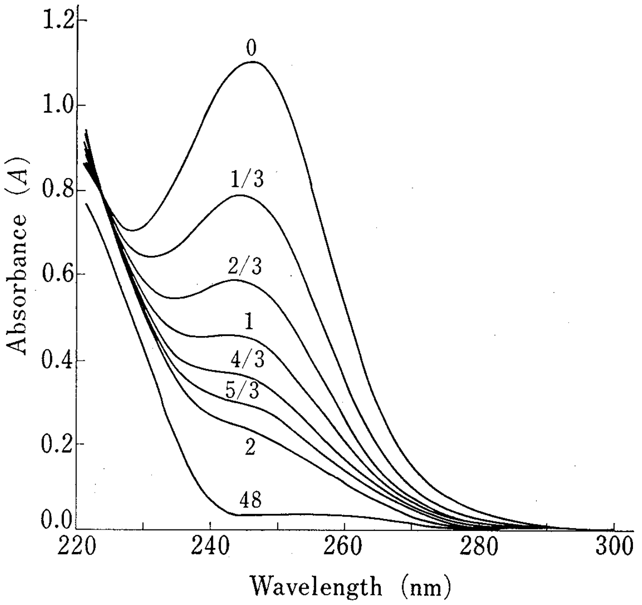


Fig. 1. Spectral Changes during the Hydrolysis of 2×10^{-3} M 5-Ethyl-1-methyl-5-phenylbarbituric Acid in 0.2 N NaOH at 50°

The number of hours after initiation of the reaction is indicated on each curve.

Results and Discussion

Spectral Changes and Rate Constants

Typical spectral changes are shown in Fig. 1 for 5-ethyl-1-methyl-5-phenylbarbituric acid (**8**) in 0.2 N sodium hydroxide solution at 50°. Plots of log $(A-A_\infty)$ at the absorption maximum *vs.* time were reasonably linear for each compound, as shown in Fig. 2. The apparent first-order rate constant (k) can be obtained from the slope.

Compound Ib can form only a monovalent anion in sodium hydroxide solution, and k may be expressed as

$$k = k'_{\mathrm{OH}}(\mathrm{OH}^-) = k'_{\mathrm{OH}}\cdot\gamma_{\pm}[\mathrm{NaOH}] \qquad \text{Eq. (3)}$$

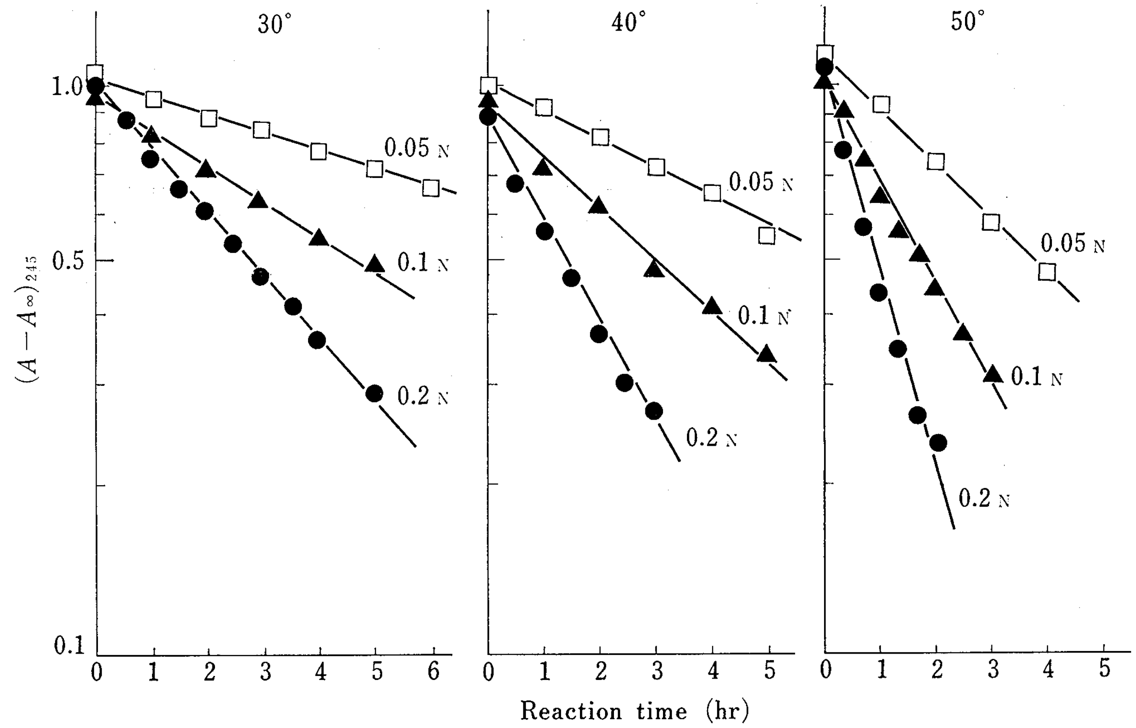


Fig. 2. Apparent First-Order Plots for the Hydrolysis of 2×10^{-3} M 5-Ethyl-1-methyl-5-phenylbarbituric Acid by NaOH at 30°, 40°, and 50°

Each plot is labeled with the NaOH concentration used. The absorbance values (A) were measured at 245 nm, and A_∞ is the final asymptotic absorbance.

where k'_{OH} is the bimolecular rate constant for hydroxyl ion attack on the ionized species of Ib, and $\gamma_{\pm}$ is the mean activity coefficient of sodium and hydroxide ions in aqueous solution.[15] The k values in sodium hydroxide solutions at various concentrations and mean values of k'_{OH} at various temperatures are listed in Table I. The variation of k'_{OH} is considered to be influenced by the substituent effect. For example, substitution of a benzyl, cyclohexyl, or α-branched group for an ethyl group retards the hydrolysis rate.

A variation of the apparent first-order rate constant was noted on alteration of the ionic strength (μ) for the hydrolyses of two compounds, **1** and **8**, at 50° in 0.1 N sodium hydroxide solution, where the extended Debye-Hückel equation was applied in conjunction with the Brönsted-Bjerrum equation.[16] The rate increases with increasing ionic strength on addition of sodium chloride (Table III). The effect is, however, moderate, and the rate constants obtained from experiments in 0.05, 0.1, and 0.2 N sodium hydroxide solution may be compared without taking into account the salt effect.

TABLE III. Effect of Ionic Strength on the Observed First-Order Rate Constants for Hydrolytic Degradation in 0.1 N NaOH at 50°

Compound	[NaOH] mol/l	[NaCl] mol/l	μ	$\sqrt{\mu}/(1+\sqrt{\mu})$	$10^2 k$ hr^{-1}	log k
5,5-Diethyl-1-methylbarbituric acid (**1**)[a]	0.1	0	0.1	0.240	10.8	−0.966
	0.1	0.1	0.2	0.309	10.9	−0.963
	0.1	0.2	0.3	0.353	11.5	−0.932
	0.1	0.6	0.7	0.456	13.8	−0.860
5-Ethyl-1-methyl-5-phenylbarbituric acid (**8**)[b]	0.1	0	0.1	0.240	42.8	−0.369
	0.1	0·1	0.2	0.309	43.8	−0.359
	0.1	0.2	0.3	0.353	46.4	−0.334
	0.1	0.6	0.7	0.456	48.9	−0.311

a) $\log k = -1.10 + 0.519\sqrt{\mu}/(1+\sqrt{\mu})$, $n=4$, $\gamma=0.952$

b) $\log k = -0.438 + 0.281\sqrt{\mu}/(1+\sqrt{\mu})$, $n=4$, $\gamma=0.979$

Relationship between Enthalpy and Entropy of Activation

Enthalpy (ΔH^*) and entropy (ΔS^*) of activation were calculated from absolute reaction rate theory, and these values are listed in Table I. Comparison of the experimental data for five compounds with those reported by Eriksson[6] showed a good agreement except for compound **1**. Leffler[17] has reviewed a large number of cases of linear entropy-enthalpy of activation relathionship; this has been called the isokinetic relationship or the compensation effect. The slope of such a linear relationship for the reaction rate gives β, the isokinetic temperature, based on the equation

$$\Delta H^* = \Delta H_0^* + \beta\Delta S^* \qquad \text{Eq. (4)}$$

where ΔH_0^* is a constant. Fig. 3 shows ΔH^* *vs.* ΔS^* plots for 5-substituted 5-ethyl-1-methylbarbituric acid derivatives; two isokinetic lines are shown using least-squares fitting. Line A is based on the values of seven compounds (**1**—**4**, **8**, **9**, and **11**), and the value of β is 358°K. In contrast, compounds which have groups branched in the α-position, and which seem to be sterically more hindered, lie on line B with the exception of **6**, and this line gives β=306°K. Statistical analysis[18] at the 5% level of significance showed that line A and line B are parallel,

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15) H.S. Harned and B.B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd Ed., Reinhold Publishing Co., New York, 1958; G. Akerlof and G. Kegeles, *J. Am. Chem. Soc.*, **62**, 620 (1940).

16) J.T. Carstensen, *J. Pharm. Sci.*, **59**, 1140 (1970).

17) J.E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

18) J. Kondo, "Applied Probability Theory," Nipponkagakugijutsuremmeishuppansha, Tokyo, 1970, p. 220.

having different intercepts. Thus, groups of compounds appear to exist that have similar reaction patterns and substituent effects.

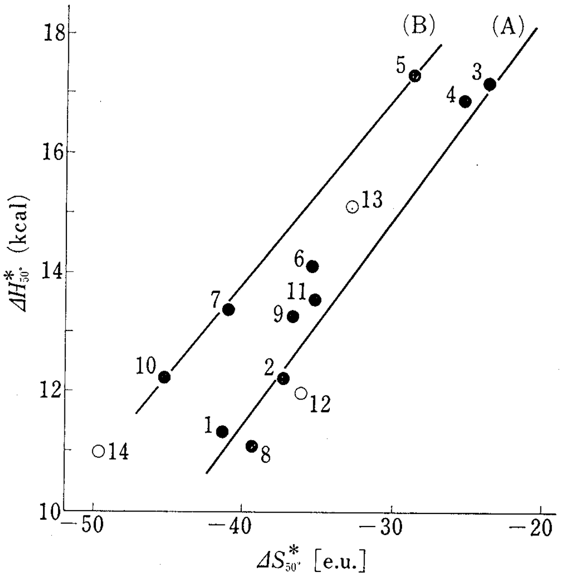

Fig. 3. Plots of Activation Enthalpy against Activation Entropy for 5-Substituted 5-Ethyl-1-methylbarbituric Acids (●)

The numbers adjacent to the circles refer to the compounds in Table I.
Line A: $\Delta H^* \times 10^3 = 25800 + 358\ \Delta S^*$, $n=7$. $\gamma=0.983$.
Line B: $\Delta H^* \times 10^3 = 26000 + 306\ \Delta S^*$, $n=3$, $\gamma=0.999$.
$(\beta)_A = (\beta)_B$; $|t| = 1.21 < t(0.05, 6) = 2.45$.
$(\Delta H_\circ^*)_A = (\Delta H_\circ^*)_B$; $|t| = 29.5 > t(0.05, 7) = 2.37$.

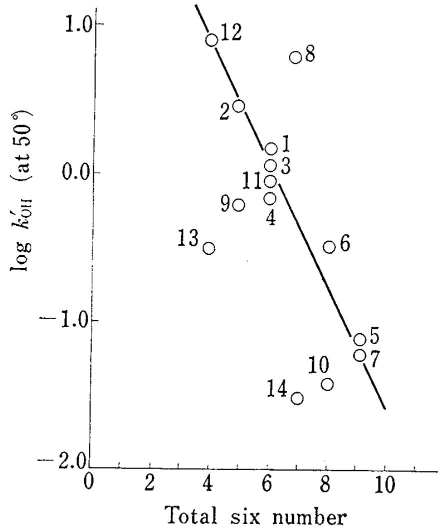

Fig. 4. Plots of log k'_{OH} against the Total "Six Number"

The numbers adjacent to the circles refer to the compounds in Table I.

Newman's Rule of Six and Hydrolytic Reactivity

Based on Eriksson's data,[6] Garrett *et al.*[7] suggested that the reactivity of barbiturates should be corrected using Newman's rule of six as a measure of steric influence on hydrolysis; however, more data on derivatives with various substituents in the 5-position seemed necessary. For the compounds in Table I, logarithmic values of k'_{OH} were plotted against the total "six number" of substituents (Fig. 4). The plot in Fig. 4 suggests a linear relation for compounds containing two interacting substituents at the 5-position, in accordance with the literature.[7] Compounds in which either or both of the substituents are phenyl, benzyl, and/or α-methylbenzyl deviate markedly from the line. Therefore, it is considered that the rate of hydrolysis of barbiturates is not a function of steric effects alone, but that electronic effects also play some role.

General Structure-Reactivity Correlation

Multiple regression analyses were carried out based on the extrathermodynamic linear equation (5), which is a rearrangement of Eq. 1.

$$\log k'_{OH} = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 \qquad \text{Eq. (5)}$$

where x_1, x_2, x_3, and x_4 are predictor variables equivalent to pK_a, $\delta_c(5)$, Six No., and χ, respectively, and b_i (i=0, 1, 2, 3, and 4) are constants. A correlation matrix between pairs of variables is shown in Table IV. The log k'_{OH} has the largest correlation with x_2, and the correlation of log k'_{OH} with x_1 or x_3 is similar. Relatively small correlations exist between other variables such as x_1 and x_2, x_1 and x_4, and x_3 and x_4. This indicates that each of the variables makes a largely independent contribution to the value of log k'_{OH}.

In order to explain the linearity, significant variables were selected by the variable decreasing method or variable increasing method. The regression between log k'_{OH} and each of the predictor variables, shown in Table V, is given by Eqs. (6)—(9). Only the F-value for the combination of log k'_{OH} and x_2 was significant at the 1% level (Eq. 9, $F_{1,12,0.05}=4.75$, $F_{1,12,0.01}=9.33$). The regression including all variables is given by Eq. (10) ($F_{4,9}=26.3$, $F_{4,9,0.01}=6.42$). When the variable x_3, which has the smallest t-value for the regression coefficient, is eliminated from Eq. 10, Eq. (11) is obtained. The F-value for Eq. 11 increased to 37.2 (Table V,

Table IV. Correlation Matrix for Each Combination of Variables

	pK_a	$\delta_c(5)$	Six No.	χ	log k'_{OH}[a]
pK_a	1.000	−0.0176	0.3595	0.0203	−0.6393*
$\delta_c(5)$		1.000	0.6309*	0.5749*	−0.6926**
Six No.			1.000	−0.0085	−0.6393*
χ				1.000	−0.5304*
log k'_{OH}					1.000

[a] Calculated using the value at 50°.
The value for a 5% level of significance is 0.526, and that for a 1% level of significance is 0.652.

Table V. Multiple Regression Analyses using the Equation
$\log k'_{\mathrm{OH}}=b_0+b_1\mathrm{p}K_a+b_2\delta_c(5)+b_3(\text{Six No.})+b_4\chi=b_0+b_1x_1+b_2x_2+b_3x_3+b_4x_4$[a]

b_0	b_1 x_1 (t value)	b_2 x_2 (t value)	b_3 x_3 (t value)	b_4 x_4 (t value)	γ Multiple correlation Coeff.	V_e Variance	$F_{p,n-p-1}$[b] Variance ratio	Equation
0.769				−0.255 χ (2.26*)	0.530	0.439	5.09*	6
17.9	−2.31 pK_a (2.86*)				0.639	0.393	8.29*	7
1.62			−0.303 Six No. (2.88*)		0.639	0.392	8.30*	8
13.3		−0.232 δ_c (5) (3.32**)			0.692	0.345	11.0**	9
27.4	−2.17 pK_a (5.06**)	−0.167 δ_c (5) (2.31*)	−0.052 Six No. (0.588)	−0.113 χ (1.49)	0.960	0.069	26.3**	10
30.3	−2.33 pK_a (7.08**)	−0.204 δ_c (5) (5.47**)		−0.081 χ (1.51)	0.958	0.065	37.2**	11
32.1	−2.36 pK_a (6.96**)	−0.236 δ_c (5) (7.54**)			0.951	0.069	52.0**	12
18.5	−2.26 pK_a (3.62**)			−0.249 χ (3.00*)	0.820	0.237	11.3**	13
2.74			−0.305 Six No. (3.88**)	−0.258 χ (3.23**)	0.845	0.220	12.6**	14
11.1		−0.158 δ_c (5) (2.79*)	−0.163 Six No. (2.03)	−0.256 χ (4.07**)	0.910	0.136	16.1**	15
15.2	−1.64 pK_a (3.79**)		−0.229 Six No. (4.03**)	−0.253 χ (4.70**)	0.936	0.099	23.4**	16

[a] The values of log k'_{OH} at 50° were applied, and the number of observations is $n=14$.
[b] F-value is the variance ratio of regression *vs.* residual (V_R/V_e), and p is the number of predictor variables included in the equation.
One asterisk indicates significance at the 5% level, two asterisks at the 1% level.

$F_{3,10,0.01}=6.55$). There is a correlation between x_2 and x_3, as indicated by the correlation coefficient, $\gamma=0.6309$ (Table IV). As a result of the elimination of x_3 from Eq. 10, the contribution of x_3 to log k'_{OH} was transferred to x_2, so that the t-value for the regression coefficient of x_2 in Eq. 11 became significant at the 1% level ($t_{0.01,10}=3.169$). Since the t-value for the regression coefficient of x_4 in Eq. 11 is the smallest, the elimination of x_4 from Eq. 11 leads to Eq. (12). The F-value for Eq. 12 was 52.0, which is larger than those obtained for Eqs. 7 and 9. Therefore, no further elimination of variables was carried out.

The regression which includes the cases whose correlation coefficients between predictor variables were rather small may be expressed by equations (13) and (14). F-value calculated for either Eq. 13 or 14 was greater than those for Eqs. 6, 7, and 8. The use of Eq. (15), which was derived from Eq. 14 by introducing x_2, resulted in an increase of the F-value, but the t-value for the regression coefficient of x_3 was reduced and its significance level fell below 5% ($t_{0.05,10}=2.228$). The t-values for regression coefficients of all variables were significant at the 1% level in the case of (16), which was derived from Eq. 13 by adding x_3. However, the F-value was 23.4 which was inferior to the value, 52.0 ($F_{2,11,0.01}=7.21$), obtained for Eq. 12. On the basis of these results, the regression expressed by Eq. 12 was found to have the largest significance.

It thus appears that, among the parameters which may reflect the substituent effect, the combination of pK_a and $\delta_c(5)$ shows a good correlation with log k'_{OH}. It thus seems likely that extended application of ^{13}C NMR spectra to physico-chemical investigations of structure-reactivity correlations may be possible.

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