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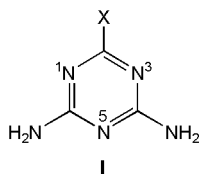
The ionization (or basicity) constants (pK_b) were determined for many 2-substituted 4,6-diamino-s-triazines (**I**) by means of the electrometric titration. **I** includes 2-alkoxy or aryloxy- (**Ia**), 2-alkyl- or 2-aryl- (**Ib**), and 2-alkylamino- or 2-arylamino-4,6-diamino-s-triazines (**Ic**). For the series with the same alkyl or aryl group, the order of the basicity was found to be **Ic** > **Ib** > **Ia**.

A study was made of relationships between the pK_b values of **I**, and the substituent constants, σ_p , σ_m , σ_p^+ , σ_m^+ , σ_p^o , σ_m^o , σ_I , σ^o , and σ^* . The Hammett relationships were observed between the pK_a values of **I**, and the substituent constants σ_m , (or the combination ones, $[0.97\sigma_m + 0.03\sigma_p]$ as well as another $[0.77\sigma_I + 0.23\sigma_R]$). The Taft relationships were also found between the pK_a values of **Ia**, **Ib**, and **Ic** and the constants σ^* , respectively. Furthermore, in the case of **Ic** a linear relationship was observed between the pK_a values and $\Sigma\sigma^*$.

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1 Introduction.

Hydroxymethylated (methylol) compounds, the initial condensation products of 2-substituted 4,6-diamino-s-triazines (**I**) with formaldehyde, are utilizable as textile finishing agents and as starting materials for plastics. A previous study [1] on the kinetics of several reactions of **I** with formaldehyde has revealed that the basicity constants (pK_b) of **I** influences the reaction rate. The determination of the pK_b values of compounds **I** is essential for the investigations of the reaction with formaldehyde and of the polymer formation of methylol compounds.



- Ia:** X = RO- (alkoxy or aryloxy group)
Ib: X = R- (alkyl or aryl group)
Ic: X = R¹R²N- (R = H, alkyl, or aryl group)

Scheme 1 Identification of three types of **I**

The pK_b values of many s-triazine derivatives have been determined by Dixon *et al.* [2], Dudley [3], and Hirt *et al.* [4], and studies have been made of the relationships between the Hammett constants and the pK_a values by Morimoto [5], Tashiro *et al.* [6], and Korolev *et al.* [7]. However, they examined only the correlation of the values with the Hammett constants σ_m and σ_p . Here, this report describes the pK_b value determination of many compounds **I** and, especially, the correlation between the pK_a values and other substituent constants, σ_p^+ , σ_m^+ , σ_p^o , σ_m^o , σ_I , σ^o , and $\Sigma\sigma^*$. Furthermore it describes their combination substituent ones, $[\alpha\sigma_m + (1 - \alpha)\sigma_p]$ and $[\alpha\sigma_I + (1 - \alpha)\sigma_R]$ ($0 < \alpha < 1$) as well.

2 Experimental.

2.1 Materials.

The compounds **11**, **12**, **16**, and **18** (Table 1) were obtained commercially and purified by recrystallization. Other com-

pounds **I** were prepared according to literature references [8,9]. Table 1 lists their melting points and the nitrogen contents.

2.2 Determination of the pK_b Values.

The pK_b values were determined generally at the concentration ($[I_0] \leq 0.0100 M$) using the electrometric titration method [2,10,11]. However, since the solubility of **17** was 0.01 g/300 ml at room temperature, this pK_b was determined by UV spectral method [10]. Titration was carried out at 25 °C, and pH was measured using a Hitachi-Horiba pH meter, Model F-5 SS, and UV absorption spectra were done by using a Hitachi spectrophotometer Model 220A. In this experiment, comparisons were not made between the pK_a values determined by the electrometric titration method and those obtained by the UV spectral method.

3 Results and Discussion.

3.1 Calculation of the pK_b Values and the α Values of Equations with Two Substituent Constants.

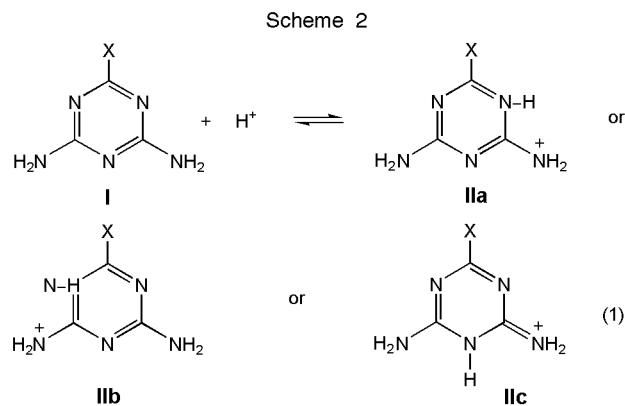
The protonation of **I** has been reported to take place at the N³ (the nitrogen atom at the 3-position), N¹ or N⁵ atom in the triazine ring as shown by Eq 1 [2,5,7,12] (Scheme 2). (The position of the proton addition is discussed later.)

The pK_b values were calculated in accordance with the references [2,10] ($pK_a = pK_w - pK_b$ [2], $pK_w = 13.997$ at 25 °C [10]). In the case of the electrometric titration, the values were calculated on the basis of hydrogen ion concentrations, not activities. The activity coefficients of the species involved in the equilibrium should be unity, when $[I_0] \leq 0.010 M$ [10,11], ($[I_0]$ = the sum of the all **I** compounds at the measured pH).

The findings of the α values were carried out by manual calculation without using any software package.

3.2 The Magnitude Order of the pK_b Values.

The pK_b values are constant until about 90 % of the concentration is protonated. This fact shows that compounds **I** produce monobasic conjugate acids in this titration range. The pK_b values are reproducible within errors less than ± 0.02 pK unit. Table 1 lists the pK_b values for compounds **I**. When R is the same alkyl or aryl group, the order of the basicity of compounds **I** is **Ic** > **Ib** > **Ia**. Since the s-tri-



Probable structure of formulae of protonation products

azine ring is a resonance hybrid [13], X at the 2-position will give an electron-donating resonance (+R) effect to the N³ and N⁵ atoms in the ring, and the electron-withdrawing inductive (-I) effect to each atom in the ring.

Since the magnitude of the +R effect of the X is in the order of R¹R²N > RO > R, the electron densities of the N³ and N⁵ atoms in **Ia**, **Ib**, and **Ic** are in the same order as R¹R²N > R > RO. This effect contributes to a decrease in the electron density of each atom in the ring and to a decrease in the +R effect. The orders of the +R and -I effects are not conformable. From the pK_b values obtained here, the basicity order of compounds **I** is **Ia** < **Ib** < **Ic**. This fact means that the sum of both the +R and -I effects cause the magnitude of the electron densities of the ring N¹ atom, at which the protonation occurs, to be R¹R²N > R > RO.

3.3 The effect of the Substituent X on the pK_b Values.

The Hammett relationship [14] holds for the pK_a values of such heterocyclic compounds as pyridine, thiophen, furan, quinoline derivatives, etc.[15]. Correlation of the pK_a values of compounds **I** with the Hammett constants, σ_p and σ_m, has been studied by Morimoto [5]. His pK_a value of **1** (= 4.15), however, differs from ours [pK_a = 3.50 = 14.00 - pK_b (= 10.50, 25° C)] [16]. Differences of 0.9 - 0.4 pK unit were also observed between the pK_a (or pK_b) values determined by Morimoto [5] and those by Dixon *et al.* [2], Dudley [3], Hirt *et al.* [4], and Roth *et al.* [23,*] for **9**, **11**, **12**, and **18** (Table 1). The pK_b values determined here agree fairly well with the values obtained by other authors [2,3,4,23].

Charton [17] has already reported that the pK_a values of *o*-substituted pyridines and quinolines correlate well with σ_m and σ_I, but poorly with σ_p. Therefore, the values obtained here were plotted against substituent constants. In case of **I**, a correlation between the pK_a values and σ_p was not observed [5,6], but an approximately linear relationship was observed between those and σ_m [5,6,7] (Figure 1). However, the points corresponding to MeO and *n*-BuHN groups deviated considerably from the line. The values of ρ, r, and pK_a at σ_m = 0 were calculated with

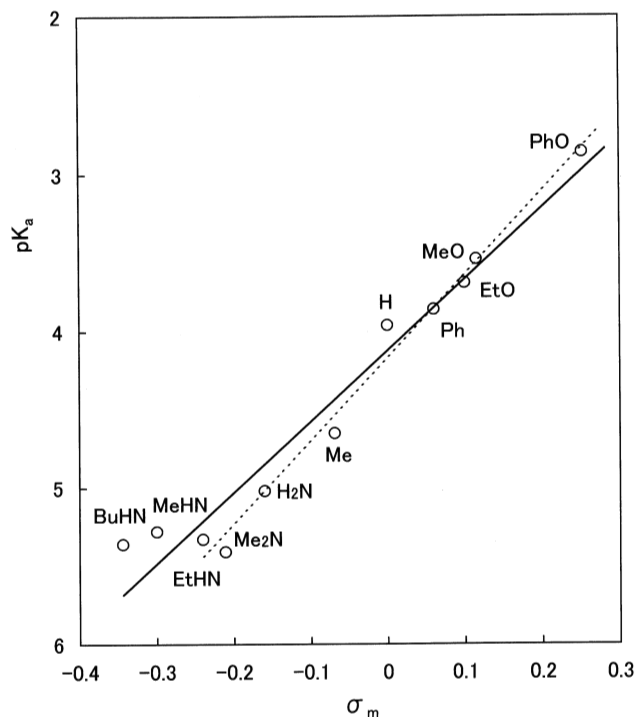


Figure 1. Plots of the pK_a values of **I** versus the substituent constants σ_m, solid line: Calculation No. 1 in Table 2, dotted line: Calculation No. 2 in Table 2.

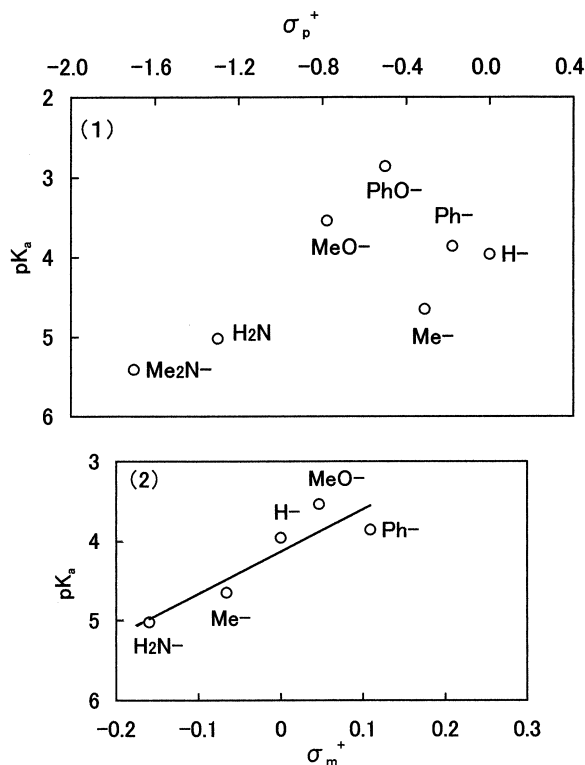
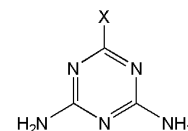


Figure 2. Plots of the pK_a values of **I** versus the substituent constants σ_p⁺ (1) and σ_m⁺ (2).

Table 1
Analytical data and Basicity Constants (pK_b) and Acidity Constants (pK_a)
of 2-Substituted 4,6-Diamino-s-triazines ($pK_a = 14.00 - pK_b$, at 25°C)



No	X	Recrystallization Solvent	mp °C		N%		pK_a	pK_b	pK_a
			Found	in Ref	Found	Calcd.			
1	CH ₃ O	dioxane	229-230	229-230 [a,b]	49.94	49.63	10.46		4.15 [d]
2	C ₂ H ₅ O	EtOH	176-178	182 [a]	45.21	45.14	10.31		3.20 [d]
3	<i>n</i> -C ₃ H ₇ O	<i>i</i> -PrOH	182-183	182-183[a,b]	41.46	41.40	10.37	10.30 [m]	----
4	<i>i</i> -C ₃ H ₇ O	water	170-171	172 [a,b]	41.46	41.40	10.20		
5	CH ₂ =CHCH ₂ O	<i>i</i> -PrOH	181-182	181-182 [a,b]	41.66	41.90	10.53	10.57 [n]	
6	<i>n</i> -C ₄ H ₉ O	EtOH	180-181	174-175 [a,b]	38.29	38.23	10.33		
7	<i>i</i> -C ₄ H ₉ O	water	188-189	186 [a]	38.03	38.23	10.30		
8	<i>s</i> -C ₄ H ₉ O	dioxane	175-176	173-174 [a]	38.24	38.23	10.16		
9	C ₆ H ₅ O	<i>n</i> -BuOH	250-252	255-258 [c]	34.15	34.47	11.14	11.2 [m]	3.70 [d]
10	C ₆ H ₅ CH ₂ O	water	188-189	187 [a]	32.07	32.24	10.40		
11	H	water	316-317	318 [k]	63.80	63.04	10.04	10.1 [m], 10.12 [n],	4.50 [d], 3.91 [s]
12	CH ₃	water	269-270	269-270 [d]	56.10	55.97	9.35	9.4 [m,n]	5.00 [d]
13	C ₂ H ₅	MeOEtOH*	306-308	292-294 [q]	50.60	50.30	9.24		5.14 [d]
14	<i>i</i> -C ₂ H ₇	MeOEtOH*-water	262-264	264-266 [q]	46.02	45.72	9.14		
15	<i>n</i> -C ₄ H ₉	MeOEtOH*-water	213-214	209-212 [t]	42.37	41.88	9.24		
16	C ₆ H ₅	water	227-228	227-228 [l]	37.58	37.41	10.14	9.14 [m]	
17	C ₆ H ₅ CH ₂	MeOEtOH*	244-246	244-245 [q]	34.90	34.80	9.72		
18	H ₂ N	water		353 [e]		66.67	8.98	9.0 [n,o,v], 8.9 [o], 9.05 [v]	5.0 [p], 5.35 [d]
19	CH ₃ NH	water	360-261	257-258 [f]	59.60	59.99	8.72	8.9 [m]	
20	(CH ₃) ₂ N	water	302-303	307-308 [g]	54.17	54.52	8.59		
21	C ₂ H ₅ NH	MeOH	169-170	171-172 [h]	54.19	54.52	8.67	8.77 [n]	
22	(C ₂ H ₅) ₂ N	<i>i</i> -PrOH	167-169	168-170 [h]	46.03	46.12	8.12	8.38 [n]	
23	HOC ₂ H ₄ NH	EtOH	224-225	225-227 [i]	49.28	49.40	8.84		
24	(HOC ₂ H ₄) ₂ N	EtOH	202-203	199-202 [j]	39.23	39.23	8.66	8.89 [n]	
25	<i>i</i> -C ₃ H ₇ NH	water	225-226	216-218 [u]	50.11	49.96	8.55		
26	CH ₂ =CHCH ₂ NH	water	178-180	178-179 [r]	50.32	50.56	8.80		
27	<i>n</i> -C ₄ H ₉ NH	<i>i</i> -PrOH	167-169	167-169 [h]	45.96	46.12	8.64		
28	C ₆ H ₅ NH	MeOH	208-209	204-205 [h]	41.85	41.56	9.32	9.35 [n]	
29	C ₆ H ₅ CH ₂ NH	water	142-143		38.78	38.86	8.80		
30	O(CH ₂ CH ₂) ₂ N	<i>i</i> -PrOH	248-250			42.84	9.04		

[a] J. Controulis and C. K. Banks, *J. Am. Chem. Soc.*, **67**, 1946 (1945). [b] The mp (°C) of compounds synthesized by Dudley et al. are as follows: 1:238, 3:182-184, 4: 170-171, 5:181-182, 6:178. J. R. Dudley, J. T. Thurston, F. C. Schaefer, D. Holm-Hansen, C. J. Hull, and P. Adams, *J. Am. Chem. Soc.*, **73**, 2986 (1951). [c] F. C. Schaefer, J. T. Thurston, and J. R. Dudley, *J. Am. Chem. Soc.*, **73**, 2990 (1951). [d] Compd. 9 (UV method: UV), the other Comps. (Electrometric titration: ET), G. Morimoto, *Nippon Kagaku zasshi*, **87**, 790 (1966). [e] M. Okano and Y. Ogata, *J. Am. Chem. Soc.*, **74**, 5728 (1952); [f] J. T. Thurston, USP 2,460,397 (1949); *Chem. Abst.*, **43**, 5052a (1949); [g] D. W. Kaiser, USP, 2,567,847; *Chem. Abst.*, **46**, 2587c (1952); [h] D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer I. Hechenbleikner, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2984 (1951); [i] F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5928 (1955); [j] S. L. Vail, J. G. Frick, and J. D. Reid, *Am. Dyestuff Repr.*, **50**, 356 (1961). [k] M. Yamashita, *J. Chem. Soc. Jpn. Ind. Chem. Sec.*, **54**, 786 (1951); [l] J. K. Simons and M. R. Saxton, "Organic Synthesis" Coll. **IV**, Wiley, New York, 1963, p. 78; [m] UV, R. C. Hirt, R. G. Schmitt, H. L. Strauss, and J. G. Koren, *Chem. Eng. Data*, **6**, 610 (1961); [n] ET, J. R. Dudley, *J. Am. Chem. Soc.*, **73**, 3007 (1951); [o] 9.0 (ET), 8.9 (UV), J. K. Dixon, N. Woodberry, and G. W. Costa, *J. Am. Chem. Soc.*, **69**, 599 (1947); [p] UV, R. C. Hirt, F. Halverson, and F. T. King, *Spectrochimica Acta*, **13**, 966 (1969); [q] Y. Ogata, A. Kawasaki, and K. Nakagawa, *Tetrahedron*, **22**, 157 (1966); [r] J. T. Ursprung and G. G. Zins (to Upjohn Co.), USP 3,270,014; *Chem. Abst.*, **50**, 10966d (1956); [s] U V, B. Roth and J. Z. Strelitz, *J. Org. Chem.*, **34**, 821 (1969); [t] K. Rehnelt, *Monatsh.*, **86**, 653 (1955); *Chem. Abst.*, **50**, 10109e (1956); [u] D. W. Kaiser (to Am. Cyanamid Co.) USP 2,567,847 (1951); *Chem. Abst.*, **46**, 2588a (1952); [v] 9.0 (ET), 9.05 (UV), I. M. Klotz and T. Askounius, *J. Am. Chem. Soc.*, **69**, 801 (1947). * methoxyethanol (ethyleneglycol monomethylether).

omission of the data for *n*-, *i*-PrO, *n*-BuO groups have not been accurately determined. The $pK_a - [0.97\sigma_m + 0.03\sigma_p]$ correlation is somewhat better (Table 2, Calculation. 3, 6).

The plots of pK_a values versus σ_m^+ gave an almost linear relationship (Figure 2, Table 2, Calculation 8). The plots of pK_a values vs. σ_m gave a better linearity than σ_m^+ . A possible explanation is as follows: Since the Hammett constants have been determined on the basis of the ionization constants of *para* and *meta* substituted benzoic acids, the direct resonance contribution of σ^+ type is already included in the equilibria of these ionization reactions. Linearity in

the plots of the pK_a values versus σ_m indicates that, therefore, the resonance (R) effect between the substituent and the reaction center is not much larger in the protonation of **I** than in the ionization of substituted benzoic acids.

The substituent constant σ^o is, on the other hand, the standard substituent constants which have been determined in such a reaction system that include no direct conjugation between the substituents and the reaction center. In plots of the pK_a values – Taft's set of σ_p^o [19], as well as Yukawa – Tsuno's set of σ_p^o [20] (Figure 3-(1)), the point corresponding to MeO group deviates greatly from the line in the both plots.

Table 2
The Relationships between the pK_a Values of **I**'s and Various Substituent Constants

Calcn. No.	Correlation	ρ [a]	95% CL [b]	i [c]	95% CL [d]	r [e]	F [f]	s [g]	n [h]	Substituents
1	σ_m	-4.54	0.769	4.12	0.152	0.9757	178	0.188	11	PhO, MeO, EtO, Ph, H, Me, H ₂ N, Me ₂ N, MeHN, EtHN, BuHN
2	σ_m	-5.45	0.639	4.18	0.0918	0.9932	424	0.0928	8	Above minus MeHN, EtHN, BuHN
3	$0.97\sigma_m + 0.03\sigma_p$	-4.53	0.741	4.08	0.150	0.9773	190	0.180	11	The same as Calcn. No. 1
4	$0.95\sigma_m + 0.05\sigma_p$	-5.41	0.585	4.10	0.0846	0.9942	512	0.0846	8	The same as Calcn. No. 2.
5	$0.96\sigma_m + 0.04\sigma_p$	-5.43	0.576	4.11	0.0831	0.9944	511	0.0846	8	The same as Calcn. No.2.
6	$0.97\sigma_m + 0.03\sigma_p$	-5.44	0.577	4.13	0.0831	0.9944	523	0.0839	8	The same as Calcn. No.2
7	$0.98\sigma_m + 0.02\sigma_p$	-5.44	0.593	4.15	0.0853	0.9941	516	0.0844	8	The same as Calcn. No. 2
8	σ_m^+	-5.30		4.13		0.9042		0.233	5	MeO, Ph, H, Me, H ₂ N
9	σ_m^o	-6.39		4.22		0.9666		0.174	5	MeO, H, Me, H ₂ N, Me ₂ N
10	σ^u	-4.80		4.12		0.9676		0.130	7	H ₂ N, Me ₂ N, H, Me, Et, <i>i</i> -Pr, Ph
11	σ_I	-4.14		4.45		0.9889		0.086	6	MeO, PhO, Me, Et, Ph, PhCH ₂
12	$0.76\sigma_I + 0.24\sigma_R$	-9.07	1.265	4.09	0.113	0.9904	295	0.113	8	PhO, MeO, Ph, H, Me, Et, H ₂ N, Me ₂ N
13	$0.77\sigma_I + 0.23\sigma_R$	-9.04	1.233	4.14	0.108	0.9908	320	0.107	8	The same as Calcn. No.12
14	$0.78\sigma_I + 0.22\sigma_R$	-8.97	1.333	4.18	0.117	0.9891	273	0.116	8	The same as Calcn. No. 12
15	$\sigma^*(RO)$	-1.15	0.135	3.56	0.0323	0.9914	533	0.0356	9	<i>n</i> , <i>i</i> , <i>s</i> -Bu, <i>n</i> , <i>i</i> -Pr, Et, Me, CH ₂ =CHCH ₂ , Ph
16	$\sigma^*(R)$	-1.30	0.116	4.61	0.0368	0.9971	861	0.0289	7	<i>n</i> -Bu, <i>i</i> -Pr, Et, Me, PhCH ₂ , H, Ph
17	$\sigma^*(RHN)$	-0.538	0.094	5.29	0.0289	0.9813	207	0.0263	9	<i>n</i> -Bu, <i>i</i> -Pr, Et, Me, CH ₂ =CHCH ₂ , HOC ₂ H ₄ , PhCH ₂ , H, O(CH ₂ CH ₂) ₂
18	$\sigma^*(R^1R^2N)$	-0.652	0.079	5.62	0.0443	0.9891	310	0.0308	10	Et ₂ N, <i>i</i> -PrHN, <i>n</i> -BuHN, EtHN, MeHN, HOC ₂ H ₄) ₂ N, HOC ₂ H ₄ HN, CH ₂ =CHCH ₂ HN, PhCH ₂ HN, H ₂ N

[a] Reaction constant; [b] 95% confidence limit (\pm) of the ρ value; [c] Intercept of regression line with the ordinate ($\sigma = 0$); [d] 95% confidence limit (\pm) of the i value; [e] Correlation coefficient (absolute value); [f] F test for significance of regression; [g] Standard deviation; [h] The number of the compounds used in the calculations.

The plots of Taft's σ_m^o set (Figure 3 -(2)) seems to give a line, of which ρ , i , and r are shown in Table 2 (Calculation 9).

The plots (Figure 4) of the pK_a versus σ^n , which were proposed by Wepster *et al.* [21], gave approximately linear

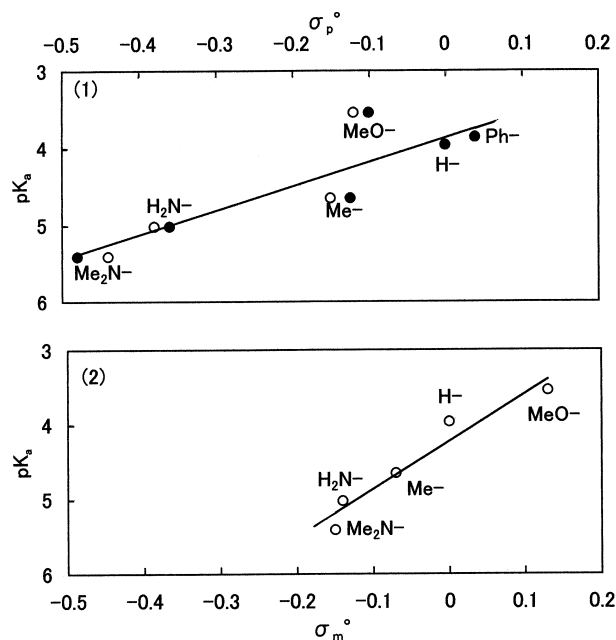


Figure 3. Plots of the pK_a values of **I** versus the substituent constants σ_p^o (1) and σ_m^o (2); \circ : Taft's set of σ_p^o , \bullet : Yukawa and Tsuno's set of σ_m^o .

relationship as for the points corresponding to Ph, H, Me, Et, *i*-Pr, H₂N, and Me₂N groups, but those corresponding to PhO, MeO, and EtO groups deviated from the line. Accordingly, a linear relationship does not hold for the plots of the pK_a values versus σ^n .

Figure 5 contains the plot of the pK_a values versus σ_I that was proposed as the inductive substituent constants by Taft [22b]. The points corresponding to Me, Et, Ph, PhCH₂, MeO, and PhO groups lie approximately on a line, but those corresponding to H, H₂N and Me₂N deviate from the line; the latter two deviations are especially large. Therefore, a linear relationship does not exist between the

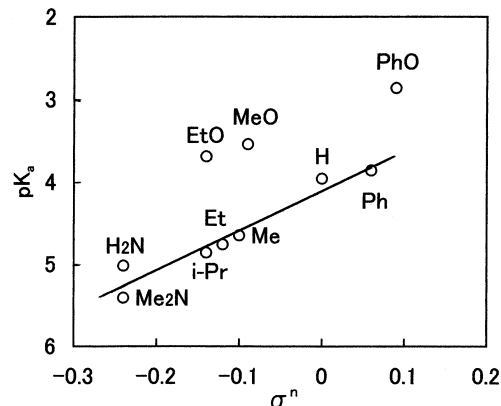


Figure 4. Plots of pK_a values of **I** versus the substituents constants σ^n .

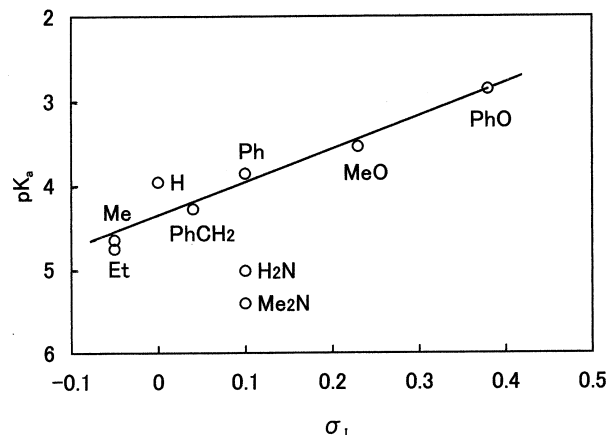


Figure 5. Plots of the pK_a values of **I** versus the substituent constants σ_I .

pK_a values and σ_I . The plots of the pK_a values versus σ_m^o , σ_p^o , σ^n , and σ_I do not give good linear relationships. These facts are attributable to the contribution of the direct resonance interaction of σ^+ type in the equilibria.

The pK_a values of substituted 2,4-diaminopyrimidines [23] correlated very successfully with $[\alpha\sigma_I + (1 - \alpha)\sigma_R^-]$ ($0 < \alpha < 1$) [24] as shown by the following: (1) the major effect of 5-substitution was inductive, but there was a greater resonance component than could be explained by the correlation with the Hammett σ_m constants, and the best correla-

tion was achieved with the equation $\log(K/K_0) = \rho[0.72\sigma_I + 0.28\sigma_R^-]$, and (2) on the other hand, the effect of 6-substitution was almost completely inductive and the equation $\log(K/K_0) = \rho[0.96\sigma_I + 0.04\sigma_R]$ best satisfied the data in this case.

In the case of **I** a good linear correlation is observed between the pK_a values and the combination parameter, $[\alpha\sigma_I + (1 - \alpha)\sigma_R]$ [23], when $\alpha = 0.77$ (Figure 6, Table 2, Calculation 13). The pK_a values versus σ_m correlation ($X = \text{PhO, MeO, EtO, Ph, H, Me, H}_2\text{N, Me}_2\text{N}$) (Table 2, Calculation 2) is somewhat better than that of the pK_a versus $[\alpha\sigma_I + (1 - \alpha)\sigma_R]$ ($\alpha = 0.24, 0.23, 0.22$) (Table 2, Calculation. 12, 13, 14) ($X = \text{PhO, MeO, Ph, H, Me, Et, H}_2\text{N, Me}_2\text{N}$).

As seen from the description above, σ_m gave the best linear correlation among several kinds of substituent constants used singly. The Hammett substituent constants contain both the factors corresponding to I and R effects, and the σ_m values express mainly the I effect and the σ_p values express the sum of I and R effects. Accordingly the substituent group at the 2-position causes more of the +R effect than the -I effect at the N¹, N³, and N⁵ atoms. Nevertheless, the best linear correlation was observed between the pK_a values and $[0.97\sigma_m + 0.03\sigma_p]$ (Table 2, Calculation 6).

This fact indicates that the substituent causes the ring N atoms the I effect to a greater extent than the R effect. Furthermore, the fairly good correlation with $[0.77\sigma_I +$

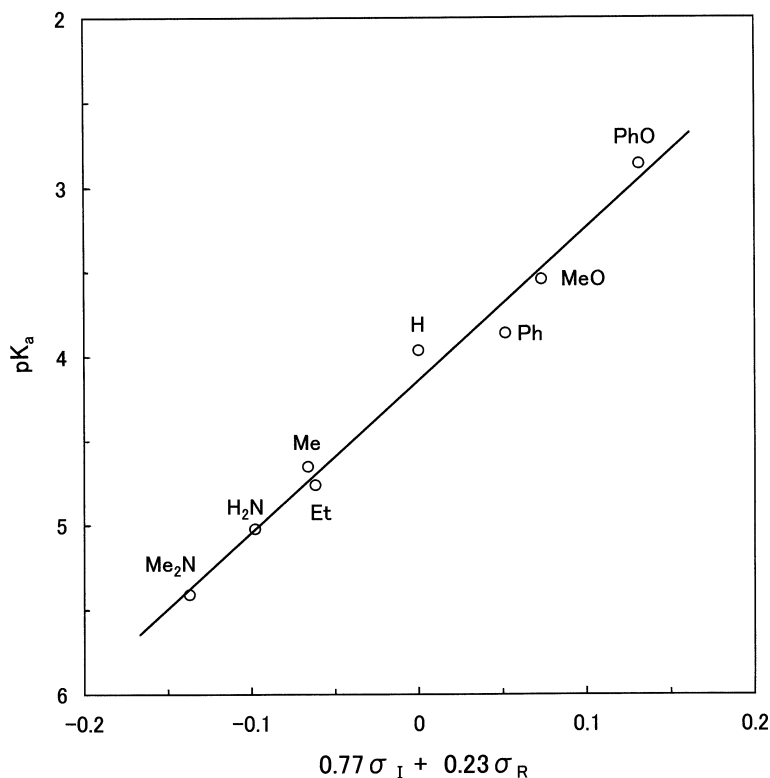
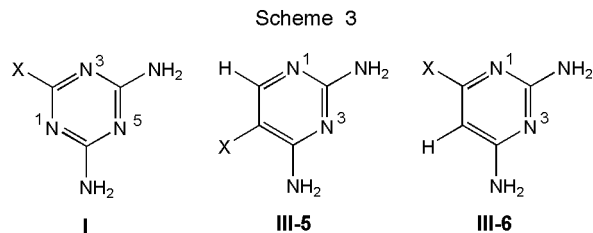


Figure 6. Plots of the pK_a values of **I** versus the combination substituent constants $[0.77\sigma_I + 0.23\sigma_R]$.



Comparison of structural formulae of **I** and **III**

$0.23\sigma_R$] (Table 2, Calculation 13) indicate that the substituent exerts significant resonance contribution to the ring N atoms. These conclusions are similar to those of studies on the proton addition to 5- and 6-substituted 2,4-diaminopyrimidines [23] as well as to *o*-substituted pyridines and quinolines [17].

3.4 The Position of Proton Addition Onto I.

The protonation of 2,4,6-triamino-*s*-triazine, **18**, has been reported to take place at the one of the three N atoms in the triazine ring [2,3,4,12]. Morimoto has reported that in the protonation of **Ia** and **Ic** in water a proton adds to the N¹ or N³ atom and in that of **Ic** adds to the N⁵ atom. On the other hand, Korolev *et al.* [7] have reported that a proton adds to the N¹ (or N³) atom in nitromethane.

In the case of **I**, N³ is equivalent to N¹. That is, excluding the amino groups, the protonation occurs at N³ = N¹ or at N⁵. When the substituent X is a resonance-effect electron donor (X_{rd}), protonation is favored at N³ = N¹, presumably when X is a resonance electron acceptor (X_{ra}), protonation is favored at N⁵.

In 5- and 6-substituted 2,4-diaminopyrimidine (**III-5** and **III-6**), the protonation takes place at a ring N atom [23]. In the case of **III-5** the position of the substituent is *meta* to both the N¹ and the N³ atoms. The position of the 2-amino group is *ortho* to both the N¹ and the N⁵ atoms, and that of 4-amino group is *ortho* to the N³ and *para* to the N¹ atom. Since the R effect is greater at the *para* position than at the *ortho* position, the protonation should take place at the N¹ atom. This is in agreement with **I**, where amino groups are both *ortho* to the N⁵ atom that does not protonate. Each amino group is *ortho* to one of other N atoms and *para* to another. In the case of **III-6** the protonation takes place again most likely at the N¹ atom.

To determine where the protonation actually occurs, the comparison can be made between the ρ values, for the pK_a 's - σ_m and σ_p correlations, of 2-, 3-, and 4-substituted pyridinium and 2-, 3-, and 4-substituted quinolinium ions [17]. Plots of the pK_a values for **I** versus σ_m , [$0.77\sigma_1 + 0.23\sigma_R$], and [$0.97\sigma_m + 0.03\sigma_p$] gave a very good linear relationship, respectively. In the protonation of **I**, the -I

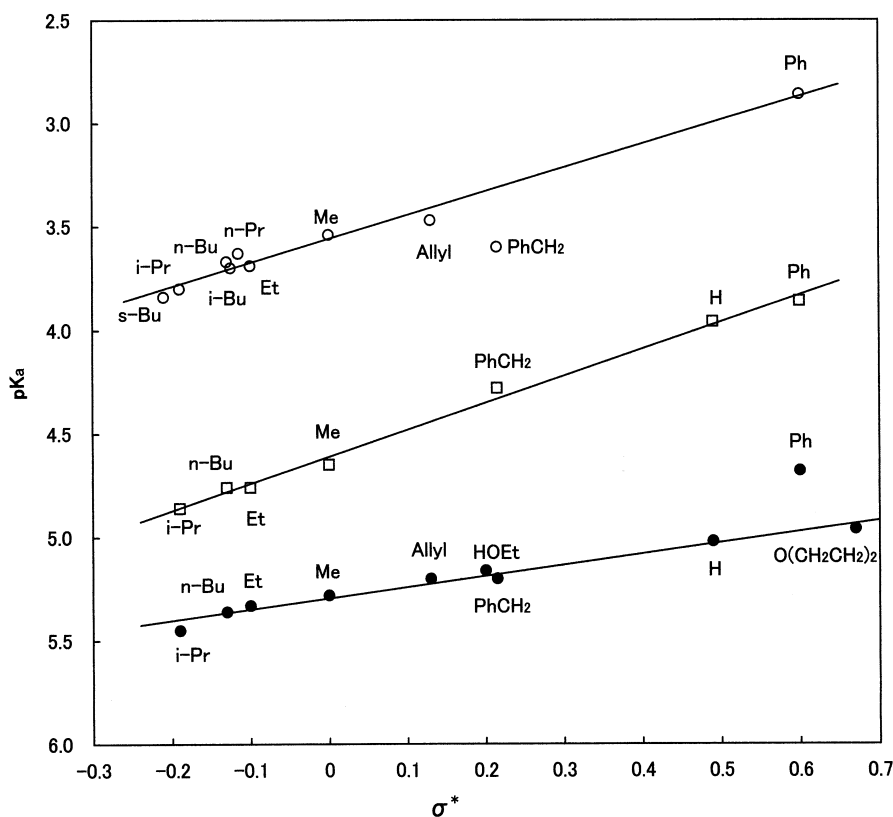


Figure 7. Plots of the pK_a values of **Ia**, **Ib**, and **Ic** versus Taft's substituent constants σ^* ; \circ : **Ia**; T-OR, \square : **Ib**; T-R, \bullet : **Ic**; T-NHR; T = 2,4-diamino-*s*-triazine ring.

effect of the X is more predominant than the +R effect. The results obtained here are in agreement with the protonation at the $N^3 = N^1$ atom, those reported for **III-5** are in accord with the protonation at the N^1 atom, and those for **III-6** are also in agreement with the protonation at the N^1 atom.

3.5 Applicability of Ingold-Taft Equation to the pK_a Values.

Taft [25] has reported that the σ^* is the substituent constants dependent only upon the net polar effect of the substituent and also is the value containing only the I effect. On the other hand, after that Charton [26] has reported that

Me_2N , $O(CH_2CH_2)_2N$, and $PhNH$ groups, the others are approximately on the line. The calculated constants and others are given in Table 2 (Calculation 18) (The three points above were excluded from the calculations.). The ρ^* value of the **Ia** series is very close to that of **Ib**. However, the ρ^* value of the **Ic** series is about a half of those of **Ia** and **Ib**. From this fact, it is understandable that a few points of the **Ic** series deviate from the line in the plots of the pK_a values of **I** versus σ_m (Figure 1).

The magnitude order of the ρ^* values is **Ib** > **Ia** > **Ic** and is opposite to that of the +R effect ($R^1R^2N > R > RO$) of

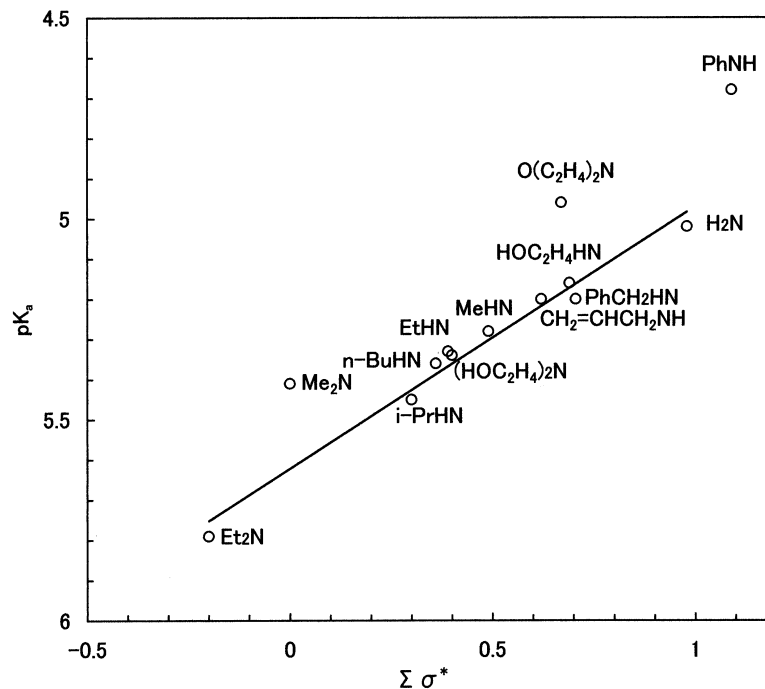


Figure 8. Plots of the pK_a values of **Ic** versus Taft's substituent constants of $\Sigma\sigma^*$.

the σ^* values are actually composed of steric effect and polarizability contributions.

However, the Taft relationship, the equation $\log(K/K_0) = \rho^*\sigma^*$ has held for aliphatic systems, in which the inductive contribution is predominant. Therefore, it can be considered that the correlation exists between the pK_a values and the σ^* values from the conclusions described above.

Thus, the pK_a values of **Ia**, **Ib**, and **Ic** were plotted against σ^* [25,27] (Figure 7). Although the points corresponding to $PhCH_2$ group in **Ia** and the Ph group in **Ic** deviate from the respective line, the points of **Ia**, **Ib** and **Ic** give a fairly good straight line. The constants ρ^* , i , r , s , and others for the three lines were calculated excluding the value of the $PhCH_2$ group in the **Ia** series and that of the Ph group in the **Ic** series. The calculation results were listed in Table 2 (Calculation 15, 16, 17).

Furthermore, the pK_a values of **Ic** were plotted against $\Sigma\sigma^*$ (Figure 8). Except for the points corresponding to

the substituents, and does not agree with the magnitude order of the -I effect ($R^1R^2N > R > RO$) of the substituents. The reason why the three ρ^* values are different and opposite to the order of the +R effect are not clear. The difference of the ρ^* values has been observed in the pK_a values of substituted aliphatic ammonium ion series [28]. It has been reported that the ρ^* values are 3.24, 3.23, 3.30 for primary, secondary, and tertiary ammonium ion series, respectively. However, the reason why the ρ^* values are different has not been clarified.

4 Summary.

The pK_a values of **I** showed very good correlations with σ_m (or $[0.97\sigma_m + 0.03\sigma_p]$), $[0.77\sigma_I + 0.23\sigma_R]$, and σ^* . However three facts remain unexplainable: (1) the deviation of the points corresponding to n -BuHN and MeO groups from the σ_m - correlation, (2) the deviation of the point corresponding to $PhCH_2$ group from the σ^* - correlation in

Ia series and that of the point corresponding to **Ph** group from the σ^* – correlation in **Ic** series and (3) the difference in the ρ^* values.

The substituent at the 2-position causes an -I effect at N¹, N³, and N⁵ atoms and a +R effect at the N³, N¹, and N⁵ atoms of the triazine ring. The conclusion obtained in this study is that the interaction between the substituent and the reaction center is predominant in the I effect, which means that the protonation takes place at the ring N³ (or N¹) atom.

In the case of substituted 2,4-diaminopyrimidine, the effects of the substituent at the 5- or 6-position on the ionization constants can be interpreted reasonably on the basis of the protonation at the ring N¹ atom [23].

REFERENCES AND NOTES

- † Correspondence address: 68-2, Higashi, Hitachino, Ushikushi, Ibaraki-ken 300-1207 JAPAN.
- [1] T. Tashiro and M. Oiwa, *J. Polym. Sci., Polym. Chem. Ed.*, **19**, 646 (1981). * In the reaction of **I** with formaldehyde at pH 7.00, a linear relationship has been observed between the logarithm of the rate constants (k_f) and the pK_b , as well as σ_m , respectively. However the relationships have not been obtained at pH 10.20, and on the whole, the k_f is larger in **I** with large pK_b value than in that with small one. And at pH 4.00, the plots of $\log k_f$ versus σ_m and the pK_b values showed the existence of the minimum k_f . That is, the pK_b value has given an influence on the k_f at pH 7.00, 4.00 and 10.20.
- In the methylene-bond formation of hydroxymethylated compounds **1** (X = MeO) with **1** in acidic aqueous solutions, the rate constants (k_m) were maximum at the $[\text{H}_3\text{O}^+] = [\text{H}_2\text{O}]/\sqrt{K_1 K_2}$ ($K_1, K_2 =$ the equilibrium constant of protonation of hydroxymethylated **1** and **1**, respectively). In the reactions of hydroxymethylated compounds **1** the maximum k_m was obtained at $[\text{H}_3\text{O}^+] = [\text{H}_2\text{O}]/K_1$ [*]. The K_1 and K_2 values can be calculated from the pK_b values. [*] T. Tashiro and M. Yasuda, *Kobunshi Kagaku (Japanese J. Polym. Sci. Technol.)*, **24**, 538 (1967), *ibid.* **25**, 400 (1967), T. Tashiro, *ibid.* **27**, 177, 530 (1970), T. Tashiro, *Makromol. Chem.*, **167**, 249 (1973).
- [2] J. K. Dixon, N. T. Woodberry, and G. W. Costa, *J. Am. Chem. Soc.*, **69**, 599 (1947).
- [3] J. R. Dudley, *J. Am. Chem. Soc.*, **73**, 3007 (1951).
- [4] R. C. Hirt and R. G. Schmitt, H. L. Strauss, and J. G. Koren, *Chem. Eng. Data*, **6**, 610 (1961).
- [5] G. Morimoto, *Nippon Kagaku Zasshi*, **87**, 790 (1969).
- [6] T. Tashiro and M. Yasuda, *Kobunshi Kagaku*, **26**, 853 (1969).
- [7] B. A. Korolev and M. A. Mal'tseva, *Zhur. Obsch. Khim.*, **43**, 1556 (1973); *J. Gen. Chem. USSR*, **43**, 1549 (1973).
- [8a] Controullis and C. K. Banks, *J. Am. Chem. Soc.*, **67**, 1946 (1945); [b] J. T. Thurston, J. R. Dudley, D. W. Kaiser, I. Hechenbleikner, F. C. Schaefer, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2981 (1951); [c] D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer, I. Hechenbleikner, and D. Holm-Hansen, *ibid.*, **73**, 2984 (1951); [d] J. R. Dudley, J. T. Thurstone, F. C. Schaefer, D. Holm-Hansen, C. J. Hull, and P. Adams, *ibid.*, **73**, 2986 (1951); [e] F. C. Schaefer, J. T. Thurston, and J. R. Dudley, *ibid.*, **73**, 2990 (1951).
- [9] J. K. Simmons and M. R. Saxton, *Organic Synthesis, Collection Volume IV*, p. 78, Wiley, New York, 1963.
- [10] A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases*, Methuen, London, Chapters 2 and 4, 1962.
- [11] D. G. Lee and R. Srivasan, *Can. J. Chem.*, **51**, 2542 (1973).
- [12] R. C. Hirt and R. G. Schmitt, *Spectrochimica Acta*, **12**, 127 (1958).
- [13] E. W. Hughes, *J. Am. Chem. Soc.*, **63**, 1737 (1941).
- [14] L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, Chap. 11, 1970.
- [15] H. H. Jaffe and H. L. Jones, "Application of Hammett Equation to Heterocyclic Compounds" in "Advances in Heterocyclic Chemistry", **3**, Ed. By A. R. Katritzky and J. M. Lagowsky, Academic Press, New York, p. 209, 1964.
- [16] T. Tashiro and M. Yasuda, *Kobunshi Kagaku*, **24**, 538 (1967).
- [17] M. Charton, *J. Am. Chem. Soc.*, **86**, 2033 (1964).
- [18a] E. Imoto, *Kagakuhan'nou ni okeru Heikou to Sokudo*, Tokyo Kagaku Dojin, Tokyo, pp. 149 – 151, 1967; [b] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958); [c] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958); [d] H. H. Jaffe, *Chem. Revs.*, **53**, 222 (1953); [e] M. Charton, *J. Org. Chem.*, **28**, 3121 (1963).
- [19] R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1969)
- [20a] Y. Yukawa and Y. Tsuno, *Nippon Kagaku zasshi*, **86**, 873 (1965); [b] Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc., Jpn.*, **39**, 2274 (1966); [c] Y. Yukawa, Y. Tsuno, and M. Sawada, *ibid.*, **45**, 1198 (1972).
- [21a] B. M. Wepster, *J. Am. Chem. Soc.*, **95**, 102 (1973); [b] A. J. Hoefnagel, J. C. Monshouwer, E. C. G. Snorn, and B. M. Wepster, *ibid.*, **95**, 5350 (1973), [c] A. J. Hoefnagel and Wepster, *ibid.*, **95**, 5357 (1973).
- [22a] R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 1045 (1957); [b] R. W. Taft, Jr. and I. C. Lewis, *ibid.*, **80**, 2436 (1958).
- [23] B. Roth and J. Z. Strelitz, *J. Org. Chem.*, **34**, 821 (1969); * They have stated that the differences between the pK_a values of **9**, **11**, **12**, and **18** determined by Morimoto and those determined by other researchers (Dudley [3], Hirt *et al.* [4], and Roth *et al.*) are ascribable to possible errors in the buffer standards.
- [24] $0 < \alpha < 1$, $\sigma_R = \sigma_p - \sigma_I$. The σ_p values were taken from McDaniel and Brown's study [18b].
- [25] R. W. Taft, Jr., *Steric Effect in Organic Chemistry*, Ed. By M. S. Newman, Wiley, New York, Chap. 13, 1956.
- [26a] M. Charton, *J. Am. Chem. Soc.*, **97**, 3631 (1975); [b] M. Charton, *ibid.* **99**, 5687 (1977); [c] M. Charton, *J. Org. Chem.*, **44**, 903 (1979).
- [27] The σ^* values of $\text{CH}_2=\text{CHCH}_2\text{HN}$, $\text{O}(\text{CH}_2\text{CH}_2)_2\text{N}$, and $\text{HOC}_2\text{H}_4\text{HN}$ groups were cited from Hall's study [28].
- [28] H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).