CHEMICAL
&
PHARMACEUTICAL BULLETIN

Vol. 14 No. 12 December 1966

[Chem. Pharm. Bull. 14(12) 1321~1332 (1966)]

UDC 545.22 : 547.853.08

177. Satoshi Mizukami and Eizo Hirai : Relationship between pKa (H_2O) of 5-Substituted-4-amino-2-methylpyrimidines and Half Neutralization Potential and the Behavior of the Compounds in Nonaqueous Solvents.

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Since Hall, Conant and Werner[1~4] established the acid-base titration technique in glacial acetic acid, nonaqueous titration has been developed as an analytical method of importance in quantitative determination of acids and bases. Numerous publications in this field continue to appear in the literatures.[5~7] However, there are only a few investigations on nonaqueous titration of pyrimidine bases.[8,9] In this paper, some 5-substituted-4-amino-2-methylpyrimidines are potentiometrically studied as a base in various organic solvents.

On the other hand, in the previous paper[10] the authors reported that on the amino-imino tautomerism of these pyrimidines the amino form existed predominantly in water. Such tautomerism, however, may be affected by solvent.[*2] One of the purposes of the present study is to examine an effect of solvent on the amino-imino tautomerism of the pyrimidines.

Results and Discussion

Potentiometric Titration

The requirements for solvent on potentiometric nonaqueous titration are as follows: (a) both of the sample and its produced salt be soluble in the solvent; and (b) the potential inflection at the end point of titration be sharp and large. Although the

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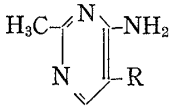
*2 For example, it was found that the ratio of the tautomeric imino isomer to the amino form of acylaminopyridines increases with increasing polarity of solvent.[11]

1) N. F. Hall, J. B. Conant : J. Am. Chem. Soc., **49**, 3047, 3062 (1927).
2) N. F. Hall, T. H. Werner : *Ibid.*, **50**, 2367 (1928).
3) N. F. Hall : *Ibid.*, **52**, 5115 (1930).
4) J. B. Conant, T. H. Werner : *Ibid.*, **52**, 4436 (1930).
5) M. Masui : Bunseki Kagaku, **8**, 511 (1957).
6) J. A. Riddick : Anal. Chem., **24**, 41 (1952); **26**, 77 (1954); **28**, 679 (1956); **30**, 793 (1958); **32**, 172R (1960).
7) C. A. Streuli : *Ibid.*, **34**, 302R (1962); **36**, 363R (1964).
8) C. W. Pifer, E. G. Wollish : *Ibid.*, **24**, 300 (1952).
9) S. Mizukami, E. Hirai : Yakugaku Zasshi, **77**, 165 (1957).
10) *Idem* : J. Org. Chem., **31**, 1199 (1966).
11) Yu. N. Sheĭnker, E. M. Peresleni, N. P. Zosimova, Yu. I. Pomerantsev : Zhur. Fiz. Khim., **33**, 2096 (1959).

latter is closely connected with the accuracy of quantitative determination, little attention has been paid to the problem. The difference between electromotive forces at end- and 99% neutralized-points is measured, and listed as E_{inf} in Table I. The reproducibility of these values is not always satisfactory. A variation of these values may be caused by a variation in liquid junction potentials in electrodes. Although the sharpness and the size of the potential inflection can not be determined in the strict sense of the word, these values may be used as a rough measure. The magnitudes of these values in a given solvent are parallel with increasing of the basicity of the pyrimidines in water.

We conveniently classify the solvent used into three groups, acidic, alcoholic and dipolar aprotic, as shown in Table I.

Table I. Half Neutralization Point (HNP) Values and Potentiometric Inflections (E_{inf} Values) at End Point of Potentiometric Titrations of 5-Substituted-4-amino-2-methylpyrimidines in Various Nonaqueous Solvents



			R =	H	CH_2OH	CH_2NH_2 1st	CH_2NH_2 2nd	$CONH_2$	$COOC_2H_5$	COOH	CHO	CN
	Solvent	pKa[a]	value	6.53	6.34[b]	8.24[b]	5.15[b]	4.97	4.53	2.14	4.46	3.51
Acidic solvents	glac. acetic acid	HNP	mV	365(2)	371(2)	c)	408(4)	393(2)	398(2)	400(2)	404(1)	452(2)
		E_{inf}	mV	52(4)	49(4)		26(5)	42(4)	37(5)	28(4)	30(4)	22(5)
	acetic acid -acetone	HNP	mV	326(2)	329(2)	c)	374(1)	350(2)	361(2)	365(1)	365(3)	422(1)
		E_{inf}	mV	50(3)	51(3)		21(2)	50(4)	47(2)	23(3)	42(3)	14(3)
	acetic acid -acetonitrile	HNP	mV	324(2)	327(1)	c)	377(2)	344(2)	348(2)	352(1)	354(2)	393(1)
		E_{inf}	mV	45(4)	43(3)		22(2)	45(3)	30(4)	21(3)	30(4)	13(4)
Alcoholic solvents	methanol	HNP	mV	108(2)	118(1)	9(2)	196(2)	191(1)	229(2)	d)	238(3)	c)
		E_{inf}	mV	35(3)	35(3)	6(5)	11(4)	15(3)	7(4)		6(5)	
	ethanol	HNP	mV	128(2)	140(2)	44(2)	215(2)	230(2)	257(2)	d)	264(3)	c)
		E_{inf}	mV	40(3)	35(3)	4(4)	10(4)	10(4)	4(5)		5(5)	
	isopropanol	HNP	mV	150(2)	157(3)	82(2)	235(2)	256(2)	c)	d)	c)	c)
		E_{inf}	mV	35(3)	35(4)	3(5)	7(4)	6(4)				
	isopropanol -ethyleneglycol	HNP	mV	76(3)	89(4)	−34(3)	170(3)	172(2)	206(2)	232(2)	208(3)	286(2)
		E_{inf}	mV	47(5)	44(4)	11(5)	23(4)	13(3)	11(3)	6(4)	9(4)	4(2)
Dipolar aprotic solvents	acetone	HNP	mV	78(1)	86(2)	31(4)	e)	d)	242(1)	d)	240(2)	335(3)
		E_{inf}	mV	112(6)	111(8)	12(13)			51(5)		52(5)	21(5)
	methyl ethyl ketone	HNP	mV	148(1)	154(1)	d)	d)	d)	290(2)	d)	300(1)	384(2)
		E_{inf}	mV	105(5)	105(5)				48(6)		40(6)	13(4)
	methyl isobutyl ketone	HNP	mV	152(3)	154(2)	d)	d)	d)	308(3)	d)	323(3)	411(3)
		E_{inf}	mV	156(8)	149(5)				55(5)		51(5)	20(3)
	acetonitrile	HNP	mV	62(3)	71(3)	22(2)	172(2)	d)	204(3)	d)	217(3)	294(4)
		E_{inf}	mV	144(7)	142(8)	8(4)	67(7)		68(6)		54(4)	43(5)

HNP: average of five values. Standard deviation is shown in parentheses.
E_{inf}: average of five values. Standard deviation is shown in parentheses.
a) Ref. 10).
b) Determined by the potentiometric method as described in the previous paper[10]
c) Any potentiometric inflection can not be detected at end point.
d) Insoluble
e) Unstable titration curve

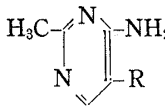
The acidic solvents satisfy all of the above requirements. Even very weak bases, the 5-cyano and 5-carboxy derivatives, which do not give any potential inflection on titration curve in water, can be quantitatively titrated in these solvents. Although the 5-aminomethyl derivative is a diacidic base, each of the titration curves in these solvents shows only one inflection at the second equivalence point.

In dipolar aprotic solvents, the magnitude of the E_{inf} is larger than that in the acidic solvents. Consequently it can be expected that quantitative determination of these pyrimidines in dipolar aprotic solvents will be more accurately carried out than in acidic solvents. Unfortunately, the formers are inferior to the latters in respect to solubility. The 5-aminomethyl derivative in acetone shows only one potential inflection at the first equivalence point and an unstable curve in further titration. This will be discussed later.

There is no point at which the titration behavior of the pyrimidines studied in the alcoholic solvents is superior to those in other nonaqueous solvents and water. The mixture of isopropanol and ethyleneglycol (1:1) is the best of this group. In the mixed solvent, the 5-cyano and 5-carboxy derivatives can be quantitatively titrated.

The results of determination in various solvents are summarized in Table II.

Table II. Determination of 5-Substituted-4-amino-2-methylpyrimidines by Potentiometric Titration in Various Nonaqueous Solvents



Solvent	R = H		CH_2OH		CH_2NH_2		$CONH_2$		$COOC_2H_5$		COOH		CHO		CN	
	%[a]	Std. dev.	%[a]	Std. dev.	%[a]	Std. dev.	%[a]	Std. dev.	%[a]	Std. dev.	%[a]	Std. dev.	%[a]	Std. dev.	%[a]	Std. dev.
Glac. acetic acid	100.0	0.2	99.8	0.2	99.9	0.2	99.7	0.2	100.3	0.3	99.6	0.3	99.8	0.3	100.1	0.5
Acetic acid -acetone	99.8	0.2	99.7	0.2	100.2	0.3	99.8	0.2	99.5	0.4	100.2	0.3	99.5	0.3	100.1	0.5
Acetic acid -acetonitrile	100.0	0.1	99.3	0.2	99.6	0.3	100.2	0.2	100.4	0.4	100.2	0.3	99.8	0.2	99.3	0.6
Methanol	99.8	0.2	99.9	0.3	99.4	0.4	100.3	0.3	99.4	0.4	—		99.5	0.4	—	
Ethanol	99.7	0.2	99.6	0.2	99.8	0.3	99.9	0.3	99.5	0.3	—		99.1	0.5	—	
Isopropanol	99.7	0.3	99.8	0.2	99.5	0.4	100.1	0.2	—		—		—		—	
Isopropanol–ethyleneglycol	99.5	0.2	100.0	0.2	99.8	0.2	100.1	0.1	99.1	0.3	99.7	0.4	99.9	0.2	96.0	0.8
Acetone	99.8	0.1	100.3	0.1	98.9	0.8	—		99.7	0.2	—		100.2	0.2	100.5	0.3
Methyl ethyl ketone	99.5	0.1	99.6	0.2	—		—		99.8	0.2	—		99.8	0.2	99.6	0.4
Methyl isobutyl ketone	99.6	0.1	99.8	0.2	—		—		100.4	0.2	—		99.9	0.2	99.7	0.2
Acetonitrile	99.8	0.2	100.2	0.1	99.9	0.1	—		100.2	0.2	—		100.2	0.2	99.9	0.2

a) Average of five values Std. dev.; standard deviation

Potentials at Half Neutralization Point

Although attempts to determine the basicity (or acidity) in organic solvents have been made by many investigators,[12~15] the methods used were not always complete because the behavior of electrolyte in solvent of low dielectric constant is more complicated than in water. Fritz[16] performed potentiometric titrations of amines in acetonitrile and made the significant observation that the potentials at half neutralization point (HNP values) of the amines could be lineally correlated with the ionization

12) L. C. Smith, L. P. Hammett : J. Am. Chem. Soc., **67**, 23 (1945).
13) M. M. Davis, H. B. Hetzer : *Ibid.*, **76**, 4247 (1954).
14) G. J. Janz, S. S. Danyluk : Chem. Revs., **60**, 209 (1960).
15) E. Grunwald, B. J. Berkowits : J. Am. Chem. Soc., **73**, 4939 (1951).
16) J. S. Fritz : Anal. Chem., **25**, 407 (1953).

constants in water. Similar results were also observed in other solvents.[17,18] Hence it was recognized that the HNP values could be used as a rough measure for relative base strength in a given solvent.

The HNP values of the pyrimidines studied in nonaqueous solvents are listed in Table I. Fig. 1 shows that in each of the solvents a linear relationship exists between the HNP values and the pKa (H_2O) values, although there are some exceptions. Each of the relationships may be expressed by the general equation (1).

$$\mathrm{HNP}=\alpha\cdot\mathrm{pKa}+\beta \qquad (1)$$

Here α is a proportionality constant. α and β values in Table III are obtained by the method of least squares.

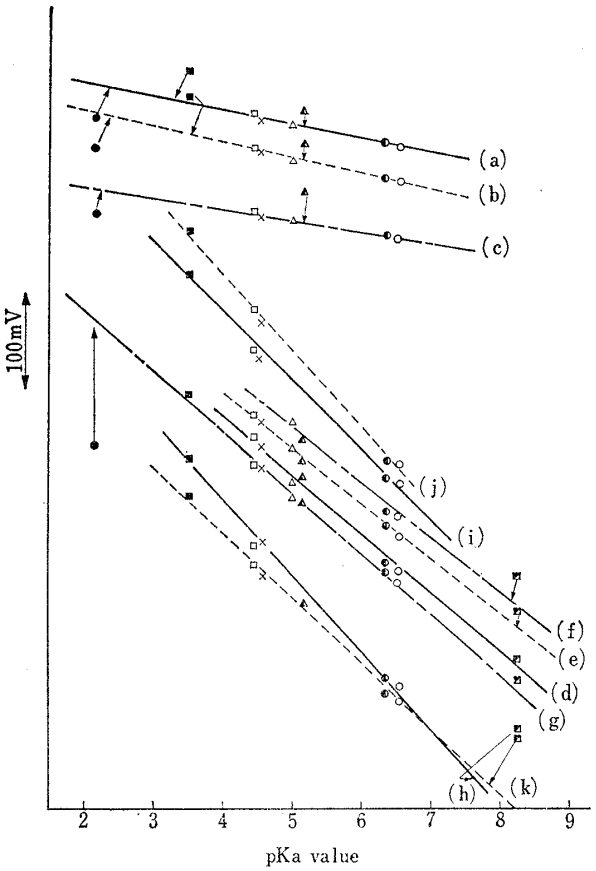


Fig. 1. Relationship between HNP Values and pKa (H_2O) Values of 5-Substituted-4-amino-2-methylpyrimidines

Substituent : ◪, CH_2NH_2; ○, H; ◐, CH_2OH; ▲, $CH_2NH_3^+ClO_4^-$; △, $CONH_2$; ×, $COOC_2H_5$; □, CHO; ■, CN; ●, COOH.

Solvent : (a) glac. acetic acid; (b) acetic acid-acetone; (c) acetic acid-acetonitrile; (d) methanol; (e) ethanol; (f) isopropanol; (g) isopropanol-ethyleneglycol; (h) acetone; (i) methyl ethyl ketone; (j) methyl isobutyl ketone; (k) acetonirile.

The basicity of the 5-carboxy derivative is considerably enhanced in the acidic solvent and the mixture of isopropanol and ethyleneglycol. Particularly, in the acidic solvents the basicity is practically identical with that of the 5-ethoxycarbonyl derivative. This will be discussed in the following paper. On the other hand, the 5-cyano derivative in the acidic solvents and the 5-aminomethyl derivative in the acidic solvents, acetone and acetonitrile show a considerable depression of their basicities.

In the previous paper,[10] we reported that the Hammett's equation can be applied to the pKa values of 5-substituted-4-amino-2-methylprimidines without modification. Accordingly it is presumed from equation (1) that the Hammett's equation may be applied to the HNP values. This expectation is realized in Fig. 2. The Hammett's equation is expressed by the following form (2).

$$\frac{F}{2.303RT}(\mathrm{HNP}^\circ-\mathrm{HNP})=\rho\sigma_m \qquad (2)$$

Here, the HNP° value corresponds to the HNP value of 4-amino-2-methylpyrimidine, the substituent constant (σm) of which is zero. F is the Faraday constant, R is the gas constant and T is the absolute temperature. The reaction constants (ρ values) are reported in Table III. Considerable deviations from the Hammett's equation are found in the cases of the 5-cyano derivative in acidic solvents and of the 5-carboxy derivative in mixed solvent of isopropanol and ethyleneglycol.

17) H. K. Hall, Jr. : J. Phys. Chem., **60**, 63 (1956).
18) C. A. Streuli, R. R. Miron : Anal. Chem., **30**, 1978 (1958).

Table III. Relationships between pKa Values and Half Neutralization Potentials in Various Solvents

Solvent	Dielectric constant	HNP = α·pKa + β (mV)	Estimated standard deviation (mV)	Hammett's ρ constant
Glac. acetic acid	6.20	HNP = −17.1 pKa + 478	±2.2	1.57
Acetic acid–acetone		−17.9 pKa + 442	±2.5	1.05
Acetic acid–acetonitrile		−13.1 pKa + 410	±2.2	1.21
Methanol	32.6	−60.1 pKa + 503	±3.6	5.52
Ethanol	24.3	−65.1 pKa + 553	±1.9	5.98
Isopropanol	18.3	−67.0 pKa + 585	±5.3	6.16
Isopropanol–ethyleneglycol		−66.7 pKa + 512	±5.5	6.13
Acetone	20.7	−84.8 pKa + 626	±7.6	7.79
Methyl ethyl ketone	18.5	−77.4 pKa + 649	±7.1	7.11
Methyl isobutyl ketone	13.1	−86.6 pKa + 709	±8.4	7.96
Acetonitrile	37.5	−76.5 pKa + 559	±6.0	7.03
Water	80.0			5.39[a]

a) Ref. 10)

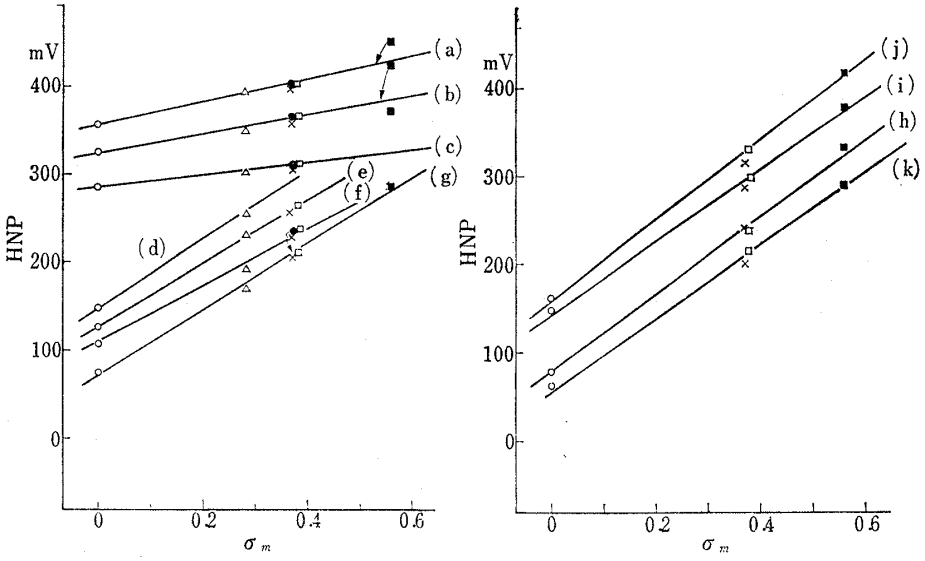


Fig. 2. Relationship between Hammett's σ_m and HNP Values of 5-Substituted-4-amino-2-methylpyrimidines in Various Solvents

Substituent: ○, H; △, $CONH_2$; ×, $COOC_2H_5$; ●, COOH; □, CHO; ■, CN.

Solvent: (a) glacial acetic acid; (b) acetic acid-acetone; (c) acetic acid-acetonitrile (−40 mV); (d) isopropanol; (e) ethanol; (f) methanol; (g) isopropanol-ethyleneglycol; (h) acetone; (i) methyl ethyl ketone; (j) methyl isobutyl ketone (+10 mV); (k) acetonitrile

Hammett[19] suggested that the ρ value have the form (3): where D is the dielectric

$$\rho = \left(\frac{B_1}{D} + B_2\right) \Big/ RTd^2 \qquad (3)$$

constant of solvent, and d is the distance from the substituent to the reaction site. B_1 was assumed to depend on purely electrostatic interation between the reacting compound and the medium, and B_2 was assumed to measure the susceptibility of the reaction to changes in charge density at the reaction site.

The ρ values shown in Table III must depend on only the term of B_1/D, since the HNP values are determined at room temperature, 23~25°, as a measure of the

19) L. P. Hammett: J. Am. Chem. Soc., **59**, 96 (1937).

relative base strength of the ring nitrogen atom (1-position) of the pyrimidines as discussed later. The ρ values increase with decreasing the dielectric constant of alcoholic and dipolar aprotic solvents, respectively. However, the value in glacial acetic acid, notwithstanding the lowest dielectric constant, is markedly smaller than in solvents of other groups. This is impossible to explain in terms of the dielectric constant of solvent.

Since at half neutralization point a base, B, and its perchlorate, BHX, coexist, the following equilibria are described in alcoholic and acidic solvents:

$$B+HS \rightleftarrows B^+H\cdot S^- \rightleftarrows B^+H+S^- \qquad (a)$$

$$B^+H\cdot X^- \rightleftarrows B^+H+X^- \qquad (b)$$

where HS represents a solvent molecule. In glacial acetic acid, a base and its perchlorate are very slightly dissociated and then exist mainly as an ion-pair[20], whereas it may not be so in alcoholic solvents.[21] On the other hand, only the equilibrium, (b), exists in dipolar aprotic solvents.[22] These matters may have some influences on the ρ values, since they are involved in the term of B_1 in the equation (3) as an electrostatic interaction between electrolyte and medium.

Differentiating Titration

From another point of view, the ρ value is a measure which indicates the extent of the relative base strength of the pyrimidines studied in a given solvent. Thus the value will be helpful to find a solvent which will facilitate a differentiating titration of a mixture of the pyrimidines.

The 5-aminomethyl derivative is a diacidic base. The difference between two basicities of this derivative is 3.09 pKa units. The potentiometric titration curves show only one potential inflection at the second equivalence point in acidic solvents, but in alcoholic solvents two inflections at the first and the second equivalence points, respectively. The first inflection is sharper and larger in the mixed solvent of isopropanol and ethyleneglycol than in other alcoholic solvents, as shown by the E_{inf} values in Table I. Fig. 3 shows the potentiometric titration curves of the mixture of the 5-hydroxymethyl derivative and the 5-formyl derivative in various solvents. The difference between the base strength of both derivatives is 1.88 pKa units. This mixture cannot be differentiated even in the mixed solvent of isopropanol and ethyleneglycol. However, in dipolar aprotic solvents two potential inflections are sufficiently detectable at each equivalence point of both the components. The size and sharpness of the first inflection increases in the following order of solvents: alcohols $\ll$acetonitrile$\leqq$methyl ethyl ketone $<$ acetone $<$methyl isobutyl ketone.

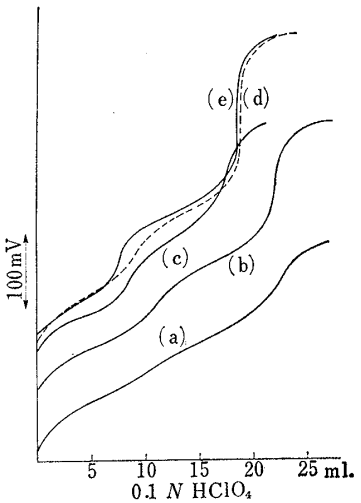


Fig. 3. Differentiating Titrations of Mixture of 4-Amino-5-hydroxymethyl-2-methylpyrimidine and 4-Amino-5-formyl-2-methylpyrimidine in Various Solvents

(a) isopropanol-ethyleneglycol; (b) acetonitrile; (c) methyl ethyl ketone; (d) acetone; (e) methyl isobutyl ketone

These experimental results indicate that the power of solvent to differentiate a mixture of the pyrimidines is effective with increasing of the ρ values. Therefore, dipolar aprotic solvents of low dielectric constant will

20) I. M. Kolthoff, S. Bruckenstein : J. Am. Chem. Soc., **78**, 1 (1956).
21) C. L. de Ligny, P. F. M. Luykx, M. Rehbach, A. A. Wieneke : Rec. trav. chim., **79**, 699 (1960).
22) T. Kashima : Kagaku no Ryoiki, extra No. **30**, 1 (1958).

be recommended as an effective solvent for potentiometric differentiating titration of a mixture of the pyrimidine bases with perchloric acid.

The Titration Behaviors in Glacial Acetic Acid

Hall and co-worker[1,2] reported that a potential change during potentiometric titration of a base with perchloric acid in glacial acetic acid is proportional to the logarithm of concentration of a base in the case of a strong base, but in the case of a weak base is proportional to the logarithm of the ratio of concentrations of a base and its perchlorate. They conventionally adopted the electrolyte theory in diluted aqueous solution to their titrations in glacial acetic acid without modification. However, Bruckenstein and Kolthoff[23] derived the equations, (4) and (5), from the theoretical and experimental discussions about acid-base equilibria in this solvent.

$$E=E_0+\frac{RT}{F}\ln K_S-\frac{RT}{2F}\ln K_B-\frac{RT}{F}\ln C_B+\frac{RT}{2F}\ln(C_B+C_{BHX}) \qquad (4)$$

$$E=E_0+\frac{RT}{F}\ln K_S+\frac{RT}{2F}\ln\left(\frac{K_{BHX}}{K_B^2}\right)+\frac{RT}{2F}\ln\left(\frac{C_{BHX}}{C_B^2}\right) \qquad (5)$$

where E is a millivoltage reading of electromotive force, K_S is the autodissociation constant of glacial acetic acid, K_B and K_{BHX} are the over-all dissociation constants of a base and its perchlorate, respectively, and C_B and C_{BHX} are the concentrations of a base and its perchlorate, respectively. The equation (4), which was derived under the condition of $K_B \fallingdotseq K_{BHX}$, indicates that plots of E against log C_B fall on a linear line, the slope of which is approximately -60 mV, because E_0, K_S, K_B and (C_B+C_{BHX}) are constant. The equation (5), which was derived under the condition of $K_B \ll K_{BHX}$, indicates that a linear correlation exists between E and log (C_{BHX}/C_B^2), and the slope is approximately 30 mV.

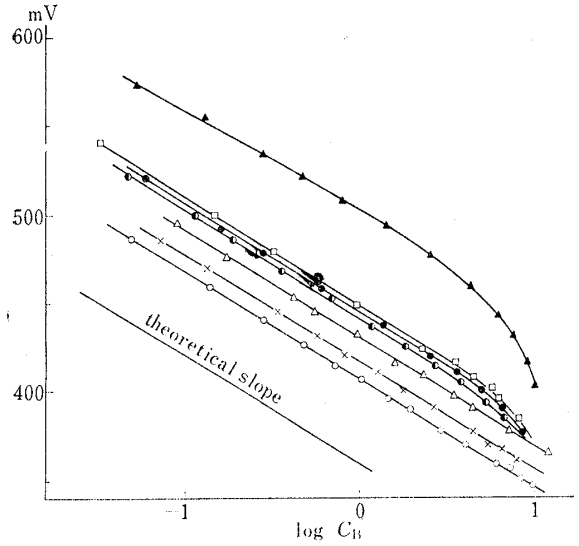


Fig. 4. Plot of E against log C_B on Titrations of 5-Substituted-4-amino-2-methylpyrimidines in Glacial Acetic Acid

Snbstituent: —○— H, —×— CH_2OH, —△— $CONH_2$, —◐— $COOC_2H_5$, —●— COOH, —□— CHO, —▲— CN

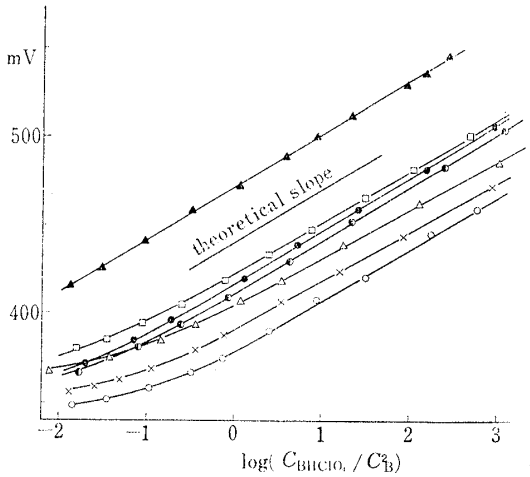


Fig. 5. Plot of E against log (C_{BHClO_4}/C_B^2) on Titrations of 5-Substituted-4-amino-2-methylpyrimidines in Glacial Acetic Acid

Substituent: —○— H, —×— CH_2OH, —△— $CONH_2$, —◐— $COOC_2H_5$, —●— COOH, —□— CHO, —▲— CN

23) S. Bruckenstein, I. M. Kolthoff: J. Am. Chem. Soc., **78**, 2974 (1956); I. M. Kolthoff, S. Bruckenstein: *Ibid.*, **79**, 1 (1957).

As shown in Fig. 4 and 5, the potentiometric titration curves of the pyrimidines obey the equation (4) with exception of the 5-cyano and the 5-aminomethyl derivatives, and only the titration curve of the 5-cyano derivative obeys the equation (5).

When a base, B_I is titrated with perchloric acid, HX, in the presence of the perchlorate of another base, $B_{II}HX$, the following equilibria will coexist in this solvent.

$$B_I + HAc \rightleftarrows B_I^+H \cdot Ac^- \rightleftarrows B_I^+H + Ac^-$$

$$B_I^+HX^- \rightleftarrows B_I^+H + X^-$$

$$B_{II}^+HX^- \rightleftarrows B_{II}^+H + X^-$$

For this situation, the equation (6) may be derived by a similar manner to the equations, (4) and (5), by Bruckenstein and Kolthoff.[23]

$$E = E_0 + \frac{RT}{F} \ln K_S + \frac{RT}{2F} \ln K_{B_IHX} C_{B_IHX} - \frac{RT}{F} \ln K_{B_I} C_{B_I}$$

$$+ \frac{RT}{2F} \ln (K_{B_IHX} C_{B_IHX} + K_{B_I} C_{B_I}) - \frac{RT}{2F} \ln (K_{B_IHX} C_{B_IHX} + K_{B_{II}HX} C_{B_{II}HX}) \quad (6)$$

Although the above situation is not an exact expression for a titration of the monoperchlorate of a diacidic base, equation (6) may be conventionally adopted to titration of the monoperchlorate of the 5-aminomethyl derivative. This equation is not equal to equation, (4) or (5), because $K_{B_{II}HX} \cdot C_{B_{II}HX} \neq 0$.

Therefore, it is reasonable that the HNP values of the 5-cyano derivative and the monoperchlorate of the 5-aminomethyl derivative deviate considerably from the equation, (1) or/and (2), in this solvent.

The 5-Aminomethyl Derivative in Acetone

This pyrimidine is slightly soluble in acetone, but dissolves on warming or standing for some days. The potentiometric titration curve of this solution exhibits only one potential inflection at the equivalence point. The HNP value is markedly lower than that estimated from the equation (1).

The evaporation of acetone from this solution at room temperature under reduced pressure gives colorless leaflets of molecular formula $C_9H_{14}N_4$, which no longer reacts with ninhydrin or carbon disulfide. Hydrolysis of this compound in diluted hydrochloric acid gives 4-amino-5-aminomethyl-2-methylpyrimidine dihydrochloride and acetone. This compound is converted into 4-amino-5-isopropylaminomethyl-2-methyl-pyrimidine by reduction with lithium aluminum hydride in tetrahydrofurane. These results indicate that the compound, obtained from the solution of the 5-aminomethyl derivative in acetone, is 4-amino-5-isopropylideneiminomethyl-2-methyl-pyrimidine.

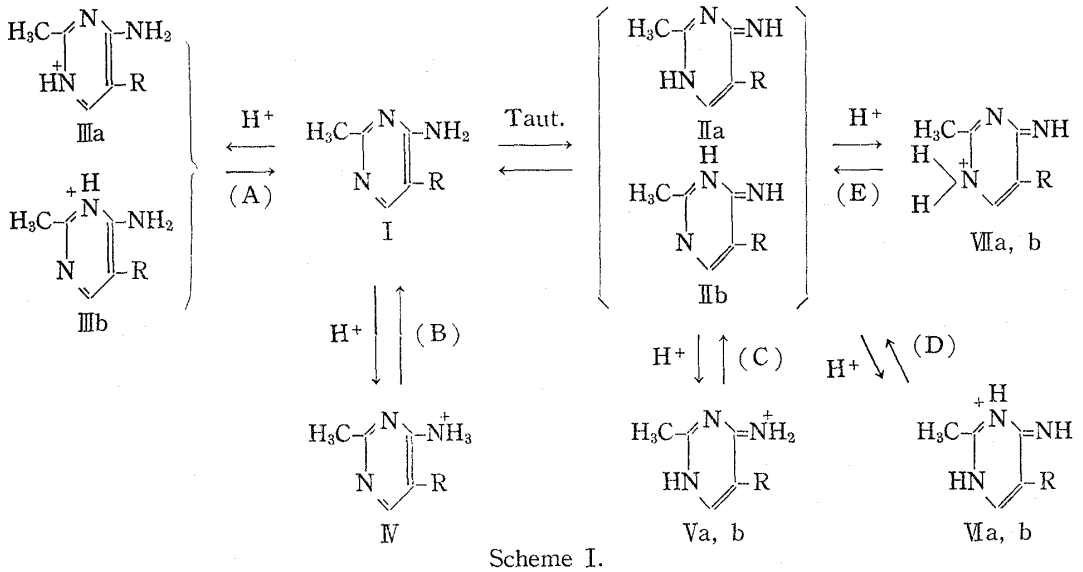
The potentiometric titration curve of the 5-isopropylideneiminomethyl derivative is entirely identical with that of the 5-aminomethyl derivative in acetone. Therefore, it is clearly indicated that the titration of the 5-aminomethyl derivative in acetone is nothing else but that of the 5-isopropylideneiminomethyl derivative produced by condensation of the former and the solvent.

The pKa values estimated by the equation (1) from the HNP values of the 5-isopropylideneiminomethyl derivative in alcoholic and dipolar aprotic solvents are in good agreement with that measured in water, 6.97.

The Amino-Imino Tautomerism in Organic Solvents

The protonation equilibria of a series of 5-substituted-4-amino-2-methylpyrimidines, if the amino-imino tautomerism is present, may be shown as in Scheme I. However, the success of the Hammett's equation for the HNP values in each of the solvents used

indicates that the 4-amino group (or 4-imino group resulted from the tautomerism) in the pyrimidines can not be an actual proton acceptor and then the equilibria, (B) and (C), must be excluded from Scheme I. Further, it is shown by the ultraviolet absorption spectra that the protonated cations of the pyrimidines in some organic solvents have essentially an identical structure with corresponding one in water as shown in Table Ⅳ. The structure of the protonated cations of the pyrimidines in water is pointed out as Ⅲa in Scheme I.[10] These results indicate that the pyrimidines exist largely as the 4-amino form and the actual proton acceptor in these molecules is the 1-position (nitrogen atom) in the ring nucleus in the organic solvents used as well as in water. The ultraviolet absorption spectra of the cation of the 5-formyl derivative in the alcoholic solvents, however, differ markedly from that in water. This phenomenon can be explained by the formation of corresponding dialkyl acetal of the 5-formyl derivative in the solvents. When the solutions of the cation in methanol and ethanol are neutralized with corresponding sodium alkoxide, the spectra are completely identical with those of dimethyl- and diethyl-acetal of the 5-formyl derivative in methanol and ethanol, respectively.



Scheme I.

Table Ⅳ. Ultra-violet Absorption Spectra of the Cations of 5-Substituted-4-amino-2-methylpyrimidine in Aqueous and Nonaqueous Solutions

R	Solvent											
	Water		Acetic acid		Acetonitrile		Methanol		Ethanol		Isopropanol	
	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε
H	244	4.12	250	4.08	241	4.10	245	4.15	247	4.15	248	4.17
$CONH_2$	247	4.13	249	4.12	246	4.13	247	4.14	248	4.15	249	4.14
	272*	3.62	278	3.62	273*	3.64	272*	3.63	272*	3.63	274*	3.62
$COOC_2H_5$	245	4.15	248	4.13	246	4.16	246	4.16	246	4.16	248	4.17
	282	3.66	280	3.63	277	3.65	281	3.64	283	3.62	283	3.64
CHO	249	4.05	251	4.06	249	4.08	246	4.10	249	4.07	251+	
	289	3.63	287	3.63	285	3.67						
CN	247	4.14	250	4.12	248	4.16	249	4.16	249	4.16	250	4.16
	279	3.64	275	3.64	276*	3.69	279	3.63	279	3.63	283	3.61
COOH	246	4.15	248	4.13								
	280	3.65	280	3.62								

* Shoulder, + Unstable

Experimental

Potentiometric Titration——All potentiometric titrations were carried out using a Yanagimoto KY-6 potentiometric titrimeter, equipped with glass and calomel (Yanagimoto No. 1200) electrodes. The salt bridge[1] listed in Table V was inserted between a solution being titrated and the calomel electrode.

TABLE V. Solvents, Titrants, and Salt Bridges used to Potentiometric Nonaqueous Titrations of 4-Amino-2-methylpyrimidines

Solvent	Titrant	Salt bridge
Glac. acetic acid Acetic acid–acetone (1:1) Acetic acid–Acetonitrile (1:1)	0.1 N $HClO_4$ in acetic acid	saturated LiCl in acetic acid
Methanol	0.1 N $HClO_4$ in methanol	saturated KCl in methanol
Ethanol	0.1 N $HClO_4$ in ethanol	saturated LiCl in ethanol
Isopropanol	0.1 N $HClO_4$ in isopropanol	saturated LiCl in isopropanol
Isopropanol–ethyleneglycol (1:1)	0.1 N $HClO_4$ in isopropanol–ethyleneglycol (1:1)	saturated LiCl in isopropanol–ethyleneglycol (1:1)
Acetone Methyl ethyl ketone Methyl isobutyl ketone Acetonitrile	0.1 N $HClO_4$ in dioxane	saturated LiCl in methanol

Approximately 1×10^{-3} mole of the sample was accurately weighed into a titration vessel and dissolved with 100 ml. of solvent. The vessel was covered with a rubber stopper through which the glass electrode, salt bridge and buret tip were set. The solution was potentiometrically titrated with 0.1N perchloric acid. An end point of titration was graphically detected by plotting millivolt readings against volume of titrant added. In order to correct a variation of the H. N. P. values caused by a variation in liquid junction potentials, aniline was used as a standard sample. Titration of aniline in each of the solvents was daily carried out by the above method.

For potentiometric differentiating titration, approximately 1×10^{-3} mole of each of the 5-hydroxymethyl and the 5-formyl derivatives was accurately weighed, mixed and dissolved in 100 ml. of solvent. The titration procedure was the same as that mentioned above.

Ultraviolet Absorption Spectra——Accurately weighed amounts of the pyrimidines were dissolved in 0.1N perchloric acid in each solvent. Each concentration required for measurement was about 15 γ per 1 ml. These measurements were made with a Hitachi spectrophotometer EPU-2A.

Solvents——All of solvents were purified and dried as follows. Glacial acetic acid, b.p. 117.5°; Glacial acetic acid, JIS special grade, was dried over phosphorus pentoxide and distilled. The middle portion was redistilled. The middle portion from this second distillation was used. Methanol, b.p. 64.5°, and ethanol, b.p. 78.3°. These solvents, JIS special grade, were dried by means of magnesium activated with iodine and distilled. Isopropanol, b.p. 82.4°; Isopropanol, JIS special grade, was distilled over freshly burned lime through a 170 cm. Widmer column. The fraction boiling at 82~82.4° was collected, shaken for 2 days with anhydrous copper sulfate, and distilled. Ethyleneglycol, b.p. 197.7°; Ethyleneglycol, JIS special grade, was distilled under reduced pressure. The middle fraction was dried over sodium sulfate. After decanting, distillation was fractionally repeated. Acetone, b.p. 56.2°; Acetone, JIS special grade, was heated under reflux with potassium permanganate for 8 hr. and allowed to stand for 3 days, more permanganate being added as the color disappeared. After distillation, the product was dried over calcium chloride, and fractional distillation was repeated. Methyl ethyl ketone, b.p. 80°, and methyl isobutyl ketone, b.p. 116°; These ketones, special grade (Wako Pure Chemical Industries, Ltd.), were treated several times with potassium carbonate solution. After removing the aqueous layer, these ketones were distilled. The products were dried for 3 days over sodium sulfate and potassium carbonate, and fractionally distilled several times. Acetonitrile, b.p. 81.6°; Acetonitrile, JIS special grade, was dried over phosphorus pentoxide and distilled. The same distillation procedure was repeated until the phosphorus pentoxide in the still pot no longer became colored. The product was distilled over potassium carbonate and finally distilled without a drying agent. Dioxane, b.p. 101.5°; Dioxane, JIS special grade, was refluxed over sodium hydroxide for 5 hr., decanted and distilled. The product was refluxed for 5 hr. over sodium, allowed to stand for 2 days and distilled.

Materials——The following pyrimidine derivatives had the melting point and properties reported in the literature and were prepared according to the cited references: 4-Amino-2-methyl, m.p. 204~206°;[24]

24) T. Matsukawa, B. Ohota, K. Shirakawa: Yakugaku Zasshi, **70**, 283 (1950).

4-amino-5-aminoethyl-2-methyl, m.p. 91～93°;[25] 4-amino-5-hydroxymethyl-2-methyl, m.p. 195～196°;[24] 4-amino-5-carboxy-2-methyl, m.p. 267～268°;[24] 4-amino-5-ethoxycarbonyl-2-methyl, m.p. 120～121°;[26] 4-amino-5-formyl-2-methyl, m.p. 193～194°;[27] 4-amino-5-cyano-2-methyl, m.p. 248～249°;[28] and 4-amino-5-carbamoyl-2-methyl, m.p. 265～266°.[10] All compounds were dried to constant weight before use.

Condensation Product of the 5-Aminomethyl Derivative in Acetone——a) In 100 ml. of acetone was dissolved 0.15 g. of this pyrimidine on warming at 40° or standing for 2 days. The evaporation of the solution at room temperature under reducted pressure gave 0.2 g. of residue. This was recrystallized from ethyl acetate to give 0.18 g. of colorless leaflets, m.p. 151～152°. Melting point showed depression by admixture with the 5-aminomethyl derivative. *Anal.* Calcd. for $C_9H_{14}N_4$: C, 60.64; H, 7.92; N, 31.44. Found: C, 60.77; H, 7.95; N, 31.48.

The above condensation product (0.2 g.) was heated in 5 ml. of 5% HCl on a steam bath for 2 hr. After cooling, the reaction mixture was divided into two parts. One part was neutralized with 10% NaOH solution, acidified with acetic acid and heated with 1 ml. of water containing 0.12 g. of semicarbazide hydrochloride and 0.15 g. of sodium acetate on a steam bath for 10 min. The separated crystals on cooling were filtered and recrystallized from ethanol to give 0.1 g. of acetone semicarbazone, m.p. 187°, which was identified with the authentic sample by mixed melting point and IR spectrum. The other part was evaporated to dryness. The recrystallization of the residue from 95% ethanol gave 0.1 g. of the dihydrochloride of the 5-aminomethyl derivative, m.p. 262° (decomp.), which was identified with the authentic sample by IR spectrum.

b) To the solution of 0.5 g. of the condensation product in 15 ml. of tetrahydrofurane, 0.5 g. of lithium aluminum hydride was slowly added at room temperature. After stirring for 1.5 hr., 8 ml. of water was dropwise added to the solution on cooling with ice-cold water. The reaction mixture was acidified with 10% HCl and evaporated to dryness. After washing with abs. ethanol, the residue was recrystallized from aqueous ethanol, m.p. 284°(decomp.). *Anal.* Calcd. for $C_9H_{16}N_4 \cdot 2HCl$: C, 42.69; H, 7.17; N, 22.13. Found: C, 42.48; H, 7.40; N, 22.08.

This compound was identified with 4-amino-5-isopropylaminomethyl-2-methylpyrimidine dihydrochloride by comparison of IR spectrum.

4-Amino-5-isopropylaminomethyl-2-methylpyrimidine was prepared by the following method. In the solution of isopropylamine in ethanol (3 g./20 ml.), 1 g. of 4-amino-5-chloromethyl-2-methylpyrimidine[29] was heated in a sealed tube at 100° for 2 hr. After evaporation of the reaction mixture under reduced pressure, the residue was extracted with abs. ethanol. The ethanol extract was concentrated to 5 ml. and 10 ml. of ether was added. By passing dry HCl gas through the solution, precipitate was separated. The recrystallization of the precipitate from aqueous ethanol gave 1.4 g. of 4-amino-5-isopropylaminomethyl-2-methylpyrimidine, m.p. 284～285°(decomp.). *Anal.* Calcd. for $C_9H_{16}N_4 \cdot 2HCl$: C, 42.69; H, 7.17; N, 22.13. Found: C, 42.47; H, 7.36; N, 21.85.

Preparation of Dialkylacetals of the 5-Formyl Derivative——In 30 ml. of abs. methanol containing 4% dry HCl was dissolved 1 g. of the 5-formyl derivative. After standing for 3 hr. at room temperature, the reaction mixture was basified with sodium methoxide and evaporated to dryness under reduced pressure. The residue is dissolved in ice-cold water and extracted with ether. The ethereal layer is washed with water, dried with Na_2SO_4 and evaporated to dryness. The recrystallization of the residue from methanol gave 0.7 g. of the dimethylacetal of the 5-formyl derivative, m.p. 108.5～109°. *Anal.* Calcd. for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.60; H, 7.27; N, 22.73.

The diethylacetal was prepared by a similar method to preparation of the dimethylacetal, m.p. 66～68°. *Anal.* Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 57.14; H, 8.40; N, 19.64.

The authors wish to express their deep appreciation to Dr. K. Takeda, Director of this Laboratory, for his helpful advice and encouragement.

Summary

The potentiometric titrations of 5-substituted-4-amino-2-methylpyrimidines were examined as a base in various nonaqueous solvents. The quantitative determinations were effectively carried out in acidic and dipolar aprotic solvents. The potentials at half neutralization point (HNP values) were used as a measure of the relative basicity

25) T. Matsukawa: Yakugaku Zasshi, **62**, 417 (1942).
26) A. R. Todd, F. Berger: J. Chem. Soc., **1937**, 364.
27) S. Mizukami, T. Amano: Reported at the 8th Kinki Local Meeting of the Pharmaceutical Society of Japan at Kyoto College of Pharmacy, October 20, 1958.
28) R. Grewe: Z. physiol. Chem., **242**, 95 (1936).
29) A. Dornow, G. Petsch: Ber., **86**, 1404 (1953).

of the pyrimidines in the solvents. The values in each of the solvents could be lineally correlated with the pKa (H_2O) values and the Hammett's σ_m for the 5-substituents. Some of the pyrimidines which deviated considerably from these linear relationships were discussed. Moreover, it was found that the differentiating titration of a mixture of pyrimidines might be facilitated with increasing of the reaction constant of the Hammett's equations. On the other hand, it was indicated by the Hammett's equations and by comparison of ultraviolet absorption spectra that these pyrimidines existed largely as the amino form in the solvents as well as in water and the actual proton acceptor in these molecules was the 1-position of pyrimidine ring.

(Received November 10, 1965)

[Chem. Pharm. Bull. 14(12) 1332~1337 (1966)]

UDC 541.121 : 547.581.2.03

178. Yoshikazu Kondo, Kazue Kondo, Tsunematsu Takemoto,*1 and Tsuneo Ikenoue*2 : Application of the Infinite Dilution Shifts in Acid-Base System to Organic Chemistry. I. Relation between the Infinite Dilution Shifts of Monosubstituted Benzoic Acids in Pyridine and the Hammett δ Values.*3

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Since the nuclear magnetic resonance (NMR) spectrum responds sharply to the electron density, it is an effective means to detect the electronegativity of a substituent. The effect of a substituent on chemical reactivity often depends on the change of electron density surrounding a reactive center and a relation is found between the chemical shift in NMR and chemical reactivity. Many studies have been carried out on the close correlation between the Hammett σ value, which is a parameter of reactivity, and the chemical shift of a proton shielding.

Gutowsky and his co-workers[1] first measured the chemical shifts of fluorine (^{19}F) for a series of substituted fluorobenzenes and proved that there is a linear relation δ_F and electronegativity of the substituents. In recent years, a number of studies have been reported on effect of substituents on the magnetic shielding of a proton bound directly to the benzene ring.[2~10] In this case, the relation between the Hammett σ values and δ_H was not quite so simple.*4 In contrast to the aromatic proton, the

*1 Kita-4-bancho, Sendai (近藤嘉和, 近藤一恵, 竹本常松).
*2 Katahira-cho, Sendai (池上恒男).
*3 Communication : Y. Kondo, K. Kondo, T. Takemoto, T. Ikenoue : This Bulletin, **12**, 514 (1964).
*4 Taft[7,11] reported that when $\delta_F^H = -0.41\,\sigma_I - 0.700\,\sigma_R$ or $\delta_F^H = -0.49\,\sigma_I - 1.04\,\sigma_R^o - 0.02$ was used, a linear relation can be obtained.

1) H. S. Gutowsky, D. W. McCall, B. R. McGrarvey, L. H. Meyer : J. Am. Chem. Soc., **74**, 4809 (1952).
2) P. L. Cario, B. P. Daily : *Ibid.*, **78**, 3043 (1956).
3) A. A. Bothner-By, R. E. Glick : *Ibid.*, **78**, 1071 (1956); J. Chem. Phys., **26**, 1651 (1957).
4) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, R. E. Glick : *Ibid.*, **81**, 5352 (1959).
5) I. Yamaguchi, N. Nakagawa : Bull. Chem. Soc. Japan, **33**, 1128 (1960).
6) R. R. Fraser : Can. J. Chem., **38**, 2226 (1960).
7) R. W. Taft, Jr. : J. Phys. Chem., **64**, 1805 (1960).
8) H. Spiesecke, W. G. Schneider : J. Chem. Phys., **35**, 731 (1961).
9) P. Diehl : Helv. Chim. Acta, **44**, 829 (1961); *Ibid.*, **45**, 568 (1962).
10) B. P. Dailey, A. Gawer, W. C. Neikam : Discussions Faraday Soc., **34**, 18 (1962).