The Basicities of Some Pyridazine Derivatives

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Changes in the basicity of a number of dimethylaminopyridazines, chloropyridazines, and pyridazones have been correlated with substituent constants by use of the Hammett free-energy relationship.

LEVISALLES [1] has determined the basicities (expressed as pH at half-neutralisation) of 28 alkylpyridazines and Fujisaka *et al.*[2] have reported the pK_a's of a variety of 3,6-disubstituted pyridazines and several 3-pyridazones. Other pyridazones and pyridazinethiones have been measured by Albert and his co-workers [3-5] and by Stanovnik and Tisler.[6] Although these and other workers [7-9] have examined a variety of pyridazine derivatives, no attempt has previously been made to correlate changes in basicity of pyridazines with substituent constants by use of the Hammett free-energy relationship (1).

$$pK_a = pK_0 - \rho\sigma \quad (1)$$

We have determined the basicities of a series of dimethylaminopyridazines (I), chloropyridazines (III), and pyridazones (V). The basicities of the dimethylamino-compounds showed a linear correlation with the appropriate *meta* σ substituent constants and the basicities of both the chloropyridazines and the pyridazones showed a satisfactory linear correlation with the corresponding *para* σ constants. The assumption that protonation occurs at the same site within a given series of compounds, an essential for meaningful correlations, is discussed below.

EXPERIMENTAL

Preparations.—All the known compounds were prepared by published methods (Table 1). 3-Amino-6-methylpyridazine, 3-dimethylamino-6-phenylpyridazine, and 1-dimethylamino-4-phenylphthalazine were kindly supplied by Dr. R. E. Rodway.

3-(p-*Chloroanilino*)-6-*dimethylaminopyridazine.*— 3-Chloro-6-(*p*-chloroanilino)pyridazine [10] (16 g, 0·067 mol) in 37% alcoholic dimethylamine solution (500 ml) was heated in an autoclave at 150 °C for 14 h. The solid obtained on evaporation of the mixture was crystallised from alcohol (charcoal) to yield yellow crystals of 3-(p-*chloroanilino*)-6-*dimethylaminopyridazine* (10 g, 40%), m.p. 193—195 °C (Found: C, 58·1; H, 5·3; Cl, 14·1; N, 22·5. $C_{12}H_{13}ClN_4$ requires C, 58·0; H, 5·2; Cl, 14·3; N, 22·5%).

3-*Benzyloxy*-6-*dimethylaminopyridazine.*— 3-Chloro-6-dimethylaminopyridazine [11] (5·2 g, 0·033 mol) was added to a solution of sodium (0·74 g, 0·033 g atom) in benzyl alcohol (50 ml). The stirred mixture was heated at 180—200 °C for 4 h. The excess of benzyl alcohol was distilled off under reduced pressure and the residue treated with water. The precipitate was crystallised from light petroleum (b.p. 40—60 °C) to give white plates of 3-*benzyloxy*-6-*dimethylaminopyridazine* (6·1 g, 80%), m.p. 65—67 °C (Found: C, 68·2; H, 6·7; N, 18·1. $C_{13}H_{15}N_3O$ requires C, 68·1; H, 6·6; N, 18·3%).

6-*Dimethylamino*-3-*pyridazone.*— 3-Benzyloxy-6-dimethylaminopyridazine (22·9 g, 0·1 mol) was heated under reflux in 5N-hydrochloric acid (150 ml) for 4 h. The cooled mixture was extracted with ether (100 ml) and the aqueous layer was separated and evaporated to dryness. A solution of the residual solid in water was basified and the precipitate that formed was collected, washed, and dried. Crystallisation from industrial methylated spirits (15 parts) gave pale yellow crystals of 6-*dimethylamino*-3-*pyridazone* (6·0 g, 43%), m.p. 192—194 °C (Found: C, 51·9; H, 6·5; N, 30·2. $C_6H_9N_3O$ requires C, 51·8; H, 6·5; N, 30·2%).

Ionisation Constants.—Ionisation constants were determined either spectroscopically or by titration in 50% methylcellosolve. Spectroscopic measurements were performed on *ca.* 10^{-4}M solutions in 1 cm cells thermostatted at 25 °C. A Unicam SP 800 spectrophotometer was used to select the analytical wavelength and to confirm the existence of an isosbestic point. Measurements of optical density were made on a Unicam SP 500 spectrometer. The spectroscopic pK_a values were calculated by use of H_A [12] for pyridazones whose pK_a was less than −0·7 and H_0 [13] or pH for the 3,6-disubstituted pyridazines and the stronger bases in the pyridazone series. The method of determination was based on that described by Albert and Serjeant [14] except that the optical density of the protonated species (D_∞) was calculated by the method of Maroni and Calmon,[15] thus avoiding the use of exceptionally strong acid with its concomitant medium effects.[16]

The titrations in 50% methylcellosolve were performed in a thermostatted bath at 25 °C on *ca.* 0·01M solutions of the bases, with standardised *ca.* N-hydrochloric acid as titrant. Changes in pH were measured with a glass and a calomel electrode with a Cambridge Bench type pH meter, which was calibrated with buffers at pH 4·0 and 9·18 before titration. The method of calculation used was that described by Albert and Serjeant.[14]

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TABLE 1

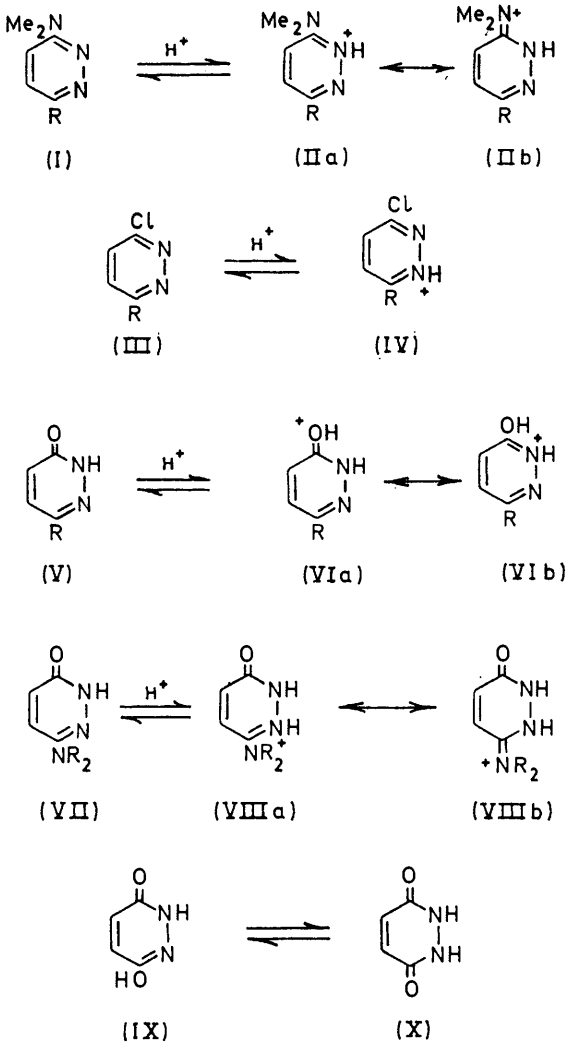
	pK_a [a]	Spread	Method of determination	Method of preparation
3-Amino-6-methylpyridazine	5·67 [b]	0·05	*c*	*d*
	5·26	0·03	*e*	
Dimethylaminopyridazines (I)				
R = Cl	2·82	0·02	*e*	*f*
R = Ph	4·49	0·02	*e*	*g*
R = H	4·59	0·02	*e*	*f*
R = OCH_2Ph	5·12	0·03	*e*	This paper
R = $NH{\cdot}C_6H_4{\cdot}Cl$-*p*	6·01	0·03	*e*	This paper
R = NMe_2	6·71 [h]	0·01	*e*	*i*
1-Dimethylamino-4-phenylphthalazine	4·73	0·02	*e*	*j*
Chloropyridazines (III)				
R = Cl	−1·50 [h]	0·03	*k*	*l*
R = Ph	−0·06	0·02	*k*	*m*
R = Me	0·89	0·01	*k*	*d*
R = $NH{\cdot}C_6H_4{\cdot}Cl$-*p*	2·10	0·03	*n*	*o*
R = NHPh	2·63	0·02	*n*	*p*
Pyridazones (V)				
R = CO_2H	−2·25	0·06	*q*	*r*
R = Cl	−2·01	0·05	*q*	*s*
R = Ph	−1·99	0·03	*q*	*m*
R = H	−1·40 [t]	0·1	*q*	*r*
R = OH	−0·97 [t]	0·01	*q*	*u*
R = Me	−0·81	0·05	*q*	*d*
R = $NH{\cdot}C_6H_4{\cdot}Cl$-*p*	−0·24	0·05	*k*	*o*
R = NHPh	−0·03	0·01	*k*	*o*
R = NMe_2	1·36	0·06	*k*	This paper

[a] Values obtained at 25 °C as the average of two separate determinations. [b] *Cf.* 5·32 ± 0·05 at 20 °C; ref. 8. [c] Titration in water. [d] W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 1947, 239. [e] Titration in 50% methylcellosolve. [f] Ref. 11. [g] W. N. Haworth and L. F. Wiggins, B.P. 656,228 (*Chem. Abs.*, 1952, **46**, 7594*c*). [h] For the purposes of correlation, log 2 must be subtracted from this value to allow for the symmetry of the molecule. [i] J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121. [j] H. M. Holava, jun., and R. A. Partyka, *J. Medicin. Chem.*, 1969, **12**, 555. [k] Spectroscopic determination in dilute sulphuric aicd by use of H_0. [l] P. Coad, R. A. Coad, S. Clough, J. Hyepock, R. Salisbury, and C. Wilkins, *J. Org. Chem.*, 1963, **28**, 218. [m] S. Gabriel and J. Colman, *Ber.*, 1899, **32**, 395. [n] Spectroscopic determination in water by use of pH values. [o] Ref. 10. [p] M. Kumagai, *J. Chem. Soc. Japan*, 1961, **82**, 227 (*Chem. Abs.*, 1962, **56**, 10,139). [q] Spectroscopic determination in dilute sulphuric acid by use of H_A. [r] R. F. Homer, H. Gregory, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, 1948, 2195. [s] S. Du Breuil, *J. Org. Chem.*, 1961, **26**, 3382. [t] *Cf.* −1·8 ± 0·3 for pyridazone and −2·2 ± 0·4 for maleic hydrazide by use of H_0 at 20 °C; ref. 3. [u] R. H. Mizzoni and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1951, **73**, 1873.

The values given in the Tables are the average of two determinations in each of which the spread did not exceed ±0·06 pH units.

DISCUSSION

We believe that for the dimethylaminopyridazines, protonation occurs *meta* to the changing substituent to give the mesomeric cation (IIa ⟷ IIb). It is reasonable to assume that protonation of the chloropyridazines will occur *ortho* to the changing substituent, on the ring nitrogen remote from the base-weakening chloro-substituent, to give the cation (IV). The site of protonation of the pyridazones (V) appears to be on the exocyclic oxygen atom to give the mesomeric cation (VIa ⟷ VIb) since on protonation a hypsochromic change in u.v. absorption occurred in all the cases studied.



An alternative possibility for the pyridazones bearing a nitrogen-containing substituent (VII) is that protonation occurs at a ring nitrogen to give the mesomeric amidinium system (VIIIa ⟷ VIIIb). We consider this to be unlikely since we would then have expected protonation to be accompanied by a bathochromic shift in u.v. absorption.

The pK_a's of the three main sets of pyridazines (I), (III), and (V) were correlated with appropriate Hammett substituent constants by least-mean-squares analyses.[17] The equations obtained are given in Table 2 together with the discrepancies between the observed and the calculated pK_a's. Of the three equations, agreement is worst for the dimethylamino-compounds. The presumably large contribution to the cation of the canonical form (IIb) could explain the poor correlation between pK_a and σ_{meta} for these compounds.

The equation for the dimethylamino-compounds could

[17] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

be improved by neglecting the 6-benzyloxy-compound. The substituent constant used for the benzyl ether was that given [18] for a variety of *meta*-alkoxy-groups, as no published value is available for the *meta*-benzoyloxy-group. The equation for the 3-pyridazones takes no account of the basicities of the 6-phenyl and 6-hydroxy-compounds. The electronic effect of a *para*-phenyl group is notoriously variable [19] and so it is not surprising that the phenylpyridazone deviates from the straight line. 6-Hydroxy-3-pyridazone (maleic hydrazide) is known to undergo the tautomerism (IX) $\rightleftharpoons$ (X) in which the hydroxy-form (IX) is preferred.[20] From the regression line of σ on pK_a, a σ value of -0.09 seems appropriate for the 6-hydroxy-substituent. This value is intermediate between the value [21] for a true hydroxy-group ($\sigma_p = -0.61$) and that [22] for a carbonyl group in this environment ($\sigma_p = 0.35$). This presumably indicates that a significant amount of the amide tautomer (X) is present in dilute sulphuric acid. It may be that the position of equilibrium of this tautomerism is affected by changing acidity and this could account for the large discrepancy between our value for the basicity of maleic hydrazide and that of Albert and Phillips.[3] The earlier workers indicated that maleic hydrazide was a weaker base than the parent pyridazone, whereas our work shows that the reverse is true. Our measurements were made over a narrow range of acidities, whereas Albert and Phillips must have used much more concentrated acid to determine D_∞ (the optical density of the protonated species). This may explain the marked difference in the spreads reported here and earlier.

TABLE 2

R	σ [a]	Theoretical pK_a	Observed pK_a	ΔpK_a
Dimethylaminopyridazines (I)				
p$K_a = 5.14 - 6.14\ \sigma_m$; $r = 0.947$, ($p < 0.005$), 6 points.				
Cl	0·37	2·87	2·82	+0·05
Ph	0·06	4·77	4·49	+0·28
OCH_2Ph	0·1 [b]	4·53	5·12	−0·59
H	0·0	5·14	4·59	+0·55
$NH{\cdot}C_6H_4{\cdot}Cl(p)$	−0·09 [c]	5·69	6·01	−0·32
NMe_2	−0·21	6·43 [d] (+0·3)	6·71	+0·02
Chloropyridazines (III)				
p$K_a = -0.21 - 6.79\ \sigma_p$; $r = 0.998$, ($p < 0.001$), 5 points.				
Cl	0·23	−1·77 [d] (+0·3)	−1·50	+0·03
Ph	−0·01	−0·14	−0·06	−0·08
Me	−0·17	0·94	0·89	+0·05
$NH{\cdot}C_6H_4{\cdot}Cl(p)$	−0·36 [c]	2·23	2·10	+0·13
NHPh	−0·40 [c]	2·51	2·63	−0·12
Pyridazones (V)				
p$K_a = -1.22 - 2.92\ \sigma_p$; $r = 0.991$, ($p < 0.001$), 7 points.				
CO_2H	0·45	−2·53	−2·25	−0·28
Cl	0·23	−1·89	−2·01	+0·12
(Ph [e]	−0·01	−1·19	−1·99	+0·80)
H	0·0	−1·22	−1·40	+0·18
(OH [e]	−0·61 [f]	0·56	−0·97	+1·53)
Me	−0·17	−0·72	−0·81	+0·09
$NH{\cdot}C_6H_4{\cdot}Cl(p)$	−0·36	−0·17	−0·24	+0·07
NHPh	−0·40	−0·05	−0·03	−0·02
NMe_2	−0·83	+1·20	+1·36	−0·16

[a] From D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420, unless otherwise indicated. Values for 3-dimethylamino-compounds are σ_{meta} and for 3-chloropyridazines and 3-pyridazones, σ_{para} is listed. [b] Estimated from values for alkoxy-groups; ref. 22. [c] Calculated by the method of M. Charton, *J. Org. Chem.*, 1963, **28**, 3121. [d] 0·3 pK_a unit should be added to this value because of the symmetry in the molecule. [e] Not included in correlation. [f] Ref. 21

The use of H_A, where applicable, for the study of protonation of pyridazones seems more logical than the previously favoured H_0 as pyridazones may be regarded as cyclic amides and protonation occurs on the oxygen atom.[23] It is noteworthy that 2-pyridones have been shown to follow H_A rather than H_0 on protonation.[24] Unfortunately our work does not permit us to decide whether 3-pyridazones do follow H_A as our determinations of D_∞ assume this to be so. Recalculation of our results with H_0 rather than H_A gave values with much larger spreads.

The three types of compound studied provide examples of protonation of pyridazines *ortho*, *meta*, and *para* to a series of substituents. Thus in the case of the chloropyridazines, where the variation of substituent has the greatest effect ($\rho = 6.79$), protonation occurs *ortho* to the substituent. In the dimethylaminopyridazines the site of protonation is *meta* to the changing substituent and in the pyridazones protonation occurs on exocyclic oxygen and *para* to the substituent. As expected, the basicity of the pyridazones varies least with the changing substituent ($\rho = 2.92$). It is remarkable that the basicities of the chloropyridazines correlate so well with σ_{para} as the site of protonation is *ortho* to the changing substituent and in general $\sigma_{ortho} \neq \sigma_{para}$.[25] The correlation could not be performed with σ_{ortho} as several required constants are not available.

There is a significant difference between the pK_a reported by Mason [8] for 3-amino-6-methylpyridazine, 5·32 at 20 °C, and our result, 5·67 at 25 °C (*ca.* 5·75 at 20 °C).[26] Examination of Levisalles' results,[1] corrected to 20 °C by Perrin's method,[26] indicates that for 12 different pyridazines the introduction of a methyl group in the 3- or 6-position results in a fairly constant increase of basicity of 0·64 ± 0·16 pH units. Comparison of our result with that reported [4] for 3-aminopyridazine, 5·19 at 20 °C, indicates an increase in basicity due to the methyl group of 0·56 pH unit which is well within the range expected.

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