Protonation of 2,4-Diaminopyrimidines. II. Dissociation Constants of 6-Amino Derivatives and Anion Effects in Moderately Strong Acid[1]

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Basic dissociation constants have been determined for the mono- and diprotonation of 2,4,6-triaminopyrimidine and several of its 5-substituted and 2-, 6-, and 4,6-N-substituted amino derivatives. The three overlapping dissociation constants for the 5-(*o*-aminophenylthio) analog were also obtained. Most of the dissociation constants for the second proton fall in the range of 10^{-2} to 10, and in a number of cases the slopes of the Hammett plots deviate significantly from 1. Furthermore, dissociation constants measured in sulfuric acid are appreciably different from those in hydrochloric acid, and Bunnett ϕ values are appreciably higher in the former solvent. It is postulated that ion-pair formation with large anions stabilizes the diprotonated species. The pK_1 and pK_2 values for the 5-substituted triamino derivatives are linearly related to the pK_1 values of the diamino analogs. However, the effect of N-substitution on pK_1 is quite different from that on pK_2 for the triamino compounds. Steric and solvation factors seem to be involved.

During a study of the acid-catalyzed cyclization of 2,4,6-triamino-5-(*o*-aminophenylthio)pyrimidines to 1,3-diazaphenothiazines,[3] it became important to know the pK_a values representing the association of the first, second, and third protons on the intermediate pyrimidines. This at first appeared to be a rather formidable problem, since the three pK_a values not only overlapped, but extended into the moderately strong acid region, where there was some doubt that the protonation followed the Hammett acidity function. Model pyrimidines, including 2,4,6-triaminopyrimidine and a number of 5-substituted and 2-, 6-, and 4,6-N-substituted derivatives, were therefore chosen for detailed studies of the first and second protonation.[4] The main purpose of this paper is to describe the properties of these compounds in mild to moderately strong acid (pH 2 to H_0 −3). An analysis of substituent effects upon the first and second dissociation constants is also presented.

Results

The pyrimidines studied, and their first and second dissociation constants and ultraviolet absorption spectra, are listed in Table I. The dissociation constants (K_1) for the symmetrical 2,4,6-triaminopyrimidines are corrected by a statistical factor of 2, since there is an equal probability of protonation on the equivalent ring atoms, N^1 and N^3, but only one possibility for proton loss. (Paper I of this series discusses the protonation at N^1, which is the most basic nitrogen of 2,4-diaminopyrimidine.)[1b] Similarly, the K_2 values for these compounds are corrected by a statistical factor of 0.5. All pK_a values were determined by spectrophotometric means.

The second protonation of these pyrimidines was found to occur in the moderately strong acid region. Measurements were made in sulfuric, hydrochloric, and perchloric acids in the case of **1**, and in sulfuric and hydrochloric acids with **3** and **9**. All other pK_2 values were measured in hydrochloric acid only.

The ultraviolet spectra of 2,4,6-triaminopyrimidine are depicted in Figure 1. Curves 5 and 6, for the diprotonated species in hydrochloric and sulfuric acids, respectively, show differing degrees of solvation shifts, which result in isosbestic loss in both the low and high wavelength region. Consequently, small vertical and lateral corrections for the isosbestic shift were made at the low wavelength minimum at 222 nm and small lateral corrections at the high wavelength maximum at 277 nm. Measurements were made at these two points only, to minimize the errors resulting from correcting or reading from a steep slope. All of the compounds presented this problem to varying degrees. Figure 2 presents one of the more difficult cases, with curve 5 showing a lateral isosbestic shift at 211 nm, a vertical shift at 254 nm, and only small species differences in the high wavelength region. The required correction was only 2.5% at 220 nm, however, since the difference in extinction coefficients between the mono- and diprotonated species at this wavelength is very large. This was the only region used for measurements with this particular compound.

Curves 3 and 4 of Figure 1, obtained at almost identical pH values in hydrochloric and sulfuric acids, respectively, illustrate that 2,4,6-triaminopyrimidine is protonated to a considerably greater extent in the latter acid at pH 1.1. Figure 2 (curves 2 and 3) shows similar phenomena with the 5-phenylthio analog. Measurements were made in increments of approximately 0.25 to 0.3 H_0 units for each pyrimidine, and least-squares plots computed for the Hammett acidity function (H_0)[5] *vs.* log I, where $I = [BH_2^{2+}]/[BH^+]$. This is illustrated for **1, 3, 5,** and **9** in Figure 3. The lines, although straight, are not parallel, and, in all three cases studied, those measured in sulfuric acid indicate a higher pK_a than in hydrochloric acid. The slopes of the lines are listed in Table I. In one experiment with **1** in hydrochloric acid, all solutions less than 0.4 M were made up to a constant chloride concentration of 0.4 M with sodium chloride. In this case, the pK_2 of **1** was raised to 1.41 ± 0.09. This value is

(1) (a) Presented in part at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, 1969. (b) Part I: B. Roth and J. Z. Strelitz, *J. Org. Chem.*, **34**, 821 (1969).

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(3) B. Roth, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963; publication in preparation.

(4) The notation used here for pK_1 is for the equilibrium $B + H^+ \rightleftarrows BH^+$; pK_2 is used for $BH^+ + H^+ \rightleftarrows BH_2^{2+}$. Compound **4** gains three protons, and presumably the other bases can become triprotonated or even tetraprotonated in strong acid; hence the reversal of the usual convention.

(5) L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.*, **54**, 2721 (1932).

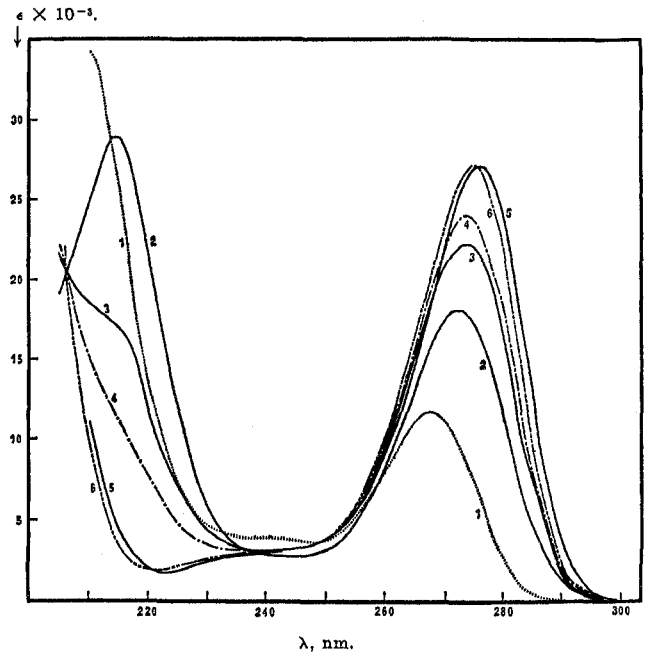


Figure 1.—Ultraviolet absorption spectra of 2,4,6-triaminopyrimidine: (1) as neutral species (pH 12), (2) as monocation (pH 4), (3) at pH 1.10 in hydrochloric acid, (4) at pH 1.09 in sulfuric acid, (5) as dication ($H_0 = -2$) in hydrochloric acid, (6) as dication ($H_0 = -2$) in sulfuric acid.

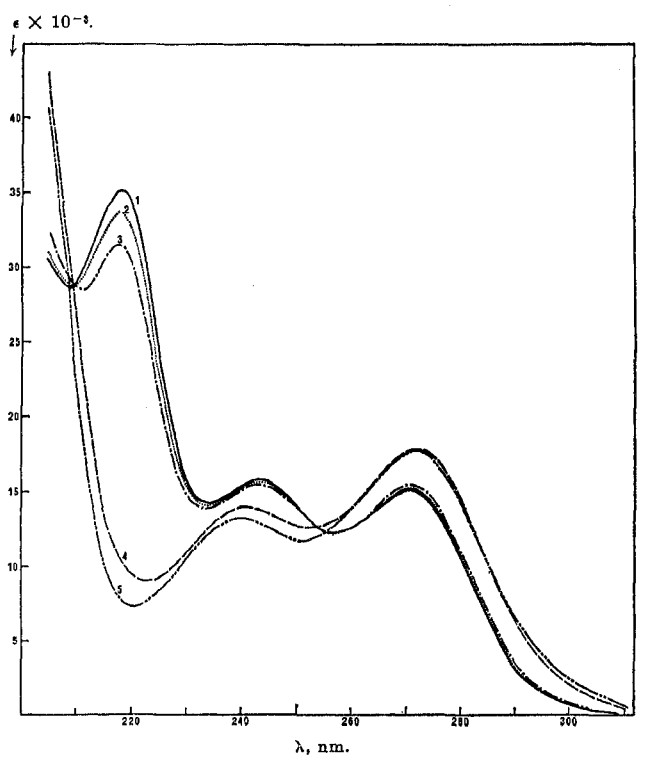


Figure 2.—Ultraviolet absorption spectra of 2,4,6-triamino-5-phenylthiopyrimidine: (1) as monocation (pH 3), (2) at pH 1.09 in hydrochloric acid, (3) at pH 1.09 in sulfuric acid, (4) at $H_0 = -1$ in sulfuric acid, (5) as dication ($H_0 = -3$) in sulfuric acid.

still considerably lower than that in sulfuric acid, despite the higher ionic strengths of the solutions.

The effect of monoanions of different size on the pK_2 of **1** was determined by swamping dilute hydrochloric acid solutions with sodium iodide, bromide, or chloride (10 × [HCl]), respectively. Results are shown in Table II. At pH 2.10, the differences are not significant, but the difference between iodide and bromide ion is significant at pH 1.55.

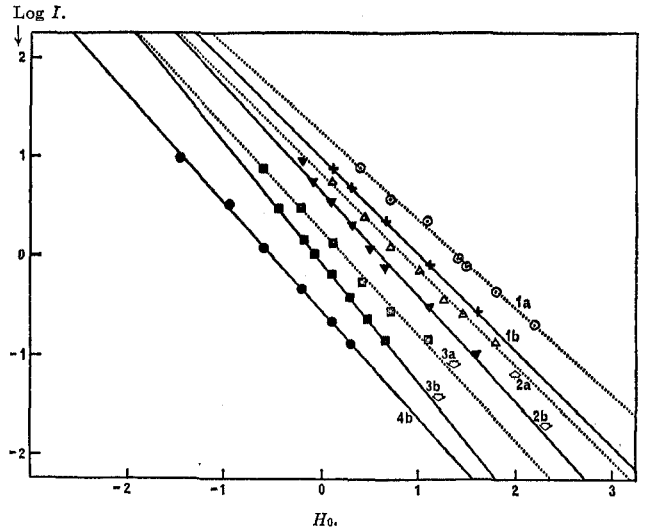


Figure 3.—Hammett plots of acidity *vs.* log ($[BH_2^{2+}]/[BH^+]$) for 2,4,6-triaminopyrimidine (1a and 1b); 2,4-diamino-6-piperidylpyrimidine (2a and 2b); 2,4,6-triamino-5-phenylthiopyrimidine (3a and 3b); 2,4,6-triamino-5-bromopyrimidine (4b). Dotted lines (1a–3a) represent sulfuric acid solutions; solid lines (1b–4b) represent hydrochloric acid.

TABLE II
EFFECT OF MONOANIONS ON DIPROTONATION OF **1**

Anion	% diprotonation pH 2.10	% diprotonation pH 1.55
I^-	12	36
Br^-	8	28
Cl^-	8	27

In the pH 7 region, divalent anions, such as HPO_4^{2-}, increase pK_1 to an extent greater than can be accounted for by the ionic strength. For example, the concentration pK_1 for **1** was found to be 6.97 in a phosphate buffer ($\mu = 0.16$), but was 6.78–6.81 in a phosphate buffer of $\mu = 0.016$, to which was added 0.36 *M* sodium chloride, sodium bromide, or sodium perchlorate. The phosphate buffer did not affect the isosbestic points in the manner described in paper I of this series.[2]

Figure 4 illustrates the ultraviolet absorption spectra of **4** as the neutral and tricationic species, as well as at three intermediate points. Since the three pK_a values overlap slightly, the separation of isosbestic points is incomplete. It was possible to calculate the pK_a values for each equilibrium at an isosbestic point for the next equilibrium, however, as indicated in Table I, footnotes *j*, *k*, and *m*, and illustrated by arrows in Figure 4. The second and third dissociation constants were also calculated at 217.5 nm (the low-wavelength maximum for curve 2, Figure 4), by use of the Thamer equation.[6] These results checked very closely with those obtained by the first method. Since these are macroconstants and do not represent protonation of a specific nitrogen, no statistical corrections were applied.

Discussion

The Pyrimidine Equilibrium $BH^+ \rightleftarrows BH_2^{2+}$.—Since the diprotonation of the triaminopyrimidines extends into the moderately strong acid region, where the acidity

(6) B. Roth and J. F. Bunnett, *J. Amer. Chem. Soc.*, **87**, 334 (1965).

TABLE

DISSOCIATION CONSTANTS AND ULTRAVIOLET ABSORPTION

Compd no.	Pyrimidine substituents 2	4	5	6	Acid for pK_2	Thermodynamic pK_2 (20°) from Bunnett plots[a,b]	pK_2 from midpoint of Hammett plots[b]	Slope, Hammett plot
1[c]	NH_2	NH_2		NH_2	HCl	1.31 ± 0.01[f]	1.31 ± 0.02[g]	−0.968 ± 0.023
					H_2SO_4	1.72 ± 0.03	1.69 ± 0.06	−0.881 ± 0.039
					$HClO_4$		1.46 ± 0.08	−1.08 ± 0.05
2[h]	NH_2	NH_2	C_2H_5	NH_2	HCl	1.55 ± 0.02	1.55 ± 0.04	−0.992 ± 0.041
3[i]	NH_2	NH_2	SC_6H_5	NH_2	HCl	0.08 ± 0.03	0.24 ± 0.01	−1.20 ± 0.019
					H_2SO_4	0.49 ± 0.08	0.52 ± 0.07	−1.05 ± 0.069
4[i]	NH_2	NH_2	$SC_6H_4NH_2(2)$	NH_2	HCl	−0.53 ± 0.04	−0.55 ± 0.04[j]	−0.983 ± 0.036
5[i]	NH_2	NH_2	Br	NH_2	HCl	−0.30 ± 0.08	−0.21 ± 0.03	−1.08 ± 0.036
6[i]	NH_2	NH_2	Cl	NH_2	HCl	−0.35 ± 0.02	−0.26 ± 0.02	−1.09 ± 0.014
7[n]	NH_2	NH_2		$NHCH_3$	HCl	1.05 ± 0.04	1.04 ± 0.05	−0.986 ± 0.041
8[n]	NH_2	NH_2		$N(CH_3)_2$	HCl	0.68 ± 0.03	0.69 ± 0.02	−1.06 ± 0.003
9[n]	NH_2	NH_2		$N(CH_2)_5$	HCl	0.58 ± 0.04	0.61 ± 0.05	−1.06 ± 0.051
					H_2SO_4	0.85 ± 0.03	0.84 ± 0.05	−0.967 ± 0.041
10[i]	NH_2	NH_2		$N(CH_2CH_2)_2O$	HCl	−0.35 ± 0.02	−0.14 ± 0.003	−1.25 ± 0.007
11[i]	NH_2	$N(CH_3)_2$		$N(CH_3)_2$	HCl	0.80 ± 0.05	0.82 ± 0.10	−1.22 ± 0.077
12[i]	NH_2	$N(CH_2)_4$		$N(CH_2)_4$	HCl	1.67 ± 0.07	1.67 ± 0.06	−1.09 ± 0.052
13[i]	$N(CH_2)_5$	NH_2		NH_2	HCl	0.86 ± 0.03	0.86 ± 0.03	−1.01 ± 0.041
14[h]	NH_2	NH_2	$CH_2C_6H_5$	NH_2				
15[o]	NH_2	NH_2	$C_6H_4Cl(4)$	NH_2				
16[p]	NH_2	NH_2	NHCHO	NH_2				
17[q]	NH_2	NH_2	$N{=}NC_6H_5$	NH_2				
18[q]	NH_2	NH_2	$N{=}NC_6H_4Cl(4)$	NH_2				
19[r]	NH_2	NH_2	NO_2	NH_2				

[a] J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899 (1966). [b] pK_2 taken as midpoint of Hammett plots, where $\log I = 0$. Rigorously, this is the thermodynamic pK_a value only when the slope is unity. In cases of marked deviation, such as **3a** and **10**, the Bunnett plots give the more accurate constant, in the absence of a new acidity function. Midpoints were calculated from the plot of $\log I = AH_0 + C$, where $I = [BH_2^{2+}]/[BH^+]$, A is the slope, C is the intercept at $H_0 = 0$, and $pK_2 = -C/A$. Data for the points were chosen between $\log I = \pm 1$. The number of points (n) and acid concentrations which are listed are the number of points and acid concentrations falling in this range. Statistical corrections of 0.5 are applied to K values for symmetrical derivatives. [c] Statistical corrections of 2 are applied to K values for the symmetrical pyrimidines. The limits recorded are the total range of values from calculations at *ca.* 10 wavelengths. [d] Observed endpoints in HCl solutions. Small medium shifts occurred in λ_{max}. [e] Reference 2. [f] Standard deviations. [g] Calculated from standard deviations of A/B in Hammett plots. [h] P. B. Russell and G. H. Hitchings, *J. Amer. Chem.*

I

SPECTRA OF 2,4,6-TRIAMINOPYRIMIDINE DERIVATIVES

				Ultraviolet absorption spectra					
				Neutral species		Monocation		Dication[d]	
ϕ[a]	n	Acid concn range, M	Thermodynamic[c] pK_1 (20°)	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$
0.24 ± 0.13	6	0.026–0.6	6.72 ± 0.01[f]	209	35.2	214	29.2	277	26.7
0.83 ± 0.32	7	0.006–0.25		237.5 sh	4.01	272	18.2		
	4	0.01–0.3		267.5	11.80				
0.22 ± 0.29	4	0.01–0.41	6.84 ± 0.02	237.5 sh	5.51	215.5	23.5	245	4.60
				274.5	11.6	240 sh	4.60	285	25.0
						280.5	17.2		
−0.91 ± 0.14	7	0.2–1.5	5.66 ± 0.06	247.5	17.0	218	35.6	241	13.2
−0.16 ± 0.34	6	0.1–1.6		265	14.9	243	16.3	273	18.5
						271	15.5		
0.65 ± 0.08	7	0.4–4.2	2.59 ± 0.05[k]	214.5	58.0	215	48.4	248[l]	14.2
			5.95 ± 0.05[m]	247.5	15.1	245.1	14.3	273	19.4
				260–265 sh	12.9	271	14.2		
−0.18 ± 0.19	6	0.4–4.2	5.17 ± 0.02	234 sh	6.75	216	23.9	252	5.30
				274.5	9.05	245 sh	4.39	289	20.0
						282	14.5		
−0.27 ± 0.05	5	0.4–2.9	5.15 ± 0.02	235 sh	5.30	215	23.4	247.5	4.35
				274	9.40	242.5 sh	4.20	288	21.0
						282	14.5		
−0.04 ± 0.40	6	0.03–0.60	7.21 ± 0.03	213	35.8	217.5	26.0	280	29.0
				270	13.3	274	20.2		
−0.29 ± 0.26	6	0.03–0.79	7.21 ± 0.03	217.5	29.4	223	20.0	285	29.0
				275	14.6	279	21.9		
−0.47 ± 0.28	8	0.026–1.0	7.20 ± 0.03	220	27.8	229	20.1	290	31.4
0.18 ± 0.11	7	0.01–0.5		277	16.5	282	24.4		
−1.06 ± 0.14	5	0.2–1.5	6.73 ± 0.04	219	29.4	231	22.3	291	32.9
				275.5	16.5	281	24.8		
−0.99 ± 0.44	7	0.1–1.0	7.18 ± 0.02	228	36.5	230	23.4	297	30.8
				279	16.9	286	24.9		
−0.55 ± 1.1	4	0.01–0.3	7.56 ± 0.02	230.2	37.5	232.5	26.7	297.5	39.2
				281	22.0	288.2	31.8		
−0.019 ± 0.13	5	0.1–1.0	6.78 ± 0.03	247.5	11.9	227.5	30.8	247.5	7.35
				275	9.00	247.5 sh	7.40	280	24.2
						280.5	15.0		
			6.55 ± 0.02	237.5 sh	8.12	242.5 sh	6.42		
				273	11.4	278.5	16.8		
			6.19 ± 0.04	271	14.4	215.5	33.1		
						276	18.4		
			5.73 ± 0.03	233.5 sh	6.71	215	28.8		
				267	10.8	272	16.3		
			4.97 ± 0.04	248	14.9	215	22.0		
				255 sh	14.3	232.5 sh	14.9		
				375	23.8	257.5	9.65		
				397.5 sh	17.5	285 sh	5.95		
						364	22.5		
						395 sh	12.3		
			4.91 ± 0.05	252	18.5	215	24.1		
				257.5 sh	16.9	235 sh	17.1		
				381	28.7	257.5 sh	11.1		
				405 sh	22.7	282.5 sh	4.21		
						369.5	27.8		
						397.5 sh	17.9		
			3.22 ± 0.04	230 sh	17.7	214	44.0		
				335	36.0	235 sh	31.3		
						322	27.6		

Soc., **74**, 3443 (1952). [i] Reference 3. [j] pK_3. pK_a values overlapped slightly; calculation was made from data at 232.5 and 276 nm, crossover points for the next equilibrium. No statistical corrections were applied to dissociation constants for this compound. [k] pK_2. Calculation from data at 265 and 295 nm, which are isosbestic points for the equilibrium $BH^+ \rightleftarrows B$, and also a region of very small change for the equilibrium $BH_3^{3+} \rightleftarrows BH_2^{2+}$. [l] Trication. [m] p$K_1$. Calculation from data at 276 nm, which is an isosbestic point for the next equilibrium. [n] B. Roth, J. M. Smith, and M. Hultquist, *J. Amer. Chem. Soc.*, **72**, 1914 (1950). [o] Prepared by Paul Stenbuck in these laboratories, mp 280–282°; see also British Patent 712,595 (1954). [p] W. Traube, *Ber.*, **37**, 4544 (1904). [q] These compounds were kindly donated by Drs. A. M. Triggle and D. J. Triggle of the State University of New York at Buffalo, Buffalo, N. Y. See J. Hampshire, P. Hebborn, A. M. Triggle, D. J. Triggle, and S. Vickers, *J. Med. Chem.*, **8**, 745 (1965). [r] S. Gabriel, *Ber.*, **34**, 3362 (1901).

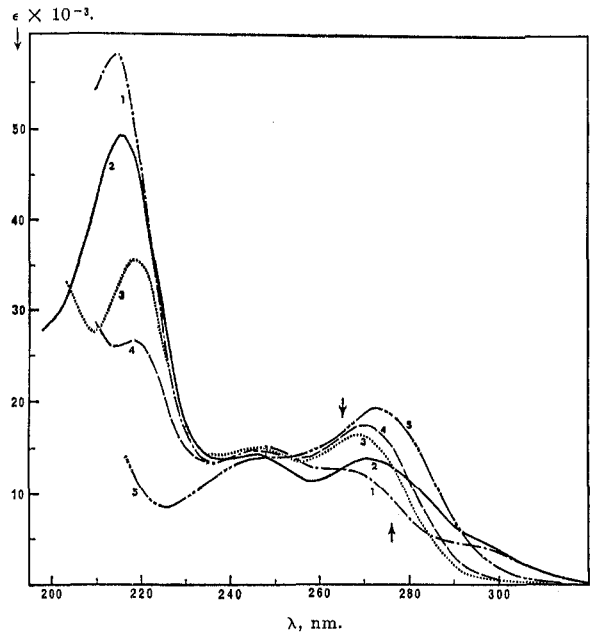


Figure 4.—Ultraviolet absorption spectra of 2,4,6-triamino-5-(*o*-aminophenylthio)pyrimidine: (1) as neutral species (pH 12), (2) at pH 4.02 (0.01 *N* acetate), (3) at pH 1.09 (in hydrochloric acid), (4) at $H_0 = -0.20$ (1 *N* hydrochloric acid), (5) at $H_0 = -3$ (hydrochloric acid).

of the solutions cannot be measured with the hydrogen electrode, the use of an acidity function approach is indicated for the measurement of pK_2. The Hammett acidity function, H_0,[5] which is defined as

$$H_0 = -\log a_{H^+} f_B/f_{BH^+} = pK_{BH^+} - \log [BH^+]/[B] \quad (1)$$

is the measure of the capability of a solution to transfer a proton to a *neutral* base B, to form its conjugate acid, BH^+. Hammett envisaged a second acidity function, H_+, for monocation–dication equilibria.[7] This function has not received extensive study, but, over certain ranges of sulfuric acid concentration, a parallelism with H_0 has been found.[8,9] Failure of certain bases to adhere exactly to the H_0 scale was found to be unrelated to a particular charge type.[10] It therefore seemed reasonable to compare log I with H_0 in our case. By definition (eq 1), the slope of such a plot should be 1. The results of Table I indicate that this is usually, but not invariably, the case with the pyrimidines tested. Figure 3 illustrates this point. Although no deviations are large, they are significant in a few cases, and the resultant pK_2 values calculated from eq 1 are inaccurate.

Bunnett and Olsen[11] have devised a method for the calculation of the thermodynamic pK_a for any base, regardless of the acidity function it follows. Use of the single acidity function H_0 in the equation

$$\log ([SH^+]/[S]) + H_0 = \phi(H_0 + \log [H^+]) + pK_{SH^+} \quad (2)$$

gives linear plots from which the desired pK_{SH^+} values can be obtained. Results by this method were found to agree well with the literature data obtained by the acidity function method, using a wide variety of substrates (S) which are not Hammett bases.[11] The slope of the plots, ϕ, is a parameter which expresses the response of the equilibrium to changing acid concentration, and may be interpreted in terms of hydration changes. The more positive the ϕ value, the greater is the hydration of SH^+ relative to S, according to the hydration hypothesis.

A comparison of the pK_2 values of Table I, calculated by the Bunnett *vs.* the Hammett method, shows them to be the same, within experimental error, except for the few cases where the slope definitely deviates from 1. The Bunnett equation values are considered to be the thermodynamic constants for the pyrimidines.

By definition, a thermodynamic pK_a value is a constant, which is not dependent on the medium. This presents an anomaly when we are faced with the data on **1**, **3**, and **9**, which show the thermodynamic pK_2 values to be higher by 0.2 to 0.4 pH units in sulfuric than in hydrochloric acid, and to be intermediate in the one case with perchloric acid. This phenomenon is not restricted to the moderately strong acid region, where the activity of water is less than 1. Much of the data was collected in solutions above pH 1, where the pH values can be determined by direct measurement. This is illustrated in Figure 1. Solutions **3** and **4** had almost identical pH values; it is clear that they differ considerably in their degree of protonation, however. This was also true of solutions at pH 1.5–1.6 with and without added salts. It could be argued that the sulfuric and hydrochloric end points (curves 5 and 6) are slightly different, and that the medium corrections may have been erroneous, which will change the pK_a values slightly. This is quite beside the main point, however. The difference in **3** and **4** suggests that the two substrates are actually different from each other, which can best be explained by different degrees of ion pairing of the diprotonated pyrimidine with chloride and bisulfate anions. Stronger ion pairing with the larger bisulfate ion (and with sulfate dianion present to a small extent) would contribute to greater stabilization of the diprotonated species. Evidence for this was also supplied by the fact that slight isosbestic shifts occurred in sulfuric acid in the pH 1.5–2.5 region if the ionic strength was not kept constant. Evidence for stabilization of the monoprotonated species by HPO_4^{2-}–$H_2PO_4^-$ anions at pH 7 was also indicated by an increase in pK_1 greater than could be accounted for by increased ionic strength.

Previous evidence for ion pairing in aqueous solution was obtained with diaminopyrimidines in phosphate buffers at pH 7.[2] Evidence for increased ion pairing as a function of monoanion size was obtained from the nmr spectra of 2,4-diaminopyrimidine hydrochloride, bromide, and iodide salts in dimethyl sulfoxide solution.[12] In the present series, iodide ion contributed more to stabilization of the dication than did bromide or chloride. Paul and Long have described similar salt effects with *p*-nitroaniline and other bases, as a function of anion size.[13]

Most of the ϕ values presented in Table I have a high standard error. This is to be expected at the low acidity of most of these experiments, since the expres-

(7) L. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX.
(8) T. G. Bonner and J. C. Lockhart, *J. Chem. Soc.*, 264 (1957).
(9) L. Michaelis and S. Granick, *J. Amer. Chem. Soc.*, **64**, 1861 (1942).
(10) R. L. Reeves, *ibid.*, **88**, 2240 (1966).
(11) See Table I, footnote *a*.
(12) B. Roth, S. Hurlbert, J. Strelitz, and G. H. Hitchings, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., 1966, to be published.
(13) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957), and references therein.

sion (H_0 + log [H$^+$]) of eq 2 approaches, and is sometimes equal to, zero. Since the margin of error in known H_0 values is relatively large,[13] it is evident that such errors will cause a large scatter in the points in this situation. In spite of this difficulty, the differences in the ϕ values of Table I are sufficiently great to make it possible to draw some reasonable conclusions about them.

The ϕ values for the equilibria in hydrochloric acid all fall in the range of +0.2 to −1.1. In general, the values become more negative with increasing alkylation of amino groups, or with the introduction of bulky 5 substituents. This would be expected on the basis of the hydration hypothesis. Since the ϕ values are not all substantially equal, it follows that this set of bases does not follow a common acidity function, as was also concluded on the basis of the Hammett plots. The ϕ values in sulfuric acid are all about 0.6–0.7 units higher than those in hydrochloric acid. By the hydration hypothesis, this would imply relatively greater hydration of the diprotonated species in sulfuric acid. We have already concluded that greater solvation occurs in the form of ion pairing with bisulfate ion. These hypotheses are probably not mutually exclusive.

The Effect of 5 Substituents on pK_1.—Figure 5 is a plot comparing the pK_1 values of the 2,4,6-triamino-5-substituted pyrimidines with those of their 2,4-diamino-5-substituted counterparts.[2] A good linear relationship is observed. A least-squares computation for the 8 substituents shown by solid circles on the graph gives the relationship

$$pK_{Tri} = 1.30 + 0.720pK_{Di} \quad (3)$$

The 95% confidence limits for the slope and intercept are, respectively, ±0.062 and ±0.367; s = 0.105 and r = 0.996. Since the diaminopyrimidines (paper I) obey the relationship

$$pK_{Di} = 7.32 - 6.96(0.738\sigma_I + 0.262\sigma_R^-) \quad (4)$$

the triaminopyrimidine constants can be calculated directly if σ is known. Stated in words, the polar effect of 5 substituents is less for the triaminopyrimidines by a factor of 0.72.

Relative Effects of Substituents on pK_1 and pK_2.—Table III shows ΔpK_a values for several groups of triaminopyrimidine derivatives. In series A, a comparison of ΔpK_1 and ΔpK_2 for the 5-substituted derivatives shows the differences to be very nearly equal for the four compounds studied. In other words, the substituent effect in the moderately strong acid region is very nearly the same as it is at neutrality. This is not true of the N-substituted derivatives, however, regardless of whether or not they are symmetrical.

Series B, the 6-(substituted amino)pyrimidines, shows the 6-methylamino, dimethylamino, and piperidino derivatives to be stronger bases than 1 by about 0.5 pH units in the pK_1 region. Such pyrimidines can be expected to protonate at N^3 rather than N^1, on both steric and electronic grounds. In contrast, other 2,4-diamino-6-substituted pyrimidines protonate at N^1.[1b] An indication that the protonation site is actually different is obtained from Figure 5 of paper I,[1b] which shows a very close correlation of 6-substituted pyrimidine pK_a values with a σ constant which is almost purely inductive. The data for the 6-dimethylamino derivative (σ = 0.065, pK_1 = 7.21) would give a point which falls way above the line. In other words, it is a stronger base than is expected from N^1 protonation. Since this substituent has a greater electron-donating capacity than does NH$_2$, protonation to give IIa and the *p*-quinonoid canonical form IIb is indicated. The protonation site for the less basic 6-morpholinopyrimidine is less certain. On steric grounds, N^3 is favored. See Scheme I.

In the pK_2 region, the 2,4-diamino-6-(substituted amino)pyrimidines are all *weaker* bases than the parent compound, and a progressive base weakening occurs in going from mono- to dialkylation. The large changes in ultraviolet spectra on diprotonation (see Table I and Figures 1 and 2) indicate that the second proton also goes on a ring nitrogen (N^1), to give IIIa. Of the possible canonical forms, IIIb–e, those most likely would

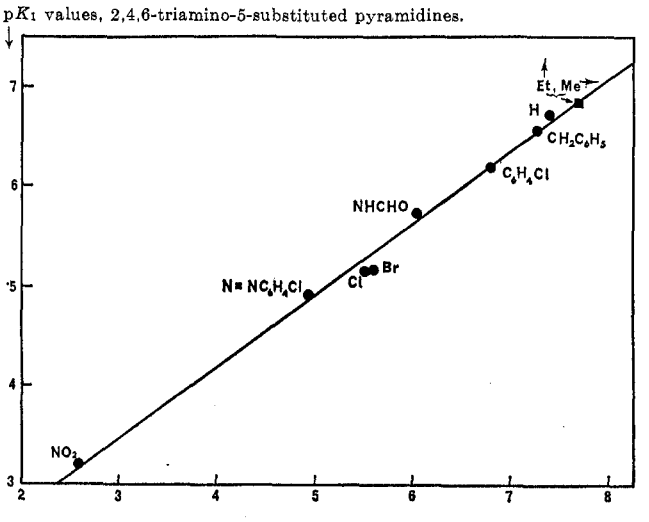


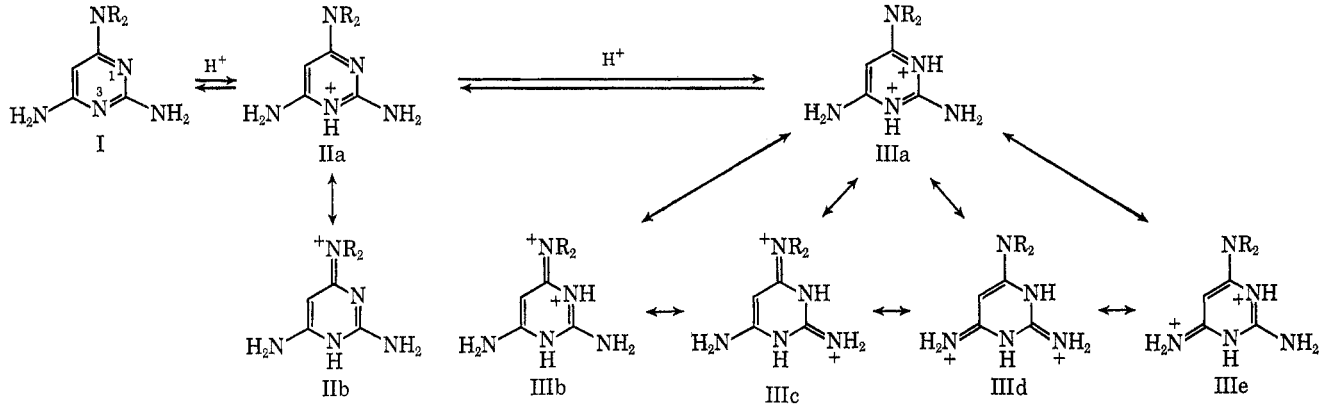
Figure 5.—Comparison of 5-substituent effects on the dissociation constants of 2,4,6-triamino- *vs.* 2,4-diaminopyrimidines.

TABLE III

COMPARISON OF ΔpK_1 AND ΔpK_2 VALUES FOR 2,4,6-TRIAMINOPYRIMIDINE DERIVATIVES

Substituent	ΔpK_1	ΔpK_2
A. pK_a (2,4,6-Triamino-5-substituted Pyrimidine) − pK_a (Compound 1)		
C_2H_5	0.12	0.24
SC_6H_5	−1.06	−1.23
Br	−1.55	−1.61
Cl	−1.57	−1.66
B. pK_a [2,4-Diamino-6-(substituted amino)pyrimidine] − pK_a (Compound 1)		
$NHCH_3$	0.49	−0.26
$N(CH_3)_2$	0.49	−0.63
N(CH$_2$)$_5$	0.48	−0.73
$N(CH_2CH_2)_2O$	0.01	−1.66
C. pK_a [2-Amino-4,6-bis(substituted amino)pyrimidine] − pK_a (Compound 1)		
$N(CH_3)_2$	0.46	−0.51
N(CH$_2$)$_4$	0.84	0.36
D. pK_a [2-(Substituted amino)-4,6-diaminopyrimidine] − pK_a (Compound 1)		
N(CH$_2$)$_5$	0.06	−0.45

SCHEME I



have their charges widely separated. Since N^1 is *ortho* to the 6-substituted amino group, the data suggest steric hindrance to diprotonation with increasing bulk. In the pyridine series, *ortho* substitution by isopropyl and *t*-butyl groups resulted in steric hindrance to protonation, but an ethyl group did not.[14] In contrast to ethyl, a methylamino group can be solvated, however. A comparison of the four ΔpK_2 values with the ϕ parameters is of interest. The latter are, in sequence, -0.04, -0.20, -0.47, and -1.06. This is suggestive of a linear correlation, and, in fact, a least-squares computation gives a correlation coefficient of 0.994 ($t = 3.9$, $s = 0.059$, and the slope is -0.72 ± 0.11). These results are no doubt fortuitous, but it is reasonable to assume that the decreasing ease of protonation is at least partially related to differences in solvation as hydrophobic groups are introduced. Considerably more data would be required to separate the various factors involved.

The C series, consisting of the 4,6-bis(dimethylamino) and pyrrolidino derivatives, shows a rather dramatic difference in the two compounds. The latter is not only a considerably stronger base in the pK_1 region, but remains a stronger base than **1** at pK_2. The C–N bond angles here are such as to greatly decrease the steric effect. The ϕ value is also less negative by 0.44 unit in the latter case.

The 2-piperidinopyrimidine (series D) has a pK_1 value very close to that of **1**, and thus it is a weaker base than the 6-piperidino analog. This is not unexpected, since there appears to be only a very small *ortho* resonance-stabilizing effect from the 2 position. In the pK_2 region, however, it is a stronger base than the 6 isomer. Since the steric effect at N^1 would appear to be the same from the 2 and 6 positions, another explanation would seem necessary. The pK_a values for this compound were corrected for the symmetry of the pyrimidine, and it is very possible that the molecule is actually not symmetrical in a medium where it is strongly solvated, if the 2-piperidino group is restricted in its rotation. In this case, pK_2 for **13** is 0.56, and ΔpK_2 is 0.75; these values are almost the same as those for **9**. The 2-piperidinopyrimidine has a less negative ϕ value, however; so the question remains unresolved.

Experimental Section

pK_a Determinations.—The pK_1 values were determined according to procedures described in paper I of this series.[2] In the pK_2 range, the H_0 values used for solutions in sulfuric and hydrochloric acids were those of Paul and Long.[13] The scale of Yates and Wai was used for perchloric acid.[15] Dilute acids above pH 1.1 were made up to a constant ionic strength of 0.1 by adding the necessary increments of the sodium salts of the corresponding acids. In the absence of salts, slight shifts in the low wavelength isosbestic points occurred in sulfuric acid as the pH changed. The second pK_a of sulfuric acid was calculated as 2 in preparing such solutions. Normally 15 to 18 spectra were carried out in the pK_2 range to make certain of the end points and isosbestic shifts, and to obtain sufficient data for Hammett plots in the proper range.

Compounds.—Most of the compounds were freshly prepared for this and related studies. Purification was accomplished by recrystallization, and finally by sublimation in many cases. A few old file samples from the Wellcome Research Laboratories were repurified before use.

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Registry No.—**1**, 1004-38-2; **2**, 24867-19-4; **3**, 24867-20-7; **4**, 4940-94-7; **5**, 24867-22-9; **6**, 24867-23-0; **7**, 24867-24-1; **8**, 24867-25-2; **9**, 24867-26-3; **10**, 24867-27-4; **11**, 24867-28-5; **12**, 24867-29-6; **13**, 24867-30-9; **14**, 24867-31-0; **15**, 24867-32-1; **16**, 24867-33-2; **17**, 2227-25-0; **18**, 2878-02-6; **19**, 24867-36-5.

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