A weighed quantity of perester ws transferred to a 10 ml volumetric flask and dissolved in cumene. Ten 1-ml aliquots were pipetted into 2-ml ampoules. The sealed ampoules were immersed in a thermostated oil bath. Temperature was controlled to ±0.1° and calibrated with an NBS certified thermometer. After a 2-min warm-up, the t_0 sample was removed and quenched at −78°. Subsequent samples were removed at 10-min intervals for 4 half-lives. The infinity sample was left in the bath for about 10 half-lives. At the end of the run, all samples were warmed to room temperature and the per cent transmittance was determined at the carbonyl maximum in the infrared spectrum. After setting the spectrophotometer at mixiumum absorption on the carbonyl peak, the scanning mechanism was disconnected and the pen was set at 0 and then 100% transmission using pure solvent in both cells. The samples were viewed in turn against pure solvent taking care to allow for the pen to come to equilibrium with each sample. Perester solutions in cumene obeyed Beer's law between 15 and 85% transmittance. The rate of decompostion was calculated from the slope of the line obtained by plotting log A_0/A_t *vs.* time, where T_0 and T_∞ are the percentage transmission of the zero and infinity sample, respectively. The enthalpies of activation, ΔH^*, were obtained from the least-squares slopes of the lines given by log k/T *vs.* $1/T$ for runs at 60, 70, 80, and 90°. The entropy of activation was calculated by substituting the value of ΔH^* and a point on the line of log k/T *vs.* $1/T$ into the equation

$$\frac{A_0}{A_t} = \frac{\log T_\infty - \log T_t}{\log T_\infty - \log T_0}$$

$$\log k/T = \log (k'/h) - (\Delta H^*/RT) + (\Delta S^*/R)$$

and solving for ΔS^* (k' = Boltzmann's constant and h = Planck's constant).

Registry No.—*cis*-α,β-Diphenylglycidic acid chloride, 18521-11-4; *trans*-α,β-diphenylglycidic acid, 18521-13-6; *trans*-α,β-diphenylglycidic acid chloride, 18521-14-7; I, 18521-16-9; III, 18521-12-5; IV, 18521-15-8.

Acknowledgment.—Support of this work by the Petroleum Research fund, administered by the American Chemical Society, is gratefully acknowledged.

The Protonation of 2,4-Diaminopyrimidines. I. Dissociation Constants and Substituent Effects

BARBARA ROTH AND JUSTINA Z. STRELITZ

Wellcome Research Laboratories, Burroughs Wellcome and Co. (U.S.A.), Inc., Tuckahoe, New York 10707

Received March 27, 1968

The basic dissociation constants of a series of approximately 70 2,4-diaminopyrimidines and condensed pyrimidine derivatives have been obtained. The major effect of 5 substitution is inductive, but there is a greater resonance component than can be accounted for by correlation with Hammett σ_m constants. Maximum correlation is achieved with the equation log $(K/K_0) = \rho[0.72\sigma_I + 0.28\sigma_R]$, in which σ_{R^-} has been substituted for σ_R with the −R substituents. The effect of 6 substitution, on the other hand, is almost completely inductive. The equation log $(K/K_0) = \rho[0.96\sigma_I + 0.04\sigma_R]$ best satisfies the data in this case. Similar relationships have been found with 4-amino-6-substituted pyrimidines. In some cases hydrogen bonding renders such correlations imprecise. Dissociation constants of 4-substituted pyrimidines can be correlated with σ_p constants, but 2-substituted derivatives appear to have a considerably greater inductive component. The shifts in ultraviolet maxima of 2,4-diamino-6-substituted, but not 5-substituted, pyrimidines have been found to have a dependence on the +R or −R character of the substituents. Ion pair formation between certain diaminopyrimidines and divalent ions in aqueous solution has been postulated on the basis of uv studies.

The 2,4-diaminopyrimidines have assumed an important role in the chemotherapy of infectious disease, as a result of their strong preferential binding to the enzyme dihydrofolate reductase, in competition with the substrate, dihydrofolic acid.[1] A great many compounds of this type have been prepared.[2] We deemed it of importance to determine the basic dissociation constants of representative 5- and 6-substituted derivatives, in order to analyze electronic and steric effects upon the basicities of these molecules, and possible relationships to enzyme binding. Although these are complicated polyfunctional systems, it seemed possible that a relation to the Hammett substituent constants for the benzoic acids would develop.

A fairly large number of pK_a values have been listed for the pyrimidines.[3] In general, these do not constitute series of compounds in which one parameter has been varied systematically for the purpose of determining substituent effects on the dissociation constants. Greenbaum[4] studied the effect of three sulfur containing 6-substituents on the acidity of uracils, and found that he could correlate the results with the acidity of *para*-substituted benzene derivatives. Mizukami and Hirai[5a] determined the basic dissociation constants of several 2-methyl-4,5-disubstituted pyrimidines. Here the results of 4 and 5 substitution were related to Hammett *para*- and *meta*-substituent effects with the

(1) (a) G. H. Hitchings, E. A. Falco, H. VanderWerff, P. B. Russell, and G. B. Elion, *J. Biol. Chem.*, **199**, 43 (1952); (b) C. A. Nichol and A. D. Welch, *Proc. Soc. Exptl. Biol. Med.*, **74**, 403 (1950); (c) W. C. Werkheiser, *J. Biol. Chem.*, **236**, 888 (1961); (d) R. C. Wood and G. H. Hitchings, *ibid.*, **234**, 2377 (1959); (e) J. J. Burchall and G. H. Hitchings, *Mol. Pharmacol.*, **1**, 126 (1965).

(2) See, for example, references in footnotes to Table I.

(3) (a) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co., London, Ltd., 1965; (b) see D. J. Brown, "The Pyrimidines," Interscience Publishers, New York, N. Y., 1962, pp 472–476, for data on pyrimidines to 1960. For more recent papers, see, for example, (c) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963); (d) D. J. Brown and T. Teitei, *ibid.*, 755 (1965); (e) D. J. Brown and N. W. Jacobsen, *ibid.*, 3770 (1965); (f) D. J. Brown and J. S. Harper, *ibid.*, 5542 (1965).

(4) S. B. Greenbaum, *J. Amer. Chem. Soc.*, **77**, 3221 (1955).

(5) (a) S. Mizukami and E. Hirai, *J. Org. Chem.*, **31**, 1199 (1966); (b) E. Hirai, *Chem. Pharm. Bull.*, **14**, 861 (1966).

TABLE I

pK_a VALUES AND ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DIAMINO-5-SUBSTITUTED PYRIMIDINES

Compd no.	5 substituent	6 substituent	Thermodynamic pK_a (20°)	Concn pK_a (20°)	Buffer for concn pK_a[a]	Ultraviolet absorption spectra: Neutral species[b] λ_{max}, mμ	Neutral species[b] $\epsilon \times 10^{-3}$	Monocation[c,d] λ_{max}, mμ	Monocation[c,d] $\epsilon \times 10^{-3}$
1[e]	CH_3		7.69 ± 0.03	7.76 ± 0.03	B	227.5 sh	9.67	271	5.47
						286	6.9		
2[f]	CH_3	CH_3	8.07 ± 0.02	8.08 ± 0.03	A	227.5 sh	8.96	273	7.30
						284.5	7.6		
3[g]	$CH_2CH(CH_3)_2$	CH_3	8.06 ± 0.04	8.14 ± 0.03	B	230	9.65	276	7.3
				8.19 ± 0.04	C	287	7.85		
4	NH_2		7.63[h]						
			2.56						
5[i]			7.40 ± 0.03[j]	7.53 ± 0.02	A	228	9.15	265.5	5.39
						282	6.90		
6[k]	$CH_2C_6H_5$		7.27 ± 0.03			230 sh	12.9	206	31.60
						287.5	7.25	217.5 sh	25.50
								272.5	5.25
7[k]	$CH_2C_6H_5$	CH_3	7.62 ± 0.04	7.67 ± 0.06	A	230 sh	11.1	275	6.75
				7.78 ± 0.04	C	285	7.65		
8[k]	$CH_2C_6H_4Cl(4)$		7.17 ± 0.05	7.25 ± 0.03	A	220	21.5	222.5	29.2
				7.36 ± 0.03	C	235 sh	14.0	270	5.50
						287	7.32		
9[k]	$CH_2C_6H_4Cl(4)$	CH_3	7.58 ± 0.05	7.63 ± 0.04	B	218	21.4	275	7.45
				7.68 ± 0.03	C	238 sh	11.7		
						285	8.20		
10[k]	$CH_2C_6H_4Cl(4)$	C_2H_5	7.71 ± 0.04	7.71 ± 0.06	A	218	21.5	223	28.40
						238 sh	11.4	275.5	7.80
						286	8.20		
11[k]	$CH_2C_6H_4Cl(4)$	n-C_3H_7	7.71 ± 0.03	7.73 ± 0.05	A	217–220	21.3	223	28.2
				7.77 ± 0.15	C	238.8 sh	11.05	276	8.05
						286	8.30		
12[l]	$CH_2C_6H_2(OCH_3)_3(3,4,5)$		7.12 ± 0.03	7.19 ± 0.02	A	227.5 sh	20.80	269	6.05
				7.24 ± 0.03	B	287	7.25		
13[m]	OCH_3		7.23 ± 0.02	7.32 ± 0.08	A	215	11.20	199.5	13.9
				7.46 ± 0.06	C	230 sh	9.30	222.5	18.2
						296	6.15	283	4.96
14[n]	C_6H_5		6.90 ± 0.05			257	9.80	208	33.6
						292	7.41	235 sh	15.2
								275 sh	5.10
15[n]	C_6H_5	CH_3	7.40 ± 0.03			240 sh	8.70	207.5	32.5
						285	8.85	225 sh	20.0
								273	7.25
16[n]	$C_6H_4Cl(4)$		6.79 ± 0.03			262	12.75	210	34.2
						290	10.60	240 sh	17.7
								277.5 sh	6.70
17[n]	$C_6H_4Cl(4)$	CH_3	7.26 ± 0.02			250 sh	8.45	208	35.0
						285	9.75	222 sh	25.8
								270	7.93
18[n]	$C_6H_4Cl(4)$	C_2H_5	7.34 ± 0.04	7.41 ± 0.03	A	220 sh	19.8	222.5 sh	23.1
				7.48 ± 0.08	C	248 sh	7.45	272	7.32
						285	8.75		
19[n]	$C_6H_4Cl(4)$	n-C_3H_7	7.35 ± 0.03			220 sh	21.5	208	35.4
						247.5 sh	8.10	222.5 sh	25.8
						286	9.45	272.5	8.10
20[n]	$C_6H_4Cl(4)$	$CH_2CH(CH_3)_2$	7.39 ± 0.03			220 sh	21.0	208	34.6
						245 sh	8.10	220 sh	25.4
						287	8.85	272.5	7.70
21[n]	$C_6H_3Cl_2(3,4)$	CH_3	7.15 ± 0.03			285	10.3	201	43.0
								208	42.9
								270.5	8.3
22[n]	$C_6H_3Cl_2(3,4)$	C_2H_5	7.20 ± 0.03			285	9.9	201	44.5
								207.5	44.4
								272	8.3
23[n]	$C_6H_4Cl(3)$		6.70 ± 0.02			208	34.0	213	39.3
						262	10.6	235 sh	16.5
						292	9.95	272 sh	6.7
24[n]	$C_6H_4Br(2)$		6.70 ± 0.05			252 sh	6.5	210	33.7
						290	7.1	267.5	4.76
25	$C_6H_2(OCH_3)_3(3,4,5)$		6.70 ± 0.05			261	9.35	208	36.7
						287.5 sh	7.37	240 sh	12.4
26	COOH		6.79 ± 0.03[o]			215[p]	32.0	220	36.6
			2.94 ± 0.03			230 sh	16.5	232.5 sh	18.5
						273	5.4	273	5.4
27[q]	NHC_6H_5		6.79 ± 0.03			238	14.65	233	19.7
						283	8.04	260 sh	9.95
								307.5 sh	2.01
28[m]	OC_6H_5		6.26 ± 0.04	6.40 ± 0.06	C	207.5	18.7	202.5	28.3
						217.5 sh	17.1	222.5	22.5
						232.5 sh	13.8	267–282.5	4.4
						269 sh	3.84		
						275	4.65		
						293	6.66		
29[m]	OC_6H_5	CH_3	6.47 ± 0.04			230 sh	13.6	203.5	28.4
						268 sh	4.57	222	26.8
						275 sh	5.87	259 sh	4.75
						287.5	7.6	267.5 sh	6.10
								273	6.70
								278 sh	6.48

TABLE I
(*Continued*)

Compd no.	5 substituent	6 substituent	Thermodynamic pK_a (20°)	Concn pK_a (20°)	Buffer for concn pK_a[a]	Ultraviolet absorption spectra: Neutral species[b] λ_{max}, mμ	$\epsilon \times 10^{-3}$	Monocation[c,d] λ_{max}, mμ	$\epsilon \times 10^{-3}$
30[m]	$OC_6H_4C(4)$		6.16 ± 0.03	6.29 ± 0.04	C	225	19.4	202.5 sh	30.8
						287	6.7	227.4	26.7
						290–292 sh	6.62	275	5.2
31[r]	NHCHO		6.03 ± 0.03			222	8.40	208	22.2
						287	5.50	270	3.70
32[s]	$SC_6H_4(OCH_3)(4)$		5.94 ± 0.03			248	20.8	212.5	39.3
						290	9.05	242.5	22.3
								270 sh	7.4
33[s]	$SC_6H_4Cl(4)$		5.70 ± 0.04	5.86 ± 0.03	C	250	20.6	213	41.3
						287.5	9.4	243	22.2
								287.5 sh	6.3
34[s]	$SC_6H_4Cl(4)$	C_2H_5	6.27 ± 0.03			207	41.0	212.7	40.9
						252	22.0	246	24.2
						285	10.35	272.5 sh	8.55
35[t]	Br		5.60 ± 0.03						
36	Cl		5.52 ± 0.05			233	10.3	208	25.3
						294	6.6	220 sh	17.2
								280	4.55
37[u]	$COOC_2H_5$		5.07 + 0.02	5.24 ± 0.02	D	214.5	24.2	240 sh	16.0
						252	15.5	277.5	5.70
						292.8	12.72		
38[v]	$N{=}NC_6H_4Cl(4)$		4.93 ± 0.05[w]			265[x]	10.5	230 sh	21.8
						292.5 sh	11.8	327	22.9
						345	21.9		
39[y]	$-C(=O)C_6H_5$		4.63 ± 0.03	4.76 ± 0.03	D	219	16.45	228	28.1
						245	12.4	255	17.3
						265	11.3	285	11.35
						312	17.45		
40[y]	$-C(=O)C_6H_4Cl(4)$		4.58 ± 0.01			217	19.0	228	28.7
						257.5	13.9	260	18.2
						313.2	19.5	285	13.9
41[y]	$-C(=O)C_6H_2(OCH_3)_2Br(3,4,5)$		4.48 ± 0.04			202.5	36.6	202.5	36.0
						222.5 sh	24.7	226	33.9
						268	12.5	252.5	16.7
						315	20.6	290	12.9
42[z]	CN		3.75 ± 0.03			212.5	27.2	220.2	41.0
						249	15.35	237.5 sh	15.9
						292.5	9.45	277.5	4.85
43	C_6H_5	CF_3	3.25 ± 0.04			202.7	38.5	210	35.0
						238 sh	10.4	225 sh	16.5
						298	7.86	262.5–280 plat	4.86
								320 sh	2.16
44[aa]	$C_6H_4Cl(4)$	OH	3.06 ± 0.02[bb]			272.5	14.6	270	18.3
			10.80 ± 0.02						
45[cc]	NO_2		2.58 ± 0.03			215	14.3	227	20.4
						255	6.06	250 sh	9.97
						350	14.34	310	7.44

[a] A, 0.1 *N* tris; B, 0.1 *N* tris containing 0.1 *N* NaCl; C, 0.067 *M* KH_2PO_4–Na_2HPO_4; D, 0.1 *N* acetate. [b] All spectra of pure species were obtained in buffers at least two pH units away from the pK_a value. Most spectra of neutral species were determined in freshly prepared 0.01 *N* NaOH solution or Sørensen pH 9 glycine–NaOH (0.01 *N*) in the case of some compounds with lower pK_a values. The use of 0.1 *N* NaOH was found undesirable, as it resulted in a significant diminishing of intensity in a number of cases, possibly due to anion formation. The use of 0.1 *N*, as opposed to 0.01 *N*, buffers at lower pH values caused no such spectral changes in the pure species, but the use of 0.01 *N* buffers permitted extension of the curves to lower wavelengths. The extinction values are not accurate to more than three significant figures at the most, but since the precision is higher in a given experiment, data are sometimes recorded to four figures for relative comparisons in that experiment. [c] Most cationic species were measured in 0.01 *N* HCl, which gave results identical with pH 4 acetate (0.1 or 0.01 *N*), in cases where the pK_a values were >6. For low pK_a values, 0.1 and 1 *N* hydrochloric acid solutions were employed. [d] Isosbestic points and λ_{min} values are available upon request from the library, Burroughs Wellcome & Co. [e] O. Gerngross, *Ber.*, **38**, 3394 (1905). [f] J. Schlenker, *ibid.*, **34**, 2812 (1901); W. Huber and H. A. Hölscher, *ibid.*, **71**, 87 (1938); mp of our sample, 192°. [g] Prepared by Elvira A. Falco in these laboratories; unpublished mp 162–64°. [h] pK_a by S. F. Mason, *J. Chem. Soc.*, 2071 (1954). [i] B. Roth and G. H. Hitchings, *J. Org. Chem.*, **26**, 2770 (1961). [j] A. Albert, R. Goldacre, and J. Phillips [*J. Chem. Soc.*, 2240 (1948)] report a pK_a of 7.26 (potentiometric). [k] E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Amer. Chem. Soc.*, **73**, 3758 (1951). [l] B. Roth, E. A. Falco, G. H. Hitchings, and S. R. M. Bushby, *J. Med. Pharm. Chem.*, **5**, 1103 (1962). [m] E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Amer. Chem. Soc.*, **73**, 3753 (1951). [n] P. B. Russell and G. H. Hitchings, *ibid.*, **73**, 3763 (1951). [o] Acidic and basic pK_a values, respectively, for a zwitterion (see text). [p] There is a very slight overlapping of the pK_a values. The spectrum described here for the neutral species was obtained at pH 4.89. No isosbestic points are recorded, due to the overlapping. Spectra were determined at eleven pH values, and the pK_a values were calculated with the aid of the Thamer equation [see B. Roth and J. F. Bunnett, *J. Amer. Chem. Soc.*, **87**, 334 (1965)]. The anion exhibits maxima at 248 mμ (ε 13,000) and 291 (9300), and minima at 230 mμ (ε 8300) and 267.5 (3700). [q] F. R. Gerns, A. Perrotta, and G. H. Hitchings, *J. Med. Chem.*, **9**, 108 (1966). [r] O. Isay, *Ber.*, **39**, 250 (1906). [s] E. A. Falco, B. Roth, and G. H. Hitchings, *J. Org. Chem.*, **26**, 1143 (1961). [t] pK_a by D. J. Brown and T. Teitei.[3d] [u] H. L. Wheeler and C. O. Johns, *Amer. Chem. J.*, **38**, 594 (1907). [v] D. J. Brown, *J. Soc. Chem. Ind.* (London), **69**, 353 (1950). [w] pK_a determined in 0.01 *N* acetate containing 20% ethanol. [x] Spectrum obtained at pH 9. In stronger alkali there was a complete change in spectrum, shifting the long-wavelength maximum to 390 mμ, with increased intensity. Curves at pH 12 and in 0.8 *N* sodium hydroxide showed no isosbestic points with the curve at pH 9, however, indicating a structural change. The azo compound could form an anion with extended conjugation through canonical forms such as

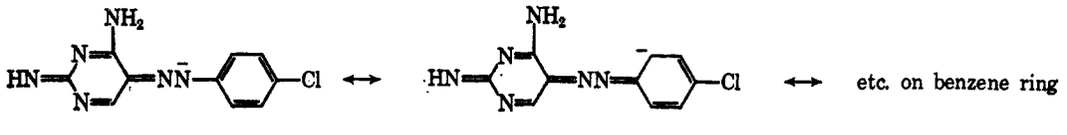


TABLE I
(*Footnotes*)

The 2-imino group would be expected to hydrolyze readily to 2-oxo, which would result in the isosbestic loss. [v] B. Roth, *et al.*, synthesis to be published. [s] W. Hüber, *J. Amer. Chem. Soc.*, **65**, 2222 (1943). [aa] Prepared by P. B. Russell in these laboratories; unpublished. [bb] Acidic pK_a; the anion, in 0.1 *N* sodium hydroxide, exhibits λ_{max} 267.5 mμ (ε 11,900); λ_{min} 244 (5150). Isosbestic points with the neutral species occur at 247.5 mμ (ε 5400) and 311 (1180). [cc] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

benzenes, respectively, as would be expected if protonation occurs at N_1. Their series were small, however, and in all cases where one substituent was varied, the substituents were of the same type (−R, −I).[6] The pK_a values for the carboxyl derivatives were incorrectly assigned as basic constants, rather than acidic dissociation constants of a zwitterion, but were corrected later by Hirai.[5b]

We were fortunate to have a great many types of 2,4-diamino-5- and -6-substituted pyrimidines available in our files. Additional compounds which were synthesized are described in the Experimental Section. The thermodynamic dissociation constants were determined by spectrophotometric means, using methods similar to those of Albert and Serjeant.[7] Concentration constants were also determined in 0.1 or 0.067 *M* buffers in many instances, for comparison with biological data in related systems.

Results

Pyrimidine and Condensed Pyrimidine Dissociation Constants.—Table I lists the basic dissociation constants and ultraviolet spectral data for 2,4-diamino-5-substituted pyrimidines and some of their 6-alkyl, substituted alkyl, or 6-hydroxyl derivatives. Table II contains similar data for 2,4-diamino-6-substituted pyrimidines. Table III lists the basic and some acidic dissociation constants, and spectral data for a number of bi- and tricyclic systems formed by fusion to the 2,4-diaminopyrimidine moiety across the 5,6 carbons. A few literature values are included. Data on the parent diamino derivative for each ring system are listed, where available, and where the parent compound has not been prepared, an attempt has been made to provide appropriate comparative data for corresponding derivatives of related systems, *e.g.*, **65** and **71**.

Azapyrimidine Dissociation Constants.—Table IV contains data on a few aza analogs of the pyrimidines. The dissociation constant for 2,4-diamino-1,3,5-triazine was reported to be 5.88 by Dudley.[8] A recent paper by Morimoto[9] on the dissociation constants of 2,4-diamino-6-substituted 1,3,5-triazines lists the dissociation constant for this compound as 4.50. We repeated this determination to verify one or the other value, and, surprisingly, obtained a value of 3.91 (compound **78**). Our ultraviolet spectrum is identical with that published by Morimoto, which would indicate that the two compounds are the same. Morimoto reported pK_a values of 4.15 and 5.00 for the 6-methoxyl and 6-methyl derivatives, respectively, whereas Dudley obtained a dissociation constant of 3.43 for the corresponding 6-allyloxyl derivative, and 4.60 for the 6-methyl analog. Comparison of the various pK_a values with the parent compound suggests that Dudley's value of 5.88 was a typographical error for 3.88, and that Morimoto's buffer standards were possibly in error.

Anion Effects on pK_a Determinations.—In determining the concentration dissociation constants for 2,4-diaminopyrimidine, it was observed that curves obtained in pH 7–8 0.067 *M* phosphate buffer deviated from the isosbestic points. This was not true in 0.1 *N* tris buffer, however. This phenomenon is illustrated in Figure 1, where it is seen that the phosphate curve has undergone a slight hypso- and hyperchromic shift in the region of the long-wavelength maximum. In more dilute phosphate solutions (0.0067 and 0.0022 *M*), this shift disappeared. Other compounds which produced this effect included the 5-, 6-, and 5,6-dimethyl derivatives of 2,4-diaminopyrimidine. When large substituents were present in the 5 position, such as isobutyl, phenyl, or benzyl, no deviation from the isosbestic point was observed. A test of several other salts, all 0.4 *N*, in the presence of 0.01 *N* tris buffer at pH 7.5, revealed no effect on the spectrum of 2,4-diaminopyrimidine when sodium chloride, sodium bromide, or sodium iodide were used, but sodium sulfate produced a deviation similar to phosphate.

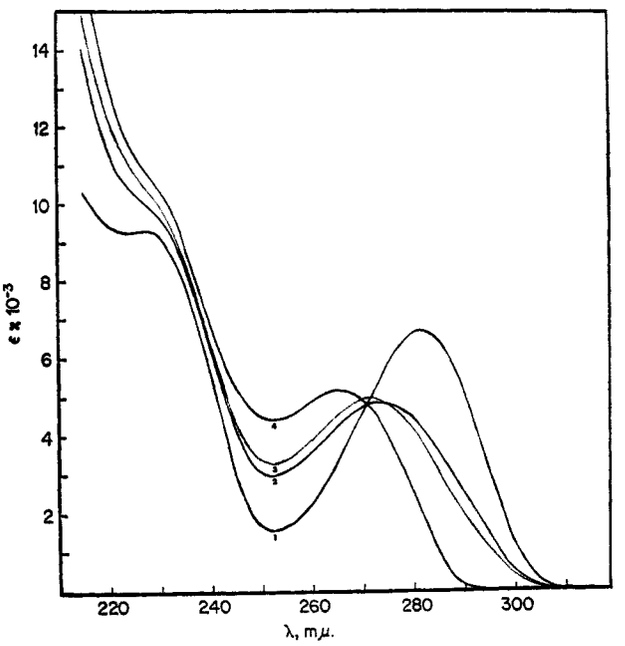


Figure 1.—Effect of buffers on the ultraviolet spectrum of 2,4-diaminopyrimidine (1) at pH 12 (0.01 *M* NaOH), (2) at pH 7.48 (0.01 *M* tris), (3) at pH 7.40 (0.067 *M* phosphate), (4) at pH 4 (0.1 *M* acetate).

It is well known from the work of Debye and Hückel

(6) The sign conventions used here for the resonance (R) and inductive (I) effects are those of C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 67 ff.

(7) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962.

(8) J. R. Dudley, *J. Amer. Chem. Soc.*, **73**, 3007 (1951); see also ref 3a.

(9) G. Morimoto, *Nippon Kagaku Zasshi*, **87**, 790 (1966).

TABLE II

pK_a VALUES AND ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DIAMINO-6-SUBSTITUTED PYRIMIDINES[a]

Compd no.	6 substituent	Thermodynamic pK_a (20°)	Ultraviolet absorption spectra: Neutral species λ_{max}, mμ	Neutral species $\epsilon \times 10^{-3}$	Monocation λ_{max}, mμ	Monocation $\epsilon \times 10^{-3}$
46[b]	COOH	7.79 ± 0.03[c]	281[d,e]	5.20	210.5	25.0
		1.35 ± 0.06			282	5.20
47	CH_3	7.63 ± 0.03[f]	227.5 sh	8.9	207	11.6
			278	7.85	267	7.52
5[g]	H	7.40 ± 0.03	228	9.15	265.5	5.39
			282	6.90		
48	NH_2	6.72 ± 0.01[h]	*Ca.* 209	35.2	214	29.2
			237.5 sh	4.01		
			267.5	11.80	272	18.2
49[i]	C_6H_5	6.70 ± 0.03	237.5	24.6	203	33.6
			305	7.65	233.7	17.8
50[j]	OCH_3	5.48 ± 0.03	232.5 sh	6.58	225	9.90
			263.2	8.35	275	9.65
51	SCH_3	5.46 ± 0.01[k]				
52	$COOCH_3$	5.32 ± 0.02	228	10.2	211	28.4
			318	7.3	288	6.30
53[l]	$SC_6H_4Cl(4)$	5.02 ± 0.04	228	27.5	224	26.6
			270 sh	7.3	292	13.4
			288	10.3		
54[m]	$SCH_2C(=O)C_6H_4Br(4)$	4.98 ± 0.04	220 sh	25.4	235 sh	17.0
			263	20.4	262	21.2
			282.5 sh	17.0	287.5 sh	17.0
55	$CONH_2$	4.90 ± 0.02	226	12.4	210.5	32.0
			312.5	5.02	285	5.48
56	OC_6H_5	4.80 ± 0.02	237.5 sh	8.50	223	14.0
			267.5	9.40	279	12.6
57	SO_3Na	4.69 ± 0.03	227	10.3	270	6.40
			292.5	6.35	310 sh	1.06
58	Cl	3.57 ± 0.01[k]	204.5	24.8	209	14.2
		3.60 ± 0.02[n]	227.5 sh	9.52	227.5	10.6
			282	7.85	297.5	7.95
59	OH	3.33[k]				
		10.78[p]				
60[o]	SH	1.73 ± 0.04	204	26.3	246	10.2
		10.19 ± 0.02[p]	226	18.7		
			307.5	25.3	323.9	36.8

[a] The pK_a values for the first and second protonation of 2,4-diamino-6-substituted aminopyrimidines will be discussed in a paper by B. Roth and J. Strelitz. [b] G. D. Daves, F. Baiocchi, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 2755 (1961). [c] pK_a value for a zwitterion; see text. [d] Spectrum of zwitterion. The anion exhibits maxima at 222.5 mμ (ε 9250), 297.5 (4200), and minima at 217 (9100), 256 (1080). [e] Isosbestic points for the zwitterion–cation equilibrium are at 222 (11,700) and at 281 (5200). The isosbestic points for the anion–zwitterion equilibrium are at 228.7 (9000), 244 (4100), 295 (4200). [f] A pK_a value of 7.7 (25°) has been reported by J. C. Gage, *J. Chem. Soc.*, 469 (1949). [g] See Table I, footnote *i*, for reference. [h] A pK_a value of 6.84 (potentiometric, 20°) was reported in Table I, footnote *j*. The present value includes a statistical factor of 2. [i] P. B. Russell, *J. Chem. Soc.*, 2951 (1954). [j] B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **73**, 2869 (1951). [k] pK_a value by D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 3172 (1962). [l] See Table I, ref *s*. [m] B. Roth, *J. Med. Chem.*, **12**, 227 (1969). [n] pK_a value obtained in our laboratories. [o] G. B. Elion, W. Lange, and G. H. Hitchings, *J. Amer. Chem. Soc.*, **78**, 2858 (1956). [p] pK_a value for the loss of a proton. Uv spectral data for monoanion are as follows: λ_{max} 222.5 mμ (ε 17,300), 237.5 (17,100), 252.5 sh (10,100), 297 (18,400); λ_{min} 230.5 (16,200), 269 (3920). Isosbestic points (B ⇄ B^-), 232.5 (15,900), 298.2 (18,200).

that dissociation constants are increased in the presence of polyvalent ions as a result of increased ionic strength.[7] This does not affect the isosbestic points, however, since the same equilibria are involved. What we report here is another phenomenon.

Discussion

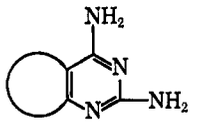
Examination of the data of Tables I and II gives indication that the effect of substituents in either the 5 or 6 position is primarily inductive in character. With the exception of alkyl or 5-amino groups, the consequence of all 5 or 6 substitution is to lower the pK_a values of the pyrimidines. This suggests a possible relationship to the Hammett *meta*-substituent constants. It would be surprising in such a complex system if there were a precise linear correlation, since one would expect deviations due to resonance interaction, hydrogen bonding, and steric interference. However, we hoped to find it possible to analyze deviations in terms of such factors.

The Relationship of Diaminopyrimidine Dissociation Constants to the Hammett σ Values. A. The Hammett Constants.—In determining these relationships, we used the available thermodynamic Hammett substituent constants (25°), based on the ionization of substituted benzoic acids. There are ten such σ_m constants with an estimated uncertainty of 0.02 pH units (not including CN).[10] For CN, we used the

(10) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

TABLE III

pK_a VALUES AND ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DIAMINOPYRIMIDO-5,6-FUSED RING SYSTEMS



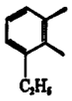
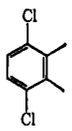
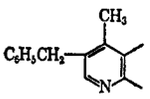
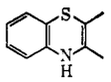
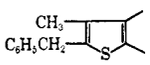
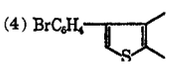
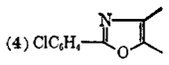
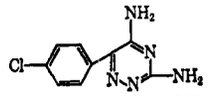
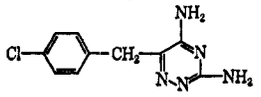
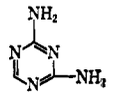
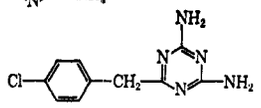
Compd no.	Fused ring system	Thermodynamic pK_a (20°)	Ultraviolet absorption spectra: Neutral species λ_{max}, mμ	Neutral species $\epsilon \times 10^{-3}$	Monocation λ_{max}, mμ	Monocation $\epsilon \times 10^{-3}$
61[a]		7.96 ± 0.03	230.2	44.5	226	37.8
			265	8.10	231 sh	35.8
			273	7.20	247.5 sh	12.2
			330	4.20	266.5 sh	5.45
					315	4.72
					325 sh	3.84
62[a]		8.29 ± 0.03	233	38.7	210 sh	14.85
			262.5 sh	6.90	227.5	33.2
			270	7.90	236	34.6
			279.5	7.20	250 sh	13.7
			335	4.38	260 sh	9.70
					270 sh	5.10
					317.5	4.53
					327 sh	3.95
63[a]		6.07 ± 0.03	238	29.4	227.5 sh	25.5
			245 sh	27.6	231	26.5
			270 sh	7.20	244	29.4
			279	8.70	262.5 sh	9.95
			288	8.10	330	4.62
			350	5.05	337.5 sh	3.66
64[b]		6.62 ± 0.06	222.5	24.2	217.5	30.2
			247	18.3	234.2 sh	14.6
			265 sh	7.45	241 sh	11.5
			340	6.75	265	6.28
					312.5	9.05
					322 sh	7.65
65[c]		6.98 ± 0.05	235	27.0	232	30.2
			269	9.85	257.5 sh	8.70
			343	5.75	267.5 sh	6.45
					320	7.02
					327.5 sh	6.50
66[d]		6.18 ± 0.03	219.5	30.4	226	27.9
			259.5	7.90	262.5	7.70
			284	7.70	294	7.20
67		5.58 ± 0.07[e]	*e*			
68		5.32 ± 0.03[f]	*f*			
69		5.09 ± 0.05[g] 10.77 ± 0.05	*g*			
70[h]		4.99 ± 0.02	255	29.2	225 sh	18.3
			292.5	6.55	266	28.9
			330 sh	2.0	290 sh	6.75
					370	1.95
71[i]		4.90 ± 0.04	209.5	29.95	206	27.2
			236	28.6	244	35.0
			277.5	15.4	272.5	11.3
			327 sh	4.34	302.5 sh	2.98
72[i]		4.47 ± 0.04	225	26.8	232.5	39.4
			275–285 sh	8.50	275 sh	8.50
					320 sh	1.92
73[j]		3.89 ± 0.04	215	25.8	219.5	24.0
			280	10.8	265	9.86
					306 sh	2.37
74[k]		3.68 ± 0.03 7.58 ± 0.02[l]	*m*		203 252.5	18.3 12.3
					270 sh	9.50
75[n]		*Ca.* 3.5[o]	230[o] 327	*p*	303 315	

TABLE III
(*Footnotes*)

[a] G. H. Hitchings and K. Ledig, in preparation. [b] R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, **77**, 2256 (1955). [c] B. S. Hurlbert, K. Ledig, P. Stenbuck, B. Valenti, and G. H. Hitchings, *J. Med. Chem.*, **11**, 703 (1968). [d] Prepared according to the procedure of British Patent 812,366 (1959); see also J. Davoll, *J. Chem. Soc.*, 131 (1960). Our product was obtained as the anhydrous base (from acetone–ethyl acetate), mp 215–218° dec. [e] B. M. Lynch, R. K. Robins, and C. C. Cheng, *J. Chem. Soc.*, 2973 (1958). [f] A. Albert, D. J. Brown, and G. Cheeseman, *ibid.*, 4219 (1952). [g] A. Albert and D. J. Brown, *ibid.*, 2060 (1954). [h] B. Roth, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., 1963; in preparation. [i] B. Roth, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., 1966; see Table II, ref *m*. [j] Table II, footnote *o*. [k] L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, **70**, 3875 (1948). [l] pK_a for loss of a proton. [m] pK_a values overlapped slightly. Spectrum of anion was as follows: λ_{max} 217.3 mμ (ϵ 14,100), 248 (5430), 290 (7550); λ_{min} 240 (5150), 263 (2600). [n] E. A. Falco, G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Amer. Chem. Soc.*, **74**, 4897 (1952). [o] Compound exceedingly insoluble; spectrum of neutral species determined in 50% ethanol; maxima quite different from those reported in footnote *n*. [p] Concentration unknown; stock solution of 50 mg/100 ml precipitated at 20° and was filtered before 1:50 dilution.

TABLE IV

pK_a VALUES AND ULTRAVIOLET SPECTRA OF AZA ANALOGS OF 2,4-DIAMINOPYRIMIDINES

Compd no.	Structure	Thermodynamic pK_a (20°)	Ultraviolet absorption spectra: Neutral species λ_{max}, mμ	Neutral species $\epsilon \times 10^{-3}$	Monocation λ_{max}, mμ	Monocation $\epsilon \times 10^{-3}$
76[a]		6.07 ± 0.03	240	11.1	202.5	30.3
			307.5	7.65	225 sh	14.7
					267.5 sh	6.40
77[b]		6.47 ± 0.03	222.5	20.5	207	35.0
			302.5	6.10	219 sh	27.2
					252.5	7.30
78[c]		3.91 ± 0.02[d]	257.5	3.64	248 sh	2.60
79[e]		3.97 ± 0.03	225 sh	18.8	208.2	41.8
			256	3.76	229 sh	12.0

[a] G. H. Hitchings, A. Maggiolo, P. B. Russell, H. VanderWerff, and I. M. Rollo, *J. Amer. Chem. Soc.*, **74**, 3200 (1952). [b] Prepared by P. B. Russell in these laboratories. [c] Prepared according to the method of D. W. Kaiser and J. J. Roemer, U. S. Patent 2,630,433 (1953). [d] See ref 8 and 9. [e] P. B. Russell, G. H. Hitchings, B. H. Chase, and J. Walker, *J. Amer. Chem. Soc.*, **74**, 5403 (1952).

value of 0.615, obtained by Briegleb and Bieber[11] from measurements in cells without liquid junction. This value has been corroborated by Fickling and coworkers, with a mean of 0.621,[12] and derived by van Bekkum, Verkade and Wepster[13] with a mean of 0.613. For C_6H_5, we used the σ_m constant 0.06 (estimated uncertainty, 0.05 pH units). All other σ_m values have an estimated reliability of only 0.1 pH unit,[10] and were considered unsuitable in deducing meaningful relationships.

To obtain usable derived σ_m values for the substituents NH_2, COO^-, SCH_3, $COOCH_3$, CF_3, and SO_3^-, we employed aniline data, as collated and assessed by Perrin.[3a] Table V lists what appear to be the most reliable thermodynamic pK_a values for aniline and 20 *meta*-substituted anilines in water at 25°. A calculation of ρ for the *meta*-substituted anilines from the ten thermodynamic σ_m values for CH_3, H, OCH_3, I, Br, Cl, F, $COCH_3$, CN, and NO_2 and the pK_a values from Table V, using the method of least squares, gives eq 1. The correlation coefficient (r) is 0.997 and the

$$pK_a = 4.582 - 2.904\sigma_m \quad (1)$$

standard error is 0.059 pH units.[14] The 95% confidence limits for ρ are ±0.184.

The following derived σ_m constants (25°) were calculated from eq 1: $COOCH_3$ (and COOH, by assumption), 0.35; SCH_3, 0.20; SO_3^-, 0.28; CF_3, 0.38. The constants for NH_2 and COO^- were calculated from the pK_a data for *m*-aminobenzoic acid (Table V), using the method of Bryson (Table V, footnotes *b* and *p*). This gave values of −0.10 for NH_2 and 0.00 for COO^-. For $COOC_2H_5$ we used the value 0.37.[10] The σ_m constant for $CONH_2$[15] remains questionable.

B. The 5-Substituted Pyrimidines.—The eight thermodynamic σ_m constants for CH_3, H, OCH_3, OC_6H_5, Br, Cl, CN, and NO_2 were plotted against the corresponding 2,4-diamino-5-substituted pyrimidine dissociation constants to obtain the circled points shown in Figure 2. The slope of the regression line (ρ) was calculated by the method of least squares (Table VI, calculation 1). Calculation 2 of this table shows the result of including the substituents C_6H_5 and $COOC_2H_5$;

(11) G. Briegleb and A. Bieber, *Z. Electrochem.*, **55**, 250 (1951).

(12) M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, **81**, 4226 (1959).

(13) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

(14) Bryson (see Table V, footnote *b*) and Biggs and Robinson (Table V, footnote *d*) obtained ρ values of 2.82 and 2.889, respectively, using their own aniline data. Van Bekkum and coworkers[13] calculated ρ as 2.941 using earlier literature aniline data. They questioned the use of *m*-OCH_3 as a primary σ constant for calculating new ρ values, since they feared that strong +R effects might cause anomalies even from the *meta* position. In the present case, the *m*-methoxy value fell right on the regression slope, however.

(15) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE V

THERMODYNAMIC DISSOCIATION CONSTANTS OF *meta*-SUBSTITUTED ANILINES (25°)[a]

Group	pK_a	Ref	Group	pK_a	Ref
CH_2CH_3	4.70	*b*	Cl	3.52	*d, n*
CH_3	4.72	*b, d, l*	F	3.55	*b, d, o*
$CH(CH_3)_2$	4.67	*b*	$COCH_3$	3.56	*b*
$C(CH_3)_3$	4.66	*b*	$COOCH_3$	3.55	*b*
$Si(CH_3)_3$	4.64	*c*	CF_3	3.49	*g*
H	*4.603*	*d*	COOH	pK_1 3.08[p]	*h*
OCH_3	4.22	*b, d, m*		pK_2 4.77	
OCH_2CH_3	4.18	*b*	SO_2NH_2	2.90	*i*
SCH_3	4.00	*e*	*CN*	*2.75*	*j*
SO_3^-	*3.7381*	*f*	SO_2CH_3	2.56	*b*
I	3.61	*d*	NO_2	*2.466*	*j*
Br	3.53	*d*	$N(CH_3)_3^+$	*1.983*	*k*

[a] See ref 3a. The values in italic type are considered to be reliable, with an estimated uncertainty of 0.005 pH unit or less; the remaining values are considered accurate to within about 0.04 pH units or less. [b] A. Bryson, *J. Amer. Chem. Soc.*, **82**, 4858 (1960). [c] R. A. Benseker and H. R. Krysiak, *ibid.*, **75**, 2421 (1953). [d] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [e] F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **74**, 1058 (1952). [f] R. D. McCoy and D. F. Swinehart, *ibid.*, **76**, 4708 (1954). [g] J. D. Roberts, R. L. Webb, and E. A. McElhill, *ibid.*, **72**, 408 (1950). [h] A. Bryson and R. W. Matthews, *Aust. J. Chem.*, **14**, 237 (1961). [i] H. Zollinger and C. Wittwer, *Helv. Chim. Acta*, **39**, 347 (1956). [j] Reference 12. [k] A. V. Willi, *Z. Phys. Chem.* (Frankfurt am Main), **26**, 42 (1960). [l] Average of 4.70 (footnote *b*) and 4.73 (footnote *d*). [m] Average of 4.20 (footnote *b*) and 4.23 (footnote *d*). [n] Other reported values are 3.46 (footnote *b*) and 3.67 (footnote *g*). [o] Average of 3.50 (footnote *b*) and 3.59 (footnote *d*). [p] Using the argument of Bryson (footnote *b*), it is possible to use these values to deduce pK_a values for the equilibria

$$NH_3^+C_6H_4COOH \overset{K_B}{\rightleftharpoons} NH_2C_6H_4COOH + H^+$$

and

$$NH_3^+C_6H_4COO^- \overset{K_C}{\rightleftharpoons} NH_2C_6H_4COO^- + H^+$$

on the assumption that the pK_a for the first equilibrium is equal to that for the corresponding methyl ester (3.55). Using pK_a values from Table V, the estimated pK_a value for the second reaction may be calculated to be 4.59. Employing other data, Bryson obtained a pK_a of 4.64 for this equilibrium.

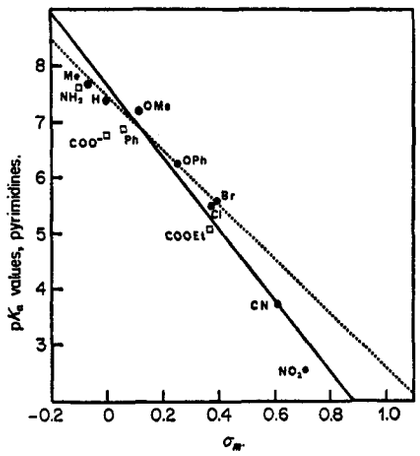


Figure 2.—Variation of pK_a with σ_m for 2,4-diamino-5-substituted pyrimidines: ●, points used for calculation of regression slope (solid line, calculation 1, Table VI); □, other substituent data; dotted line calculated from +R substituents only (calculation 3, Table VI).

this causes very little change in the value of ρ. The NH_2 substituent was not included in any calculations, because of uncertainty concerning the nature of the protonated species, relative to the other compounds.

The nature of the deviations from the regression slope (solid line) of Figure 2 suggests a curvature, or two separate slopes. When the calculations were repeated with the elimination of the −R substituents, the resultant ρ value was quite different, as shown in calculation 3 of Table VI, and the dotted line of Figure 2. The standard error is half that of calculation 2, and all points except OCH_3 lie very close to the line.

It would appear from these observations that a considerable degree of resonance interaction is involved in the 5-substituent effects on basicity. A test of the relationship of the dissociation constants to σ_p (calculation 5, Table VI) shows considerably poorer correlation than the results against σ_m, however. Taft

TABLE VI

RELATIONSHIP OF BASICITIES OF 2,4-DIAMINO-5- AND -6-SUBSTITUTED PYRIMIDINES TO HAMMETT σ VALUES

Calcn no.	Correlation	Hammett ρ value	95% confidence limits (±)	Intercept[a]	95% confidence limits (±)	r[b]	F[c] regression	Std error	n[d]	Substituents
5 series										
1	σ_m	6.38	1.30	7.66	0.52	0.9798	144	0.392	8	Me, H, OMe, OPh, Br, Cl, CN, NO_2
2	σ_m	6.28	1.09	7.57	0.41	0.9782	178	0.366	10	Me, H, OMe, OPh, Br, Cl, CN, NO_2, Ph, COOEt
3	σ_m	4.85	1.20	7.48	0.30	0.9840	125	0.187	6	Me, H, OMe, OPh, Br, Cl
4	σ_m	5.41	1.17	7.38	0.39	0.9882	166	0.254	6	Me, H, Ph, Br, Cl, CN
5	σ_p	3.96	1.50	6.43	0.59	0.9074	37	0.740	10	Same as calcn 2
6	$0.803\sigma_m, 0.197\sigma_p$	5.97	0.75	7.33	0.28	0.9883	337	0.268	10	
7	$0.808\sigma_m, 0.192\sigma_{p^-}$[e]	5.42	0.52	7.31	0.21	0.9932	585	0.205	10	
8	$0.712\sigma_I, 0.288\sigma_R$	8.38	1.45	7.29	0.36	0.9785	180	0.364	10	
9	$0.738\sigma_I, 0.262\sigma_{R^-}$[f]	6.96	0.77	7.32	0.24	0.9912	433	0.237	10	
10	$0.720\sigma_I, 0.280\sigma_{R^-}$[f]	6.51	0.47	7.28	0.13	0.9986	1466	0.086	6	Same as calcn 4
11	$0.766\sigma_m, 0.234\sigma_{p^-}$[e]	4.95	0.48	7.26	0.17	0.9975	811	0.116	6	
6 series										
12	σ_m	7.95	2.96	6.79	0.55	0.9373	43.4	0.524	8	Me, H, NH_2,[g] Ph, OMe, SMe, OPh, Cl
13	σ_m	9.40							7	Above minus NH_2
14	$0.888\sigma_I, 0.112\sigma_m$	7.76	0.93	7.33	0.22	0.9930	422	0.178	8	Same as calcn 12
15	$0.960\sigma_I, 0.040\sigma_R$	8.16	0.88	7.31	0.20	0.9940	517	0.161	8	

[a] Intercept of regression line with ordinate (σ = 0). [b] The correlation coefficient. [c] F test for significance of regression. [d] The number of compounds used in the calculation of ρ. [e] *vs.* σ_p− values of 0.678 for COOEt, 1.00 for CN, and 1.27 for NO_2, and σ_p values as before for the remaining substituents. [f] *vs.* σ_R− values of 0.36 for COOEt, 0.41 for CN, and 0.64 for NO_2, and σ_R values for the other substituents. [g] pK_a value for NH_2 includes a statistical factor of 2.

and coworkers[16] have separated the σ_m and σ_p values into independent inductive (σ_I) and resonance (σ_R) components, and have found that normally the resonance component for σ_p is about three times that for σ_m. It seemed plausible in our pyridimine case that these ratios were different. Taft made the basic assumption that the effect of *meta* and *para* substituents on the free energy change behaves approximately as the sum of an inductive and a resonance contribution. It would be of considerable value to be able to express these contributions as fractions on an absolute scale. Recognizing that the limits of such a scale (as defined by the various σ values extant) depend on the system, we selected Taft's σ_I and σ_R constants as a point of departure. If we use the assumption that steric and hydrogen bonding effects are negligible, then it should be possible to obtain a linear free energy relationship from the equation

$$\log (K/K_0) = \rho[\alpha\sigma_I + (1 - \alpha)\sigma_R] \quad (2)$$

where α is a constant between 0 and 1. Bryson[17a] first used an equation of this type with naphthylamines. Yukawa and Tsuno[17b] found a corresponding equation for electrophilic substitutions to be useful, where part correlation with σ_{p^+} and part with σ_p is assumed. Yoshioto and coworkers[17c] proposed an analogous equation for σ_{p^-} *vs.* σ_p.[18] Charton[19] has written this equation in general terms (eq 3), where a, b, and h are

$$Q_x = a\sigma_{I,x} + b\sigma_{R,x} + h \quad (3)$$

constants. By means of multiple linear regression analysis, the best values for the coefficients can be immediately obtained, with the aid of a computer.[20]

We wrote the equation specifically as

$$pK_a = i - \rho[\alpha\sigma_I + (1 - \alpha)\sigma_R] \quad (4)$$

where i is the intercept, and the slope ρ is a composite of ρ_I and ρ_R. The slope then is the sum of $a + b$ of eq 3, and α is obtained from their ratio. The statistical data reported here were obtained by solving for $[\alpha\sigma_I + (1 - \alpha)\sigma_R]$, and carrying out linear regression analyses using this as the single independent variable.

This equation was tested for ten substituents, first using σ_m–σ_p combinations, since these familiar constants provide orientation, and then using σ_I–σ_R. The σ_p values were taken from McDaniel and Brown,[10] the σ_I values were those of Taft,[16] and σ_R values were obtained from their difference. The results are shown in calculations 6 and 8 of Table VI. The correlation coefficient and standard error of calculation 8 are almost identical with those of calculation 2. The σ_m–σ_p correlation is somewhat better, and indicates that there is greater resonance interaction than can be accounted for by σ_m alone. Graphical examination of the results of calculation 8 (Figure 3, dotted line and squares) illustrates that the nitro group shows the greatest deviation from the line. As with *p*-nitroaniline, this 5-substituted pyrimidine would be expected to have decreased basicity as a result of "extra" ground-state resonance of type I. The same argument

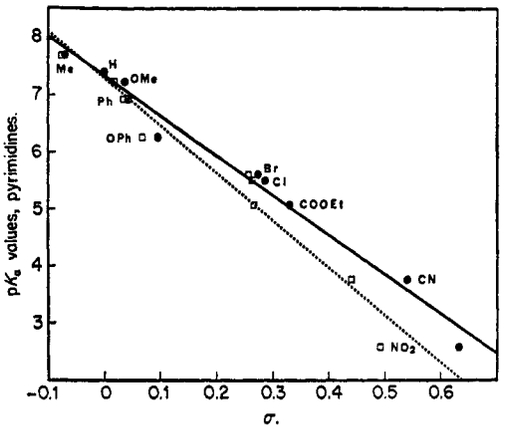
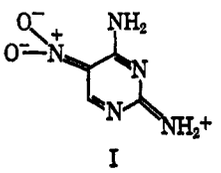


Figure 3.—Variation of pK_a with σ_I–σ_R combinations for 2,4-diamino-5-substituted pyrimidines: dotted line (□), regression slope for calculation 8, Table VI; solid line (●), slope for calculation 9, Table VI.



I

can be applied to the other 5(−R)-substituted pyrimidines, but the contribution to such forms would be less. The failure of the Hammett equation to apply in the normal fashion in such cases has been discussed at length by Jaffé[15] and Taft,[16] and the use of σ_{p^-} constants with the −R substituents has been recommended.

We then substituted σ_{p^-}[21] and σ_{R^-} values (from σ_{p^-}–σ_I) for σ_p and σ_R with the NO_2, CN, and COOEt substituents, as shown in calculations 7 and 9. The results show a considerable improvement over 6 and 8, and illustrate that, as expected, the resonance end point of eq 4 varies with the environment. Results of calculation 9 are illustrated in Figure 3 (solid line and circles). Some deviations from linearity are still present, but an analysis of possible substituent interactions suggests the major reason for these deviations.

The most basic nitrogen atom in 2,4-diaminopyrimidine is N_1. Perrault and Pullman postulated this as a result of molecular orbital calculations.[22] Roth and coworkers[23] have confirmed this experimentally

(16) (a) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y. 1956, Chapter 13, pp 578–580, 594–597; (b) R. W. Taft, *J. Amer. Chem. Soc.*, **79**, 1045 (1957); (c) R. W. Taft and I. C. Lewis, *ibid.*, **80**, 2436 (1958); (d) R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960); (e) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963).

(17) (a) A. Bryson, *J. Amer. Chem. Soc.*, **82**, 4862 (1960); (b) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **32**, 971 (1959); (c) M. Yoshioto, K. Hamamoto, and T. Kubota, *ibid.*, **35**, 1723 (1962).

(18) See C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. II, S. G. Cohen, G. Streitwieser, and R. W. Taft, Ed., Interscience Publishers, New York, N. Y., 1964, pp 323–400, for a review of the approaches which have been used to the problem of varying conjugative effects.

(19) (a) M. Charton, *J. Org. Chem.*, **30**, 3341 (1965) (also private communication); see also (b) M. Charton, *ibid.*, **29**, 1222 (1964); (c) M. Charton *J. Amer. Chem. Soc.*, **86**, 2033 (1964); (d) M. Charton, *J. Org. Chem.*, **30**, 3346 (1965).

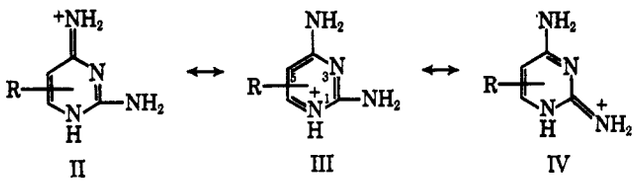
(20) We are indebted to Professor Marvin Charton for providing us with a FORTRAN program for multiple linear regression analysis, suitable for use with one to three independent variables, which we adapted for use with a GE-235 computer. Prior to obtaining this program, we solved the equation by substituting values of α in steps of 0.01 between 0 and 1, and solving in each case by the least-squares method until a maximum value for the regression coefficient was obtained. The results checked by the two methods.

(21) These values were taken from Table VII, p 22, of Jaffé's review,[15] where the notation σ^* is used instead of σ^-.

(22) A. M. Perault and B. Pullman, *Biochim. Biophys. Acta*, **52**, 266 (1961).

(23) B. Roth, S. Hurlbert, J. Strelitz, and G. H. Hitchings, Abstracts, 152nd Meeting of the American Chemical Society, New York, N. Y., 1966; to be published.

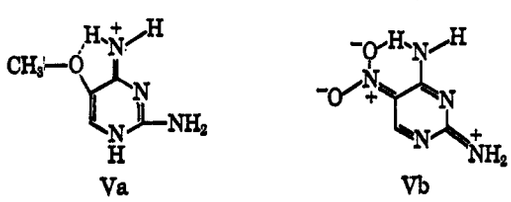
with salts of 2,4-diaminopyrimidine and analogs by means of nmr studies, which show coupling of the protons at N_1 and C_6 at low temperatures. Protonated 2,4-diaminopyrimidines (III) would be expected to be resonance stabilized by *p*- and *o*-quinonoid forms II and IV. A 5 substituent, *meta* to N_1, should not contribute noticeably to the resonance forms of the cation, but could, on the other hand, interfere with the



II III IV

p-quinonoid form II by steric means if the bulk were sufficient. Such interference has been demonstrated in the case of pyrimethamine (**18**) by means of nmr studies.[23] On the other hand, the 4-amino substituent may interfere with coplanarity of a 5 substituent in some cases. The resultant decrease in resonance stabilization of the base might cause the net steric effects to be negligible.

Hydrogen bonding between the protons of the 4-amino group and an oxygen-containing substituent in the 5 position is a more likely cause for deviations in the Hammett relationships. Calculations 4, 10, and 11 of Table VI show the results of computation with non-oxygen-containing substituents only. The correlation coefficient now reaches a high value of 0.9986 in calculation 10, and the standard error is also markedly improved. The α value, however, remains very nearly constant in calculations 8–10. These facts suggest that the substituents with lone pair electrons are indeed involved in interactions which disturb the linearity of the free energy relationship. Although both the base and the cation of the oxygen-containing compounds would be subject to hydrogen-bonding forces, stabilization of a derivative such as 2,4-diamino-5-methoxypyrimidine in the protonated form would probably be favored slightly by hydrogen bonding of the methoxy group to the positive 4-amino trigonal center (Va); entropy would favor this over bonding of the base, where the amino group can rotate freely. The reverse argument would hold for the nitro derivative, where the base would be stabilized (Vb).



Va Vb

C. The 6-Substituted Pyrimidines.—The eight substituents CH_3, H, NH_2, OMe, OC_6H_5, Cl, SMe, and C_6H_5 were selected for plotting σ_m *vs.* the pyrimidine dissociation constants, and the regression slope (solid line) shown in Figure 4 was calculated from these data (Table VI, calculation 12). The dissociation constant for the NH_2 derivative was corrected by a statistical factor of 2, since there are two equivalent ring N atoms which can be protonated. Calculation 13 (dotted line, Figure 4) omits the NH_2 group. The substituents COOMe, $CONH_2$, COO^-, and SO_3^- were not included in any calculations, since H-bonding forces between

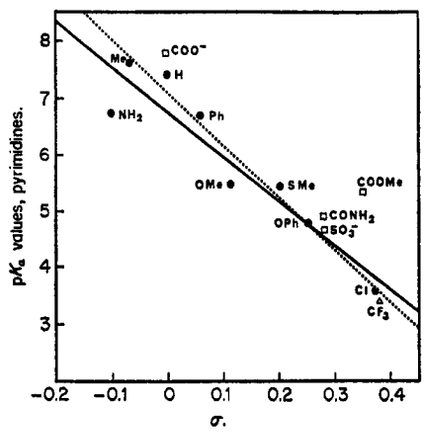
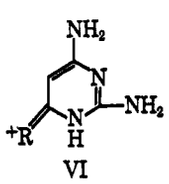


Figure 4.—Variation of pK_a with σ_m for 2,4-diamino-6-substituted pyrimidines: ●, points used for calculation of regression slopes; solid line, calculation 12, Table VI (n = 8); dotted line, calculation 13 (n = 7); □, other data; △, estimated point.

the oxygen-containing groups and the protonated pyrimidine would be expected to stabilize the protonated form, and thus increase the basicity (see Figure 4). Furthermore, the latter two substituents exist as zwitterions in the neutral form of these pyrimidines.[24] The point shown in Figure 4 for the CF_3 substituent is an estimated value, based on the dissociation constant of 2,4-diamino-5-phenyl-6-trifluoromethylpyrimidine (**43**), compared with the corresponding 6-unsubstituted and 6-methyl analogs **14** and **15**. It was not used in any calculations.

The σ_m correlation of calculation 12 shows a regression which is significant at the 1% level, but which has a large standard error. In a test against σ_p (not including NH_2), r was found to be 0.233, a number indicative of no correlation. This may at first seem surprising, since the 6 substituents are *ortho* to the protonation site, and since steric interference to protonation should be small, as inferred by analogy to the 2-substituted pyridines.[25] However, the 6 substituents are *meta* to the positive trigonal 4-amino center of cation III, and seem to contribute very little to the π system in this situation. This becomes more apparent when we examine the relationship of the NH_2 and OMe substituent constants to the other values. It will be observed from Figure 4 that these two substituents fall way out of line relative to the others. By resonance theory, the 6 substituent should add to the stabilization of the positive charge of the cation with form VI, in addition to II–IV. The result would



VI

(24) Both 2,4-diamino-5- and 6-carboxypyrimidines occur as zwitterions in the neutral species. This is readily ascertained by observing the changes that occur in uv spectra with pH. Proceeding from the anion to the neutral species in both cases causes large hypsochromic shifts in the long-wavelength maximum. In the case of the 5-carboxypyrimidine the shift is practically identical with that produced by protonation of the corresponding ester. With the 6-carboxyl derivative, the shift occurs from a higher wavelength with the ester, but qualitatively, the type of change is the same. In protonating the carboxyl derivatives, the uv changes that occur involve mainly the extinction values in the low-wavelength region. These phenomena have been discussed by Albert[7] as criteria for zwitterions.

(25) H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).

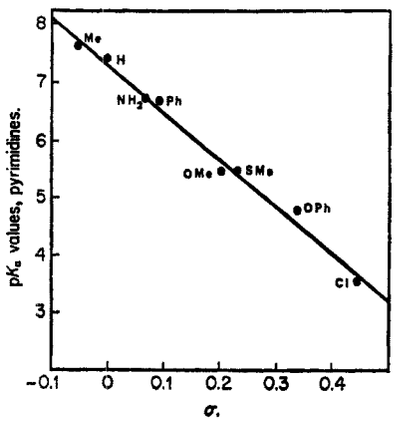


Figure 5.—Variation of pK_a with $0.96\sigma_I-0.04\sigma_R$ for 2,4-diamino-6-substituted pyrimidines (calculation 15, Table VI).

be an increase in basicity, especially with the 6-amino derivative, since this contains the most strongly electron-releasing substituent of the group. Actually, 2,4,6-triaminopyrimidine is a *weaker* base than the 2,4-diamino derivative. This was first noted by Albert and coworkers,[26] and we have corroborated this fact (Table II, **48**).

If the 6-substituent effect were purely inductive, through σ bonds and field effects, then a 6-amino group would decrease the basicity in the manner actually observed. Taft's σ_I constants, derived from aliphatic series reactivities, demonstrate this, since σ_I for NH_2 is 0.10,[16b] whereas σ_m is negative (−0.10). Comparison of these constants with Taft's σ_R value of −0.76 for NH_2[16b] leads to the inference that there is a 23% resonance contribution to this σ_m constant.

If there were a residual resonance component in the 6-substituent effect, then maximum correlation would again be expected from eq 4. Calculations with $\sigma_I-\sigma_R$ and $\sigma_I-\sigma_m$ combinations are shown in Table VI, calculations 14 and 15. Maximum correlation is seen in calculation 15, which shows only a 4% average resonance component. Figure 5 depicts this result graphically.

Charton[19c] has found that *ortho* substituted pyridines and quinolines behave in a similar manner, in that correlations are good with σ_m and with σ_I, but poor with σ_p. Clews and Cochran[27] determined the crystal structure of 4-amino-2,6-dichloropyrimidine. The C_6-Cl bond length was found to be 1.757 Å, in good agreement with the value 1.76 Å for a pure single bond. They concluded that this Cl atom makes no appreciable resonance contribution to the molecule. Such facts corroborate our findings that 6 substituents of pyrimidines which protonate at N_1, as exemplified by 2,4-diamino derivatives, exert their electrical effects almost completely through inductive and field forces.

Hammett Relationships with Other Pyrimidine Bases.—Thanks to the extensive collections of Brown[3b] and Perrin[3a] of dissociation constants of pyrimidines and their conversion thereof to thermodynamic values wherever possible, other correlations of substituent effects in these compounds can be made and compared with the correlations derived above. Perrin's corrected values for the dissociation constants of 2- and 4-substituted pyrimidines, 4-amino-6-substituted pyrimidines and 2-methylamino-4-substituted pyrimidines (see Table VII) are the only series, aside from the 2- and 4-pyrimidones, for which sufficient information was available to make $\sigma-\rho$ correlations. The results of these correlations are listed in Table VIII.

In the case of the 2- and 4-substituted pyrimidines, it was expected that the substituents should be able to attract or repel electrons through the π system, since resonance forms VII, VIII, and IX (exemplified for a 4(−R)-substituted pyrimidine) should be possible, for the base and cation, respectively (Scheme I). Calculations 16, 17, 19 and 20 show the results of correlations between the 2 and 4 substituents and σ_p. Although the correlations are reasonably good for both series, they are improved in each case by use of eq 4, with $\sigma_I-\sigma_R$ combinations. (No σ_I constant was available

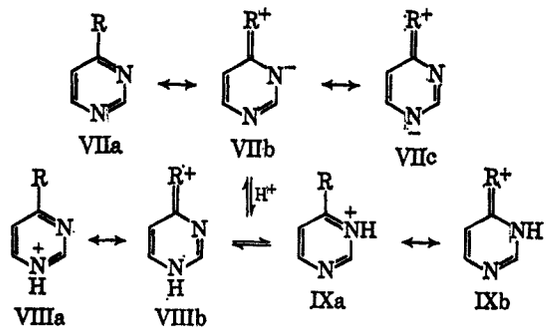
TABLE VII

THERMODYNAMIC DISSOCIATION CONSTANTS OF PYRIMIDINES (20°) (LITERATURE DATA)

Substituents	pK_a[a]	Ref
H	1.23[l] (u)	*b*
2-NHMe	3.99[l]	*c*
2-NMe_2	3.93[l]	*d*
2-NH_2	3.45[l]	*b*
2-SMe	0.59[l]	*e*
2-COOMe	−0.68[l] (u)	*f*
4-NMe_2	6.32	*d*
4-NHMe	6.09	*d*
4-NH_2	5.69	*b*
4-OMe	2.5 (u)	*d*
4-SMe	2.41	*e*
4-Me	1.91	*b*
2-MeNH-4-NH_2	7.53	*g*
2-MeNH-4-OMe	5.74	*h*
2-MeNH-4-Cl	2.59	*g*
4-NH_2-6-NHMe	6.30	*i*
4-NH_2-6-Me	6.16 (u)	*j*
4-NH_2-6-OMe	4.00	*k*
4-NH_2-6-Cl	2.10 (u)	*k*

[a] The dissociation constants of this table are classified by Perrin[3a] as approximate, with an uncertainty of ±0.04 pH unit, unless value is followed by (u), meaning "uncertain," or greater than 0.04 pH unit. [b] See Table I, footnote *j*. [c] Reference 3c. [d] D. J. Brown and L. M. Short, *J. Chem. Soc.*, 331 (1953). [e] A. Albert and G. B. Barlin, *ibid.*, 3129 (1962). [f] S. F. Mason, *ibid.*, 1247 (1959). [g] D. J. Brown and N. W. Jacobsen, *ibid.*, 3172 (1962). [h] D. J. Brown and N. W. Jacobsen, unpublished data. [i] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 1978 (1960). [j] J. R. Marshall and J. Walker, *ibid.* 1004 (1951). [k] D. J. Brown and J. Harper, *ibid.*, 1298 (1961). [l] The pK_a values of these symmetrical pyrimidines were corrected for σ correlations by subtracting 0.30 from the values shown (statistical correction of 2 applied to the dissociation constants).

SCHEME I



(26) See Table I, footnote *j*.

(27) C. J. B. Clews and W. Cochran, *Acta Cryst.*, **2**, 46 (1949).

TABLE VIII

THE APPROXIMATE REACTION CONSTANTS AND INTERCEPTS FOR HAMMETT PLOTS OF PYRIMIDINE BASICITIES (LITERATURE DATA)

Calcn no.	Correlation	Hammett ρ value	95% confidence limits (±)	Intercept	95% confidence limits (±)	r	F regression	Std error	n	Substituents
2-Substituted pyrimidines										
16	σ_p	3.66	0.54	0.64	0.32	0.9944	352	0.234	6	NMe_2, NHMe, NH_2, H, SMe, COOMe[a]
17	σ_p	3.67	0.81	0.64	0.42	0.9928	205	0.270	5	Calcn 16 minus NHMe[a]
18	$0.599\sigma_I, 0.401\sigma_R$	8.55	1.23	0.95	0.24	0.9970	493	0.175	5	
4-Substituted pyrimidines										
19	σ_p	5.85	1.73	1.38	0.91	0.9683	75	0.617	7	NMe_2, NHMe, NH_2, Me, H[b], SMe, OMe
20	σ_p	5.97	2.42	1.37	1.10	0.9599	47	0.684	6	Calcn 19 minus NHMe
21	$0.341\sigma_I, 0.659\sigma_R$	9.13	3.02	1.05	0.98	0.9730	71	0.563	6	
2-Methylamino-4-substituted pyrimidines										
22	σ_p	5.72	1.83	3.89	0.68	0.9945	180	0.282	4	NH_2, H[b], OMe, Cl
23	$0.468\sigma_I, 0.532\sigma_R$	11.08	2.89	3.71	0.58	0.9963	271	0.230	4	
4-Amino-6-substituted pyrimidines										
24	σ_m	9.38	4.24	5.47	0.84	0.9891	91	0.332	4	Me, H, OMe, Cl
25	$0.868\sigma_I, 0.132\sigma_m$	7.93	0.31	5.72	0.079	0.9999	12090	0.029	4	
26	$0.977\sigma_I, 0.023\sigma_R$	7.99	0.33	5.72	0.084	0.9999	10678	0.031	4	

[a] pK_a values for all substituents include a statistical factor of 2. [b] pK_a value for this substituent includes a statistical factor of 2.

for NHMe, hence the two n values.) Although the data are insufficient for α to be quantitative, it appears that the inductive component is almost twice as great with the 2 series as the 4, and that in the latter series it is greater than with σ_p alone. (The 4-methoxy pK_a value is the most questionable of the whole group; this accounts for the high standard errors in this series.) These results suggest that substituents *para* to a ring N contribute much more to the π resonance system than do groups *ortho* to a ring N in the pyrimidine series, and suggest, further, that the 4-substituted pyrimidines are protonated mainly on N_1, rather than N_3. Experimental evidence verifies N_1 protonation.[28] The results with the 2-methylamino-4-substituted series (calculations 22–23) are qualitatively similar to the 4 series.

The 4-amino-6-substituted pyrimidines show properties very much like those of the 2,4-diamino-6-substituted derivatives, in that the effect of the 6 substituents is almost completely inductive. Calculations 24–26 show tests against σ_m, $\sigma_I-\sigma_m$, and $\sigma_I-\sigma_R$ combinations. The correlation is seen to be almost perfect with combinations having only about 2% resonance character. This strong corroboration of the results with the 2,4-diamino-6-substituted pyrimidines provides good evidence for the nature of the free energy effects of this type of 6 substitution. The Hammett ρ value, 7.99 (calculation 26), also agrees statistically with the value 8.16 of Table VI, calculation 15, for the 2,4-diamino-6-substituted series.

In summary, the effects of substituents in various positions in the pyrimidine nucleus on the dissociation constants can be interpreted reasonably on the basis of protonation on the N_1 ring nitrogen. The ratios of inductive and resonance contributions often differ from what is observed in the benzene system, however, with the result that the Hammett σ_m and σ_p constants alone do not suffice for making precise correlations.

Basicities of 2,4-Diaminopyrimido-Fused Ring Systems and of Azapyrimidines.—The analyses of Albert and coworkers[26,29] on the dissociation contants of aromatic systems containing nitrogen and other heteroatoms are so extensive that there would seem to be little room here for additional comment. However, a few specific remarks may be made concerning the compounds of Tables III and IV.

It should be noted that one cannot extrapolate directly from the relative basic strengths of the parent heterocycles to the basicities of the diamino derivatives. Not only are new resonance systems introduced with the diamino substituents, but some parent compounds are covalently hydrated[29c] and have anomalously high pK_a values. For example, quinazoline and pteridine, both covalently hydrated, have pK_a values of 3.51 and 4.12, respectively; their diamino counterparts (**61** and **68**) have pK_a values of 7.96 and 5.32.

Fusion of a benzene ring to 2,4-diaminopyrimidine (**5**) to produce 2,4-diaminoquinazoline (**61**) results in an increase in basicity, since there is less loss in resonance energy in going to the *p*-quinonoid protonated form with the naphthalene-type system than with a single aromatic ring. Substituents in the benzene ring (**62** and **63**) have a considerable effect on the dissociation constants of the diaminoquinazolines. Introduction of ring nitrogen atoms to form a pyridopyrimidine (**64**) and a pteridine (**68**) lowers the dissociation constants by about 1.3 units per nitrogen, as a result of electron depletion from the π layer.

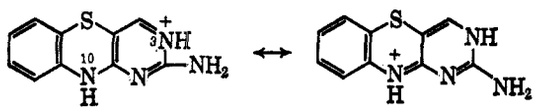
Some interesting comparisons may be made between various five-membered ring systems, either alone or fused to a benzene ring, as opposed to their fusion to 2,4-diaminopyrimidine. For example, imidazole [pK_a 6.95 (+), 14.2 (−)] is a stronger base than pyrrole [−0.27 (+), 16.5 (−)] or 1,2,3-triazole [1.17 (+), 9.42 (−)]; this is also the case with benzimidazole [5.53 (+), 13.2 (−)] compared to indole [−2.4 (+)] and benzotriazole [1.6 (+), 8.57 (−)]. On the other

(28) See, for example, D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 4035 (1955).

(29) See, for example, (a) A. Albert, The Chemical Society, Special Publication No. 3, The Chemical Society, London, 1955, p 124; (b) see Table III, footnote *g*. (c) A. Albert in "Physical Methods in Heterocyclic Chemisty," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, and references therein.

hand, the basicity of the diaminopyrimidine five-membered fused ring analogs decreases directly with the number of nitrogen atoms introduced in the five-membered ring (see **66**, **67**, **69**, and **74**), since protonation now occurs in the pyrimidine ring. (The ionization of the triazolopyrimidine system has been discussed by Felton[29a] in comparisons with benzotriazole and purine.) The thiazole and oxazole analogs of the diaminopurines (**73** and **75**) are weaker bases than the purines. This is also true of thiazole *vs.* imidazole, for example. Albert has offered explanations for related effects.[29c]

2,4-Diamino-1,3-diazaphenothiazine (**70**) is a rather weak base, as might be expected from the inductive effect of the sulfur and NH on the 5 and 6 positions of the pyrimidine ring. This compound is a weaker base by 0.7 pH units than the monoamino analog, 2-amino-1,3-diazaphenothiazine[30a] (thermodynamic pK_a (20°), 5.71 ± 0.02[30b]). The 6-inductive effect may provide the explanation for the rather large decrease in basicity on adding the second amino group. However, it is also possible that the two compounds are protonated on different nitrogen atoms. The monoamino derivative would very likely become protonated at N_3 (Xa), rather than at N_1, since resonance stabilization could occur through the nitrogen of the center ring (Xb). The diamino derivative, on the other hand, may be protonated at N_1, with resonance stabilization through the 4-amino group of the same ring. The uv spectra of the two compounds are quite different from each other, which tends to support this suggestion.



Xa Xb

Thieno[2,3-*d*]pyrimidines **71** and **72** are also rather weak bases, again made weaker than 2,4-diaminopyrimidine by the inductive effect of the sulfur in the 6 position. A comparison between **71** and the analogous pyridopyrimidine (**65**) shows the former to be a weaker base by two pH units.

Table IV illustrates the marked decrease in basicity which results from replacing the 5 carbon of a 2,4-diaminopyrimidine by nitrogen. 2,4-Diamino-1,3,5-triazine (**78**) has a dissociation constant which is 3.5 pH units lower than that of 2,4-diaminopyrimidine. The symmetrical triazines are much weaker bases than their asymmetric analogs, as can be seen by comparing the pK_a values of **77** and **79**. The asymmetric triazine **77** is a weaker base than its diaminopyrimidine counterpart by only 0.7 pH units.

Quantum mechanical calculations on the unsubstituted 1,2,4-triazine[31] indicate that the two Kekulé structures are not identical in the ground state, but that the structure with a single bond between the adjacent nitrogen atoms is the more stable of the two. This would imply less depletion of electrons from the π shell than would be the case with the symmetrical triazine, and thus higher basicity for the unsymmetrical compound. Various calculations of the electronic structure of the very reactive 1,3,5-triazine have been made, accompanied by comparisons of aromaticity of the di- and polyazines.[32] Although the introduction of amino groups offers redress of electrons to the π shell, the symmetrical triazines retain their relatively low basicity.

Substituent Effects on Ultraviolet Spectra of Diaminopyrimidines.—The uv spectrum of 2,4-diaminopyrimidine is characterized by low-wavelength maxima at 205 and 228 mμ, and a lower intensity band at 282 mμ. Protonation results in a large increase in intensity of the low-wavelength bands, but a hypo- and hypsochromic shift of the 282 mμ maximum. A change in solvent from water to ethanol to cyclohexane does not shift the position of the maxima of the neutral species of this compound, which would indicate that $\pi \rightarrow \pi^*$, rather than $n \rightarrow \pi^*$, transitions are involved.

The electronic spectra of pyrimidine and a number of its substituted derivatives have been investigated in detail by Mason.[33] The characteristics of the band of longest wavelength of pyrimidine indicate it to be an $n \rightarrow \pi^*$ transition, since binding of the lone pair electrons by solvation or protonation causes pronounced blue shifts. Similar shifts are produced by +R substituents, particularly in the 4 and 6 positions of the pyrimidine ring. With the shorter wavelength $\pi \rightarrow \pi^*$ band, both +R and −R groups have a bathochromic effect on the maximum.[34] Mason has found that when amino or hydroxy groups are present, their lone pair electrons are strongly conjugated with the ring. In general, the $n \rightarrow \pi^*$ transitions are submerged and two $\pi \rightarrow \pi^*$ transitions are observed instead. This would apply to our diamino case.

The effect of 6 substituents on the long-wavelength band of 2,4-diaminopyrimidine is dependent in general on the +R or −R character of the substituents. Most +R substituents produce a blue shift; −R substituents give the reverse effect (Table IX). These results

TABLE IX

EFFECT OF 6 SUBSTITUENTS ON POSITION OF LONG-WAVELENGTH MAXIMUM IN ULTRAVIOLET SPECTRA OF 2,4-DIAMINOPYRIMIDINES

Substituent	$\Delta\lambda_{max}$, 282mμ	Substituent	$\Delta\lambda_{max}$, 282 mμ
OCH_3	−19.0	SO_3^-	10.5
OC_6H_5	−14.5	COO^-	15.5
NH_2	−14.5	C_6H_5	23.0
CH_3	−4.0	$CONH_2$	30.2
Cl	0.0	$COOCH_3$	36.0
SCH_3	4.0[a]		
$SC_6H_4Cl(4)$	6.0		

[a] Data of D. J. Brown and N. W. Jacobsen, footnote *k*, Table II.

indicate that the one-electron charge density at the 6 position is larger in the lower π orbital of the transition than in the higher orbital, and that inductive effects are operating on the energy intervals, according to Mason's interpretation.[32] The conjugative effects

(30) (a) B. Roth and L. A. Schloemer, *J. Org. Chem.*, **28**, 2659 (1963); (b) new determination, this paper.

(31) A. Maccoll, *J. Chem. Soc.*, 670 (1946).

(32) (a) S. F. Mason, *J. Chem. Soc.*, 1240 (1959); (b) M. N. Adamov and I. F. Tupitsyn, *Vestn. Leningr. Univ., Ser. Fiz. i Khim.*, **17**, 47 (1962); *Chem. Abstr.*, **59**, 7351 (1963); (c) V. I. Berezin, *Dokl. Akad. Nauk SSSR*, **155**, 629 (1964); *Chem. Abstr.*, **60**, 15716 (1964); (d) W. Woznicki, *et al.*, *Bull. Acad. Polon. Sci., Ser. Sci., Math. Astron. Phys.*, **12**, 655 (1964); *Chem. Abstr.*, **63**, 5117 (1965).

(33) See Table VII, footnote *f*; also S. F. Mason, *J. Chem. Soc.*, 1253 (1959).

(34) See D. J. Brown, "The Pyrimidines," John Wiley & Sons, Inc., New York, N. Y., 1962, Chapter XIII; S. F. Mason in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1963, Chapter VII.

TABLE X

EFFECT OF 5 SUBSTITUENTS ON POSITION AND INTENSITY OF LONG-WAVELENGTH MAXIMUM IN ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DIAMINOPYRIMIDINES

Substituent	$\Delta\lambda_{max}$, 282 mμ	Δε, 282 mμ
OCH_3	14.0	−750
Cl	12.0	−300
COOEt	10.8	5800
$N{=}NC_6H_4Cl(4)$	10.5	4900
CN	10.5	2550
C_6H_5	10.0	1950
COO^-	9.0	2400
$CH_2C_6H_5$	5.5	350
NHCHO	5.0	−1400
CH_3	2.5	700
NHC_6H_5	1.0	1100

of substituents generally shift the $\pi \rightarrow \pi^*$ transitions to longer wavelengths, and this is the effect produced by 5 substituents (Table X).

It is tempting to try to correlate such data with other aromatic substituent effects. Perfect correlations are not to be expected, since the uv maxima involve perturbations of the excited as well as the ground state, whereas dissociation constants, for example, involve the ground state. Also, there is the hazard with the uv data that comparisons are not always being made with the same transition. In fact, there seems to be no useful correlation between the data of Table IX and the Hammett σ_m constants ($r = 0.306$). Correlations with Taft's σ_R constants gave a correlation coefficient of 0.818, which is still only suggestive of a trend. Similar results were obtained with the electrophilic substituent constants (σ_p^+) of Brown and Okamoto[35,36] ($r = 0.802$), and with σ_p ($r = 0.780$). However, when the σ_p^+ constants were divided into two groups, by means of graphical inspection, it was possible to obtain high positive correlations within each group. A plot of the shifts in λ_{max} *vs.* σ_p^+ is shown in Figure 6. The lines as drawn fit the equations $\Delta\lambda_{max} = 23.0\sigma_p^+ - 0.70$ (for OCH_3, OC_6H_5, CH_3, H, and Cl), and $\Delta\lambda_{max} = 26.4\sigma_p^+ + 20.7$ (for NH_2, SCH_3, C_6H_5, COO^-, $CONH_2$, and $COOCH_3$). The correlation coefficients are 0.959 and 0.974, respectively. It is also to be noted that the two lines are nearly parallel. It is possible that the conjugative parameters which are involved in these shifts differ among the two groups. However, these correlations can only be considered as highly speculative at this point.

Platt[37] has found that the added intensity in the benzene 260-mμ transition by monosubstitution is proportional to the square of a "spectroscopic moment" induced by the substituent. Table X gives intensities for the long-wavelength maximum of the 5-substituted pyrimidines. (Changes were small in the 6 series). However, we see no relationship to the spectroscopic moments of Platt, or, indeed, to any other parameter.

Mason[33,34] found that a benzyl anion model was satisfactory in developing a molecular orbital theory to account for the spectral differences between the neutral and charged forms of the monosubstituted

(35) (a) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **79**, 1913 (1957); (b) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).

(36) J. Hine, "Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 90.

(37) J. R. Platt, *J. Chem. Phys.*, **19**, 263 (1951).

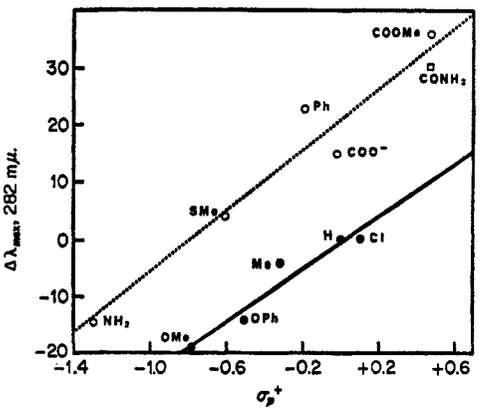
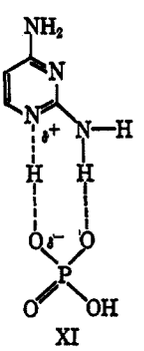


Figure 6.—Variation of long-wavelength maximum of 2,4-diamino-6-substituted pyrimidines as a function of σ_p^+: dotted line, regression slope for substituents represented by open circles and square (latter is an estimated value); solid line is for closed circles.

amino- and hydroxypyrimidines. More complicated models would seem to be required for may of the diaminopyrimidine derivatives, where strong conjugation with the ring occurs involving more than one substituent. 2,4-Diaminopyrimidine and its 5-substituted derivatives all undergo hypsochromic shifts on protonation, as do the monoamino derivatives. However, the 6-substituted derivatives vary from compound to compound. The $COOCH_3$, $CONH_2$, COO^- and CH_3 substituents produce hypsochromic shifts, but the NH_2, OCH_3, OC_6H_5, Cl and SO_3^- substituents give bathochromic shifts in the order listed. Separate models would seem to be required to explain these facts, an investigation of which is beyond the scope of this paper.

Anion Effects on pK_a Determinations.—The loss of isosbestic points in the spectrum of partially protonated 2,4-diaminopyrimidine which is caused by divalent ions indicates a change in the equilibrium to include more than two species. This suggests that ion pairs are formed in the more concentrated buffer solutions between the dianion and the protonated pyrimidine. Evidence that this is the case in nonaqueous media has been obtained from the nmr spectra of various diaminopyrimidine salts, which show marked differences from each other in deuterated dimethyl sulfoxide solution.[23]

If ion pairs are indeed formed in aqueous solution in the region of the N_1 nitrogen and the 2-amino group, as for example in structure XI, charge delocalization to



XI

give the *p*-quinonoid form (II) would be decreased, and as a result spectral changes should be seen. The observed hypsochromic shift is in line with the argument

that more energy would be required for breaking these hydrogen or semicovalent bonds[38] in order to undergo the transition to the excited state. The fact that these effects are observed with the simple diaminopyrimidines, but not with derivatives containing bulky 5 substituents, suggests steric interference to charge delocalization in the latter case. If the charge remained localized in the N_1 region in any event, the spectral changes would not be observed on ion pair formation. This will be discussed further in a paper dealing with nmr spectra of these pyrimidines.[23]

Relationship of Dissociation Constants to Physiological Activity.—Most of the compounds which are listed in Tables I–IV have been tested for their competitive inhibitory action against folic acid or congenors in microorganisms which require these nutrilites,[39] and many of them have also been tested in an *in vitro* screen for their ability to inhibit the enzyme dihydrofolate reductase.[16] All of the compounds which have useful activity against these systems have pK_a values above 6, and the most active compounds have pK_a values of 7 or higher. This suggests that it is the protonated form of the pyrimidines which is interacting with this enzyme system, and *in vitro* studies of binding activity as a function of pH confirm this.[40] This does not preclude physiological activity of the nonprotonated derivatives in other systems, however. Indeed, such a difference provides a basis for specificity of action for these compounds.

Experimental Section

pK_a Determinations.—pK_a values were determined in aqueous solution with a Cary 15 spectrophotometer. Solutions were normally prepared by weighing *ca.* 12.5-mg samples of compound into 25 ml of water or 95% ethanol at 20°. The solutions were then diluted 1:50 or 1:100 into aqueous buffers. The presence of 1–2% ethanol in the final solution was found to exert no observable effect on the spectra or pK_a values, and in many instances was required to dissolve the compounds initially. Buffers, acids, and bases which were used for the thermodynamic pK_a determinations included HCl in the pH range below pH 3.5, 0.01 *N* NaOH, 0.01 and 0.002 *N* acetate, 0.0067 and 0.0022 *M* Na_2HPO_4–KH_2PO_4 mixtures, 0.01 tris, and 0.01 glycine–NaOH. These were prepared just before use from 0.1 *N* or 0.067 *M* stock solutions, which were mixed to the approximate desired pH and diluted with freshly boiled double-distilled water. In the acetate and phosphate range, curves were run in both 0.01 and 0.002 acetate or 0.0067 and 0.0022 *M* phosphate at slightly different pH values. Values in the more dilute solutions were usually very slightly lower than those in 0.01 or 0.0067 *M* solutions. These are recorded as the thermodynamic pK_a values, with no further correction. Most of the pH values were determined on a Beckman Model G pH meter, using Beckman Standard buffers, standardized at every two pH units. The final experiments were carried out with a Beckman research model pH meter. These values did not differ by more than 0.01 pH unit from values obtained simultaneously on the Model G. The experiments were carried out in a room maintained at 20 ± 1°; the cell compartment in the spectrophotometer was maintained at 20 ± 0.2°.

The pK_a calculations were carried out by taking spectral readings at 12 or more suitable wavelengths. The values were calculated from the equation $pK_a = pH - \log [(\epsilon_a - \epsilon_x)/(\epsilon_x - \epsilon_b)]$. All data were rejected in which the curves did not pass precisely through the isosbestic point. The deviations recorded in the tables represent the total range of pK_a values obtained, rather than the standard deviations. Experiments where the error is relatively large represent situations where the two species did not differ greatly in extinction coefficients, or where it was necessary to take readings from a steep slope.

Compounds.—Most of the compounds used for these investigations were file samples which had been prepared in the Wellcome Research Laboratories. Old samples which showed signs of deterioration were repurified by recrystallization or sublimation. In a few cases, the compounds were freshly prepared, using the reference procedures. New compounds are described below. Melting points are corrected.

2,4-Diamino-5-chloropyrimidine.—2,4-Diaminopyrimidine (5.5 g, 0.05 mol) was chlorinated by dissolving in 50 ml of water and slowly bubbling in one-half the theoretical amount of chlorine gas at room temperature. The solution was neutralized, and the pale yellow precipitate isolated. After two recrystallizations from absolute ethanol, cream needles were obtained weighing 2.1 g, mp 215–216°.

Anal. Calcd for $C_4H_5ClN_4$: C, 33.23; H, 3.49; N, 38.76. Found: C, 33.55; H, 3.38; N, 38.34.

2,4-Diamino-5-carboxypyrimidine.—2,4-Diamino-5-carbethoxypyrimidine (107 mg) was hydrolyzed by heating on the steam bath for 30 min with a mixture of 1.2 ml of 1 *N* NaOH and 1 ml of ethanol. Neutralization with acid produced a white precipitate, yield 107 mg (hydrated). The substance was very insoluble in methyl Cellosolve, dimethylformamide, water, and dilute ethanol. A 50-mg sample was recrystallized from 55 ml of 10:1 water–ethanol: weight of vacuum-dried (100°) product, 39 mg; mp 295–305° dec.

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.95; H, 3.93. Found: C, 39.18; H, 4.10.

The product rapidly picked up water, and was difficult to analyze.

Sodium 2,4-Diamino-6-sulfopyrimidine.—A mixture of 7.2 g (0.05 mol) of 2,4-diamino-6-chloropyrimidine, 6.3 g (0.05 mol) of Na_2SO_3, and 70 ml of water was heated in a glass-lined autoclave at 145° for 25 hr. The cooled solution produced a heavy white precipitate, which was purified by recrystallization twice from water.

Anal. Calcd for $C_4H_5N_4NaO_3S$: C, 22.64; H, 2.38; N, 26.41; S, 15.11. Found: C, 22.44; H, 2.62; N, 26.07; S, 14.64.

When the same reaction was carried out at 100° for 16 hr, most of the starting material was recovered.

2,4-Diamino-6-carboxamidopyrimidine.—A 5.17-g sample of 2,4-dichloro-6-pyrimidinecarbonyl chloride[41] was added dropwise at 0° to 25 ml of alcoholic ammonia (saturated at 0°); a white precipitate separated. Another 25 ml of alcoholic ammonia was added, and the mixture was heated in an autoclave at 160° for 16 hr. The chilled mixture produced a tan precipitate; this was recrystallized from water (with Darco-G60) three times (1 g/250 ml). White crystals were obtained which decomposed above 300°.

Anal. Calcd for $C_5H_7N_5O$: C, 39.21; H, 4.61; N, 45.73. Found: C, 38.99; H, 4.65; N, 45.59.

Methyl 2,4-Diamino-6-pyrimidinecarboxylate Hydrochloride.—A mixture of 0.50 g of 2,4-diamino-6-pyrimidinecarboxylic acid[42] and 500 ml of anhydrous methanol was saturated with anhydrous HCl and heated under reflux for 3 hr while bubbling HCl through the solution. The pyrimidine dissolved rapidly, and the solution remained clear. Removal of the solvent under vacuum left a residue of 700 mg. An initial attempt was made to purify the product by conversion to the free base with sodium bicarbonate. However, it was found easier to purify the hydrochloride salt. This was accomplished by crystallization from MeOH–Et_2O with Darco G-60, which produced a white crystalline product.

Anal. Calcd for $C_6H_8N_4O_2 \cdot HCl$: C, 35.22; H, 4.43; N, 27.38; Cl, 17.33. Found: C, 35.21; H, 4.33; N, 27.62; Cl, 16.90.

2,4-Diamino-6-phenoxypyrimidine.—A mixture of 7.2 g (0.05 mol) of 2,4-diamino-6-chloropyrimidine, 4.7 g (0.05 mol) of phenol, 2.0 g of NaOH, and 70 ml of water was heated in an autoclave at 140–150° for 20 hr. The chilled mixture consisted of a colorless solution which contained a brown oil. A crystalline solid separated after this was extracted with ether, dry wt 0.45 g. Recrystallization four times from ethyl acetate produced colorless crystals melting at 176–177°.

Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.99; N, 27.71. Found: C, 59.47; H, 5.02; N, 27.96.

(38) G. W. Ceska and E. Grunwald, *J. Amer. Chem. Soc.*, **89**, 1371 (1967).

(39) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood, and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).

(40) Unpublished data of J. Burchall and R. Ferone, these laboratories.

(41) H. Gershon, *J. Org. Chem.*, **27**, 3507 (1962).

(42) See Table II, footnote *b*.

When this reaction was carried out at 100° for 22 hr, most of the starting material was recovered. No other conditions were tried.

2,4-Diamino-5-phenyl-6-trifluoromethylpyrimidine.[43]—A solution of 11.5 g (0.5 mol) of sodium in 250 ml of absolute ethanol, to which had been added a mixture of 58.6 g (0.5 mol) of phenylacetonitrile and 55.0 g (0.5 mol) of ethyl trifluoroacetate, was heated under reflux for 24 hr, cooled, and poured into 2.5 l. of water. Ether extraction of the insoluble oil, and acidification of the aqueous layer to about pH 2 (H_2SO_4) produced an oil which was isolated by ether extraction. This ethereal solution was washed with saturated $NaHCO_3$, followed by water, and then dried (Na_2SO_4). Removal of the ether, followed by trituration with petroleum ether, produced a crystalline residue, 47 g (54%). This crude α-trifluoroacetylphenylacetonitrile was methylated with diazomethane according to the procedure of Russell and Hitchings.[44] A 9-g portion (*ca.* 0.047 mol) of the crude crystalline methylated product was mixed with a salt-free guanidine solution prepared from 4.5 g (0.047 mol) of guanidine hydrochloride and 1.15 g (0.05 mol) of sodium in 200 ml of butanol. After this mixture had been heated under reflux for 18 hr and chilled to 0°, a cyrstalline product separated. Recrystallization (EtOH) produced 3 g of the desired product as white crystals, mp 277–278.5°.

Anal. Calcd for $C_{11}H_8F_3N_4$: C, 51.97; H, 3.57; N, 22.04. Found: C, 51.90; H, 3.54; N, 22.11.

2,4-Diamino-5-(3′,4′,5′-trimethoxyphenyl)pyrimidine[45] was prepared from 3,4,5-trimethoxyphenylacetonitrile and ethyl formate, using procedures described by Russell and Hitchings.[44] The intermediates were not characterized. The pyrimidine was purified as the hydrochloride by recrystallization from dilute ethanol, followed by treatment with 2 *N* NaOH and recrystallization of the free base from a 90:10 acetone–water mixture. Colorless crystals were obtained, mp 190–193°.

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.77; H, 6.18; N, 20.11.

Registry No.—**1**, 18588-37-9; **2**, 7132-61-8; **3**, 18588-39-1; **5**, 156-81-0; **6**, 7319-45-1; **7**, 18588-42-6; **8**, 18588-43-7; **9**, 7331-23-9; **10**, 16974-65-5; **11**, 18588-46-0; **12**, 738-70-5; **13**, 18588-48-2; **14**, 18588-49-3; **15**, 18588-50-6; **16**, 17039-14-4; **17**, 3275-44-3; **18**, 58-14-0; **19**, 18588-54-0; **20**, 18588-55-1; **21**, 7761-45-7; **22**, 18588-57-3; **23**, 18588-58-4; **24**, 18588-59-5; **25**, 7331-22-8; **26**, 18588-61-9; **27**, 3765-90-0; **28**, 18593-41-4; **29**, 18620-58-1; **30**, 7331-20-6; **31**, 18620-60-5; **32**, 18620-61-6; **33**, 18620-62-7; **34**, 18620-63-8; **36**, 18620-64-9; **37**, 15400-54-1; **38**, 18620-66-1; **39**, 18620-67-2; **40**, 18620-68-3; **41**, 18620-69-4; **42**, 16462-27-4; **43**, 18620-71-8; **44**, 18620-72-9; **45**, 18620-73-0; **46**, 16490-14-5; **47**, 1791-73-7; **48**, 1004-38-2; **49**, 3308-24-5; **50**, 3270-97-1; **52**, 18620-79-6; **53**, 18620-80-9; **54**, 18620-81-0; **55**, 18620-82-1; **56**, 18620-83-2; **57**, 18620-84-3; **58**, 156-83-2; **60**, 56-08-6; **61**, 1899-48-5; **62**, 18620-88-7; **63**, 18620-89-8; **64**, 2312-91-6; **65**, 4871-70-9; **66**, 18620-92-3; **70**, 4940-95-8; **71**, 18620-94-5; **72**, 18620-95-6; **73**, 18620-96-7; **74**, 18620-97-8; **75**, 18620-98-9.

Acknowledgment.—The authors wish to express their deep indebtedness to Professors J. F. Bunnett and Marvin Charton for their many helpful suggestions concerning the treatment of the data in this paper. We are very grateful to Dr. G. H. Hitchings for his vigorous support of this program, and for his continued advice and encouragement. Mr. Ronald R. Gauch and Mr. Neil Kaufman provided statistical and programming assistance. Discussions with Drs. Richard Baltzly, Stuart Hurlbert, and Morton Harfenist were very helpful. The room-temperature pK_a measurements on many of these pyrimidines, which were carried out by Robert Bases in 1953, provided useful orientation for the present studies. The analyses were carried out by Dr. Samuel Blackman and his staff.

(43) This compound was prepared by Dr. Stuart Hurlbert in these laboratories.

(44) See Table I, footnote *n*.

(45) This compound was prepared by Michael Salzman in these laboratories.

Chemiluminescence from the Reaction of Bis[1-(1H)-2-pyridonyl]glyoxal with Hydrogen Peroxide and Fluorescent Compounds

L. J. BOLLYKY, B. G. ROBERTS, R. H. WHITMAN, AND J. E. LANCASTER

Chemical Department, Central Research Division, American Cyanamid Company, Stamford, Connecticut 06904

Received May 22, 1968

The reaction of 2-hydroxypyridine with oxalyl chloride gives the N-acylated product bis[1-(1H)-2-pyridonyl]-gloyoxal (V). Acid-catalyzed reaction of V with hydrogen peroxide produce strong chemiluminescent light emission in the presence of fluorescent compounds such as rubrene. Quantum yields up to 0.15 einstein mol^{-1} are obtained in dimethyl phthalate solvent in the presence of strong acid catalysts (aqueous $pK_a < 2.0$) such as trichloroacetic acid. A good agreement of fluorescence and chemiluminescence spectra indicates that the emitting species is the first singlet excited state of the fluorescer. The emission efficiency depends strongly on the fluorescer structure. A 1:1 hydrogen peroxide to glyoxal stoichiometry is indicated. The main products of the reaction are 2-hydroxypyridine and carbon dioxide and small amounts of carbon monoxide. Oxygen was not obtained in significant amounts. The pyridonylglyoxal reaction is considered in correlation with other peroxalate chemiluminescent reactions.

Chemiluminescence has been reported from the reaction of several oxalic acid derivatives with hydrogen peroxide and fluorescent compounds.[1-6] Unusually high quantum yields were obtained from electronegatively substituted aryl oxalates[3] (0.24 einstein mol^{-1}), oxalic anhydrides[4] (0.14 einstein mol^{-1}), phthalimido oxalate[5] (0.09 einstein mol^{-1}), and oxalyl

(1) E. A. Chandross, *Tetrahedron Lett.*, 761 (1963).

(2) M. M. Rauhut, B. G. Roberts, and A. M. Semsel, *J. Amer. Chem. Soc.*, **88**, 3604 (1966).

(3) L. J. Bollyky, M. Loy, B. G. Roberts, R. H. Whitman, A. V. Iannotta, A. M. Semsel, and M. M. Rauhut, the 153 National Meeting of the American Chemical Society, Miami Beach, Fla, April 1967, Abstract O-169; M. M. Rauhut, L. J. Bollyky, B. G. Roberts, M. Loy, R. H. Whitman, A. V. Iannotta, A. M. Semsel, and R. A. Clarke, *J. Amer. Chem. Soc.*, **89**, 6515 (1967).

(4) L. J. Bollyky, R. H. Whitman, B. G. Roberts, and M. M. Rauhut, *ibid.*, **89**, 6523 (1967).

(5) L. J. Bollyky, R. H. Whitman, and B. G. Roberts, *J. Org. Chem.*, **33**, 4266 (1968).

(6) D. R. Maulding, R. A. Clarke, B. G. Roberts, and M. M. Rauhut, *ibid.*, **33**, 250 (1968).