1042. *Prediction of the Strengths of Some Organic Bases*

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Methods based on the Hammett equation are described for predicting the approximate pK_a values, in water, of 5-, 6-, 7-, and 8-substituted naphthylamines, quinolines, isoquinolines, and their nitrogen analogues, and of imidazole, pyrazole, and their derivatives.

A recent Review[1] described methods which enable the approximate pK_a values of many organic bases in water to be predicted. The present Paper extends the range of substances that can be discussed in this way to include two further large groups of bases not previously dealt with. These comprise 5-, 6-, 7-, and 8-substituted naphthylamines, quinolines, isoquinolines, and their nitrogen analogues, and imidazole, pyrazole, and their derivatives.

It had earlier been shown that the Hammett equation,[2] which provides a convenient method for predicting the approximate pK_a values of substituted anilines and pyridines in water, can also be applied satisfactorily to 2-, 3-, and 4-substituted 1-naphthylamines and quinolines, and to 1-, 3-, and 4-substituted 2-naphthylamines and isoquinolines.[1] To discuss the effects of substituents in other positions, a quantitative theory of substituent effects is necessary. For the present purposes, the simple theory proposed by Dewar and Grisdale[3] is used to afford approximate σ-constants (for insertion into the Hammett equation) of substituents in aromatic rings remote from the basic centre. This theory states that in fused-ring aromatic systems the σ-constant, σ_{ij}, for a substituent at position j is a function of (i) the field set up by the substituent, (ii) the distance from the reaction centre, i, (iii) the combined π-inductive–mesomeric effect of the substituent, and (iv) the formal charge produced at position j when the group $-CH_2^-$ is attached at position i. According to the relationships derived by Dewar and Grisdale, the σ-constants for substituents at positions 5, 6, 7, and 8 in the naphthalene series are calculable directly from the corresponding σ_{meta} and σ_{para} constants for substituted benzene. The expressions are given in Table 1.

Substituted Naphthylamines and Quinolines.—The σ-constants obtained in this way can be used to predict the pK_a values of naphthylamines substituted in these positions by applying the Hammett equation for anilines at 20°:[1]

$$pK_a = 4{\cdot}57 - 2{\cdot}81\Sigma\sigma$$

if a σ-constant of 0·24 and 0·08 for the annelated benzene ring of 1- and 2-naphthylamine,

[1] J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.
[2] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, ch. 7; *Chem. Rev.*, 1935, **17**, 125.
[3] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3548.

TABLE 1

Theoretical σ-constants for naphthalene derivatives

Reaction centre	Subst.	Eqn.* for	Reaction centre	Subst.	Eqn.* for
1	3	σ_m	2	4	σ_m
1	4	$1{\cdot}40\sigma_p - 0{\cdot}35\sigma_m$	2	5	$0{\cdot}58\sigma_m$
1	5	$0{\cdot}35\sigma_m + 0{\cdot}35\sigma_p$	2	6	$0{\cdot}58\sigma_m$
1	6	$0{\cdot}58\sigma_m$	2	7	$0{\cdot}50\sigma_m$
1	7	$0{\cdot}35\sigma_m + 0{\cdot}35\sigma_p$	2	8	$0{\cdot}35\sigma_m + 0{\cdot}35\sigma_p$
1	8	σ_m			

* Derived from relationships in ref. 3.

respectively, is included. Table 2 compares experimental [4] results with calculations using the relationships in Table 1 and literature [1] values of σ_{meta} and σ_{para} constants. Except for 8-nitro-1-naphthylamine, where steric factors and hydrogen-bonding are probably important, predictions are, on average, within about ±0·2 pH unit of the

TABLE 2

Comparison of predicted and experimental * pK_a values of substituted naphthylamines

Subst.	pK Predicted	pK Exptl.	Subst.	pK Predicted	pK Exptl.
		1-Naphthylamine series			
5-Cl	3·82	3·34	5-OH	4·14	3·96
6-Cl	3·29	3·48	6-OH	3·70	3·97
7-Cl	3·32	3·48	7-OH	4·14	4·20
6-OMe	3·70	3·90	5-NO_2	2·43	2·73
7-OMe	4·14	4·07	6-NO_2	2·74	2·89
8-OH-3,6-$(SO_3^-)_2$	3·30	3·63	7-NO_2	2·43	2·55
			8-NO_2	1·90	2·79
		2-Naphthylamine series			
7-Cl	3·82	3·71	5-NO_2	3·19	3·01
5-OH	4·15	4·07	6-NO_2	3·19	2·62
7-OH	4·18	4·25	7-NO_2	3·35	3·10
6-OMe	4·15	4·64	8-NO_2	2·88	2·73
7-OMe	4·18	4·19			

* Values taken from ref. 4.

experimental values. However, this is not a very stringent test of the method because the maximum shift in the pK_a values of the naphthylamines, resulting from substitution, is only 1·4 pH units.

In the same way, the pK_a values of 5-, 6-, 7-, and 8-substituted quinolines and isoquinolines can be predicted by applying the Dewar and Grisdale method to calculate the σ-constants, and then using the regression line for pyridines,[1]

$$pK_a = 5{\cdot}25 - 5{\cdot}90\Sigma\sigma.$$

The benzene rings in quinoline and isoquinoline are assigned σ-constants of 0·06 and −0·03, respectively. Predicted and experimental pK_a values are compared in Table 3. Agreement is often poor when quinoline has at position 8 a substituent (such as an amino-group or a carboxylate anion) that readily forms hydrogen-bonds, either intramolecularly or with water. With these exceptions, the average difference between predicted and experimental values is about 0·4 pH unit. This is comparable with the corresponding figure, 0·3 pH unit,[1] for 2-, 3-, and 4-substituted quinolines. The reasonable agreement for the 8-fluoro-, -chloro-, -bromo-, -methyl, and -methylthio-compounds suggests that there is little steric interaction in this series.

Extension to Systems Containing Two or More Ring Nitrogens.—To extend the method

[4] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

much more widely, it is assumed that the second, and subsequent, ring nitrogens in heteroaromatic bases such as pyrimidine, quinoxaline, and pteridine can be considered as substituents,[5,6] so that σ-constants can be assigned for use with the appropriate Hammett equation. Thus, pyridazine and pyrazine are derived from pyridine by substitution of a =CH– by =N– in the α- and γ-positions, respectively. From their experimental pK_a values [4] (corrected by subtracting a statistical factor of 0·30 = log 2 to allow for the two equivalent sites for protonation in the neutral molecules), and the regression line for

TABLE 3

Predicted and experimental * pK_a values of substituted quinolines

Substituent	pK Predicted	pK Exptl.	Substituent	pK Predicted	pK Exptl.
5-Br	3·6	3·62	5-OH	5·4	5·18
6-Br	3·5	3·91	6-OH	4·5	5·15
7-Br	3·6	3·87	7-OH	5·4	5·46
5-Cl	3·7	3·65	5-SH	4·1	3·27
7-Cl	3·7	3·85	6-SH	4·0	3·91
4,6-Cl_2	2·8	2·81	5-Me	5·4	5·20
4,7-Cl_2	2·3	2·80	6-Me	5·1	5·22
6-Br-4-Cl	2·2	2·83	7-Me	5·3	5·05
7-Br-4-Cl	2·2	2·83	6-OMe	4·5	5·03
4-Cl-6-F	2·4	2·95	5-SMe	4·6	4·46
4-Cl-7-F	2·7	3·04	6-SMe	4·4	4·71
4-Cl-6-OEt	3·2	3·82	6-CO_2^-	5·2	4·82
4-Cl-6-OMe	3·1	3·93	6-CO_2Me	3·8	3·80
4-Cl-7-OMe	3·8	4·32	5-NH_2	6·6	5·42
4-Cl-6-Me	3·8	3·96	6-NH_2	5·45	5·59
5-NO_2	1·8	2·69	7-NH_2	6·6	6·61
6-NO_2	2·5	2·72	4-NH_2-7-Cl	7·6	8·23
7-NO_2	1·8	2·40	4-NH_2-6-OMe	8·4	8·93
8-Br	2·6	3·13	8-OH	4·2	5·05
8-Cl	2·7	3·12	8-SH	3·4	2·01
8-F	2·9	3·37	8-Me	5·3	5·05
5-Cl-8-OH	3·0	3·8	8-SMe	4·0	3·46
7-Cl-8-OH	3·0	4·0	8-CO_2^-	5·5	6·82
5,7-Cl_2-8-OH	1·7	1·89	8-NH_2	5·8	3·95
8-OH-7-I-5-SO_3^-	2·8	2·56	4-NH_2-8-OH	8·1	6·91
8-OH-5-SO_3^-	3·9	4·11	5-NH_2-8-OH	5·9	5·67
8-NO_2	0·7	2·55			

* Taken from ref. 4.

substituted pyridines, the corresponding σ_{ortho} and σ_{para} constants for =N– are obtained. However, because its pK_a value is not known accurately, pyrimidine was not used to obtain σ_{meta}. Instead, a mean value of $\sigma_{meta} = 0{\cdot}60$, based on the p$K_a$ values of many substituted pyrimidines, was taken. Comparison of the pK_a values of the pyridine- and pyridine 1-oxide-carboxylic acids with substituted benzoic acids affords the σ-constant for the groups $=\overset{|}{N}H^+$ and $=\overset{|}{N}^+–O^-$. Thus, from the relevant information summarised in Table 4 and Tables of σ_{meta} and σ_{para} constants, the pK_a values of many heteroaromatic bases can be predicted. This range can be further extended by including apparent σ_{ortho} constants, two sets of which have been tabulated for the aniline and pyridine series.[1] These apparent constants (which are valid only for the reaction conditions under which they are determined) can be used because a constant *ortho*-substituent has little effect on either the σ-constants of other substituents or the ρ-values for reactions or equilibria.[5,7]

In Table 5, experimental pK_a values of some parent heteroaromatic bases are compared with predictions based on Table 4. Where alternatives exist, bases are assumed to protonate at the most strongly basic centre. For example, 3-aminopyridine (pK_a 6·00)

[5] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[6] H. H. Jaffé, *J. Chem. Phys.*, 1952, **20**, 1554.
[7] H. H. Jaffé, *Science*, 1953, **118**, 246.

TABLE 4

Data for prediction of pK_a values of heteroaromatic bases

σ-Constants for ring substitution in benzene derivatives

Substituent	σ_0	σ_m	σ_p	Notes
$=NH^+$	3·21	2·18	2·42	*a*, *b*
$=N-$	0·56	0·60	0·83	*b*, *c*
$=N^+-O^-$		1·48	1·35	*d*

Regression line for substituted pyridines [e] at 20°: $pK_a = 5{\cdot}25 - 5{\cdot}90\,\Sigma\sigma$.
Regression line for substituted anilines [e] at 20°: $pK_a = 4{\cdot}57 - 2{\cdot}81\,\Sigma\sigma$.

σ-Constants for annelating a benzene ring

	σ_α	σ_β
Pyridine series	0·06	−0·03
Aniline series	0·24	0·08

[a] From pK_a values of pyridinecarboxylic acids. [b] Data from ref. 4. [c] From pK_a values of azapyridines, allowing for statistical factor. [d] From pyridine 1-oxide carboxylic acids (H. H. Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527). [e] From ref. 1.

behaves as a substituted pyridine (predicted pK_a 6·19), protonating on the ring nitrogen, and not as a substituted aniline (predicted pK_a 2·75). A change of 0·17 units in a σ-constant alters the predicted pK_a for a substituted pyridine by 1 pH unit, so that the calculations are very sensitive to the σ-constants that are taken. Nevertheless, in most cases the pairs of values in the Table are in reasonable agreement, the average variation, expressed as the difference in pK_a values divided by the number of σ-constants, being

TABLE 5

Predicted and experimental * pK_a values of some heteroaromatic bases

Substance	pK Predicted	pK Exptl.	Substance	pK Predicted	pK Exptl.
Cinnoline	2·1	2·32	1,5-Naphthyridine	2·35 †	2·84
Phthalazine	2·4 †	3·45	1,6-Naphthyridine	3·4	3·76
Quinazoline	1·9	1·95 ‡	1,7-Naphthyridine	2·6	3·61
Quinoxaline	0·3 †	0·56	1,2,4-Triazanaphthalene	−1·4	−0·82
Acridine	4·5	5·58	Phenanthridine	5·1	4·55
Benzo[c]cinnoline	2·1 †	2·20	1,5-Phenanthroline	2·2	4·10
Phenazine	0·0 †	~1·2			

* Taken from ref. 4. † Including a statistical factor of 0·30. ‡ True pK_a value (J. W. Bunting, unpublished). The pK_a as ordinarily measured is an equilibrium one involving a covalently-hydrated cation.

approximately ±0·5 pH unit per substituent. The number of bases that can be compared in this way is limited by the strong tendency of many of the cations, for example of pteridine, 1,4,5,8-tetra-azanaphthalene, and many of the triazanaphthalenes, to add a molecule of water reversibly across one of their C=N bonds, so that the observed pK_a values are composite ones.[8]

In predicting pK_a values of substituted heteroaromatic bases, it is seldom necessary to begin with unsubstituted pyridine and sum all the σ-constants. More usually, the experimental pK_a value of a closely related compound (lacking only one or two of the substituents) is available from the literature (*e.g.*, ref. 4). The approximation is made that the effect of these substituents is the same as in the corresponding pyridine (including quinoline) derivative or, in appropriate cases, aniline (including naphthylamine), *i.e.*, that the additivity relationship continues to apply. An estimate of the resulting difference in pK_a can be obtained from the σ-constants for these substituents, using $\Delta pK_a = -2{\cdot}81\Sigma\sigma$ for anilines or $\Delta pK_a = -5{\cdot}90\Sigma\sigma$ for pyridines. The unknown pK_a should then

[8] For reviews, see A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1; D. D. Perrin, *ibid.*, p. 43.

be given approximately by the sum of ΔpK_a and the experimental pK_a value for the simpler compound. The principle is applied to some representative examples in Table 6.

TABLE 6

Prediction of pK_a values of substituted heteroaromatic bases

Substance	Ref. matl. (exptl. pK_a)	Predicted $-\Delta pK_a$	pK_a	
			Predicted	Exptl.
Quinoline, 4-NH_2-7-Cl	Quinoline, 4-NH_2 (9·13)	1·24	7·9	8·23
Quinoline, 4-NH_2-6-OMe	Quinoline, 4-NH_2 (9·13)	0·41	8·7	8·93
Quinoline, 4-Cl-6-Br	Quinoline, 4-Cl (3·72)	1·24	2·5	2·83
Cinnoline, 7-NH_2	Cinnoline (2·32)	−1·69	4·0	4·83
Cinnoline, 3-NH_2-6-Cl	Cinnoline (2·32)	−0·35	2·7	3·24
1,6-Naphthyridine, 3-NO_2	1,6-Naphthyridine (3·76)	2·07	1·7	2·32
Quinoxaline, 5-NH_2	Quinoxaline (0·56)	−1·39 *	2·0	2·59
Quinoxaline, 6-OH	Quinoxaline	−0·23 *	0·8	1·40
Acridine, 1-NH_2	Acridine (5·58)	−1·69	7·3	6·00
Acridine, 2-NH_2	Acridine (5·58)	−0·53	6·1	5·84
Acridine, 3-NH_2	Acridine (5·58)	−1·69	7·3	8·00
Acridine, 2-CO_2^-	Acridine (5·58)	−0·35	5·9	5·26
Acridine, 3,6-$(NH_2)_2$	Acridine (5·58)	−3·38	10·0	9·65
Acridine, 3,7-$(NH_2)_2$	Acridine (5·58)	−2·22	7·8	8·11
Acridine, 2-OH	Acridine (5·58)	0·41	5·2	5·48
Acridine, 2-SO_3^-	Acridine (5·58)	0·18	5·4	4·78
Benzo[*f*]quinoline, 3-NH_2-1-Me	Benzo[*f*]quinoline (5·11)	−2·60	7·7	7·10
Benzo[*g*]quinoline, 3-NH_2	Benzo[*g*]quinoline (5·01)	−0·84	5·9	4·74
Benzo[*h*]quinoline, 2-NH_2-4-Me	Benzo[*h*]quinoline (4·21)	−2·60	6·8	6·70
Phenanthridine, 6-NH_2	Phenanthridine (4·55)	−1·59	6·1	7·27
Phenanthridine, 9-NH_2	Phenanthridine (4·55)	−0·53	5·1	6·84
Phenanthridine, 3-OH	Phenanthridine (4·55)	−0·53	5·1	4·78
Phenanthridine, 8-OH	Phenanthridine (4·55)	0·35	4·2	4·35
1,10-Phenanthroline, 5,6-$(OMe)_2$	1,10-Phenanthroline (4·94)	−0·12	5·1	4·40

* Correction applied for statistical factor.

In this group of twenty-four substances, all but four of the predicted values lie within ±1 pH unit of the experimental values, the average difference being 0·6 pH unit. The exceptions (1·2, 1·2, 1·3, and 1·7 pH units) are all amino-derivatives of monoaza-anthracenes or -phenanthrenes. In one case (3-aminobenzo[*g*]quinoline) experimental results lead to the unexpected conclusion that the amino-group is base-weakening.

Substituted Imidazoles and Pyrazoles.—Hammett [2,9] suggested that unsaturated five-membered rings containing a heteroatom can be considered to be derived from benzene by replacement of a vinyl (−CH=CH−) group by the heteroatom. He suggested, further, that such heteroatoms might be able to be treated as substituents in benzene rings, and hence be assigned σ-constants for use with the Hammett equation. This would lead to the expectation that, in a five-membered ring, substituents in positions α or β to a reaction centre would require the same σ-constants as for *ortho*- and *meta*-substitution in benzene rings. On this basis, the pK_a values of substituted imidazoles should be derivable from the Hammett equation for pyridines if a σ_{meta} constant of −0·34 (calculated from the pK_a of imidazole, corrected by a statistical factor) is assigned to the −NH− group Similarly, for pyrazoles, the σ_{ortho} constant should be 0·42. Although the theoretical basis of the argument is tenuous, it does provide a simple method for predicting, for the first time, the pK_a values of these two groups of bases. Some experimental and predicted values are compared in Table 7. Omitting 5-nitroimidazole, where the difference exceeds 3 pH units, the average agreement is within ±0·4 unit (maximum difference 0·9 pH unit).

Extension of the method to thiazoles, azapyrazoles, and fused-ring systems such as benzimidazoles is less successful. From the results in Table 8, differences of up to 2 pH units must be expected.

[9] L. P. Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 96; *Trans. Faraday Soc.*, 1938, **54**, 156.

TABLE 7

Predicted * and experimental pK_a values for substituted imidazoles and pyrazoles

Derivative	Basic pK_a Predicted	Basic pK_a Exptl.	Derivative	pK_a Predicted	pK_a Exptl.
		Imidazole series			
4-($C_2H_4NH_3^+$)	5·8	5·78	2,4-Me_2	8·8	8·36
2-Me	7·7 †	7·85	4-Me	8·0	7·52
5-Ph	6·9	6·00	2-Et	7·7 †	~8·00
5-NO_2	3·1	~−0·05			
		Pyrazole series			
3-($C_2H_4NH_3^+$)	1·3	~2·02	3,5-Me_2	4·2 †	~4·38
3-Me	3·5	~3·56			

* Using Hammett equation for pyridines. † Corrected by statistical factor.

TABLE 8

Predicted [a] and experimental pK_a values for other bases containing five-membered rings

Compound	pK_a Predicted	pK_a Exptl.	Compound	pK_a Predicted	pK_a Exptl.
Thiazole, 2-NH_2	4·0 [b]	5·36	1,2,3-Triazole	3·6 [c]	~1·17
Thiazole, 4-($C_2H_4NH_3^+$)	0·9 [b]	1·68	1,2,4-Triazole	3·7	~2·30
Thiazole, 5-$CONH_2$	0·8 [b]	~0·6	1,2,3,4-Tetrazole, 5-NH_2	2·0	~1·76
Benzimidazole	6·6 [c]	5·53	Benzothiazole, 2-NH_2	3·7 [b]	4·48
Benzimidazole, 2-NH_2	8·2 [c]	7·51	Benzoxazole, 2-NH_2	3·7 [d]	3·70
Benzimidazole, 5-NH_2	7·5	6·07	1,5-Diazaindene	6·5	8·24
Benzimidazole, 5,6-Me_2	7·3	6·09	1*H*-Indazole	2·9	1·22
Benzimidazole, 2-Pr^i	7·3 [c]	6·21	1*H*-Indazole, 3-NH_2	4·5	3·12
Benzimidazole, 2-Me-5(or 6)-NO_2	4·6	4·37	1*H*-Indazole, 5-NH_2	4·1 [e]	5·12
Benzimidazole, 2-Et	7·3 [c]	6·23	Benzotriazole	3·2 [c]	~1·6
Benzimidazole, 2-Me-5,6-(NO_2)	1·9 [c]	~0·7	1*H*-Imidazo[4,5-*b*]pyridine	3·4	3·92
Benzimidazole, 4-NO_2	2·8	3·33	1*H*-Imidazo[4,5-*c*]pyridine	4·0	6·10
Purine	0·5 (N^1), 0·8 (N^7)	2·30	Pyrazolo(4′,5′-4,5)pyrimidine, 6-NH_2	3·4 (N^3)	4·96
Purine, 8-NH_2	2·4 (N^7)	4·64	Pyrazolo(5′,4′-4,5)pyrimidine, 6-NH_2	4·2 (N^3)	4·55
Purine, 2,6-(NH_2)$_2$	4·5 (N^3)	5·09			
Purine, 2,6,8-(NH_2)$_3$	5·1 [f] (N^3)	6·23			

[a] Using Hammett equation for pyridines. [b] Taking σ_{meta} for −S− = 0·48 (from the pK_a of thiazole). [c] Statistical correction applied. [d] Taking σ_{meta} for −O− = 0·48, as for −S−; compare σ_{meta} = 0·12 for OMe, 0·15 for SMe. [e] As a substituted aniline. [f] 3·0 (N^1), 3·8 (N^7).

Discussion.—The methods outlined above are based on the use of ordinary σ-constants (obtained mainly from substituted benzoic acids) in the Hammett equation. The selection of this set of values is to some extent arbitrary because, with some substituents, σ-constants vary appreciably and depend on the type of system from which they have been obtained. Thus, sets of σ^+ (or σ_e) and σ^- constants have been proposed for use when reaction involve substantial changes in resonance contributions (+*M* and −*M* effects, respectively).[10] It is likely that the selection of the appropriate type of constant would improve the accuracy of some of the pK_a predictions but, in view of the other assumptions involved, this increased complexity is probably not warranted. With the usual σ-constants, reasonable agreement between predicted and experimental pK_a values is found in most cases; the main exceptions occur when hydrogen-bonding, steric effects, or resonance contributions become important.[11]

In the absence of data from model compounds, or of spectroscopic evidence, there may be uncertainty as to the protonation site in a compound containing more than one basic

[10] H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1959, **78**, 815; R. W. Taft and I. C. Lewis, *J. Amer. Chem. Soc.*, 1959, **81**, 5343; R. W. Taft, S. Ehrensen, and R. E. Glick, *ibid.*, p. 5352.

[11] For a qualitative discussion of factors influencing the pK_a values of heterocyclic acids and bases, see A. Albert, " Physical Methods in Heterocyclic Chemistry," vol. I, ed. A. R. Katritzky, Academic Press, New York, 1963, ch. 1.

centre. As discussed for 3-aminopyridine, this site can usually be indicated by finding the basic centre which gives the greatest predicted pK_a value. For example, this approach confirms that in amino-derivatives of heteroaromatic nitrogen bases protonation occurs first on a ring nitrogen atom. In 8-aminopurine, the proton probably adds to N^7 and not to N^1 (predicted pK_a values 2·4 and 0·9, respectively). In purine, itself, the predicted pK_a values are 0·5 (for N^1), 0·8 (for N^7), and 0·3 (for N^9 in the tautomeric form), and are too close for any particular protonation site to be assigned with confidence. In 2,6-diaminopurine, on the other hand, predicted pK_a values are 2·5 (for N^1), 4·5 (for N^3), and 2·2 (for N^7), so that N^3 is apparently the most strongly basic centre. This supports the suggestion that, in substituted purines, protonation can occur in either the imidazole or the pyrimidine ring, depending on the substituents and their locations.[1]

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