Prediction of Tautomeric Equilibria for *N*-Arylamidines

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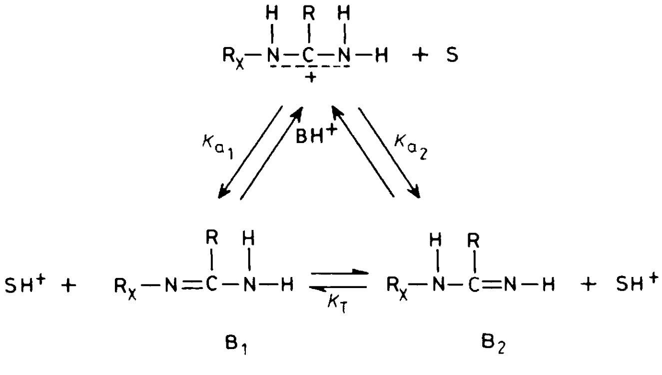
The influence of substitution at amidine nitrogen atom on tautomeric equilibria and basicities of *N*-arylamidines is discussed. It is shown that tautomeric equilibrium constants (as pK_T) can be correlated with σ^o substituent constants, but measured pK_{a_m} values of tautomeric mixture should obey a non-linear relation with σ^o constants. The methods of prediction of pK_T value are proposed, and applied to *N*-arylformamidines and acetamidines.

The possibility of predicting tautomeric equilibrium constants as well as pK_a values of organic compounds, particulary those which are biologically active, is for several reasons an important question in organic chemistry.[1]

In the case of compounds containing an amidine group ($-N{=}\overset{|}{C}-N<$), unsubstituted, *N*-monosubstituted, and *N,N'*-disubstituted amidines all display prototropic tautomerism, and the tautomeric equilibrium depends on the effects of the substituents at the nitrogen atoms.[2–4] In the previous paper,[5] which concerned unsymmetrically and symmetrically *N,N'*-disubstituted amidines, it was shown that the application of correlation analysis methods to the study of tautomeric and acid-base equilibria has led to the prediction of both the pK_T values and the pK_a values of individual tautomers. In the case of *N*-monosubstituted amidines, only Katritzky *et al.*[6,7] have determined pK_T values for several *N*-monosubstituted acetamidines, and have discussed the substituent effect on pK_T, but they did not report any attempts to find a quantitative relationship between structural parameters and tautomeric equilibria.

pK_a *of* N-*Arylamidines*.—It is well known that the protonation of tautomerizing *N*-monosubstituted amidine yields only one amidinium cation, which as the conjugate acid (BH^+) of both tautomeric bases (B_1 and B_2) in the solvent S dissociates as shown in the Scheme.



Scheme.

According to Brönsted theory,[8] the measured (called macroscopic) dissociation constant K_{a_m}, defined as $K_{a_m} = [(B_1) + (B_2)](SH^+)/(BH^+)$, is the sum of microscopic constants K_{a_1} and K_{a_2}.

$$K_{a_m} = K_{a_1} + K_{a_2} \qquad (1)$$

For unsubstituted amidines, where $R_x = H$, both microscopic constants are identical ($K_{a_1} = K_{a_2} = K_{a_H}$), and thus the measured pK_{a_m} can be expressed as

$$pK_{a_m} = pK_{a_H} - \log 2 \qquad (2)$$

If the pK_a value of one of the tautomers is negligible with respect to the pK_a of the second one, the measured pK_{a_m} value is approximately equivalent to the pK_a value of the less basic tautomer (*e.g.* if $K_{a_1} \gg K_{a_2}$ then $K_{a_m} \cong K_{a_1}$ and $pK_{a_m} \cong pK_{a_1}$).

Systematic studies[9] on the influence of substitution at both nitrogen atoms on the basicity of N^1,N^1,N^2-trisubstituted amidines have led to the derivation of some general equations enabling the prediction of the pK_a value of any amidine in ethanol. It was found[9] that the pK_a of amidines can be predicted with satisfactory accuracy (error <0.3 units of pK_a) on the basis of equation (3) where $\Delta pK_{a_{PA}}$ and $\Delta pK_{a_{SA}}$ are the differences in the pK_a of the primary R_xNH_2 and $PhNH_2$, and of the secondary R_yR_zNH and MePhNH amines, respectively.

$$pK_a = pK_a^o + \alpha_{Im}\Delta pK_{a_{PA}} + \alpha_{Am}\Delta pK_{a_{SA}} \qquad (3)$$

Equation (3) for symmetrically *N,N'*-disubstituted tautomerizing amidines gives equation (4):

$$pK_a = pK_a^o + (\alpha_{Im} + \alpha_{Am})\Delta pK_{a_{PA}} \qquad (4)$$

It was also shown[9] that the basicity of amidines containing different types of substituents at the nitrogen atom can be predicted on the basis of substituent constants expressed on the uniform scale σ^o, mentioned in references 10 and 11, and the Hammett equation (5):

$$pK_a = pK_a^o - \rho_i\sigma_i^o \qquad (5)$$

On this basis it can be assumed that in the case of *N*-arylamidines (R_x = *m*- or *p*-C_6H_4X) the pK_a values of both tautomers B_1 and B_2 should obey equations (6) and (7), respectively, where $pK_{a_1}^o$ and $pK_{a_2}^o$ are the microscopic pK_a values of amidines containing an unsubstituted phenyl ring at the imino or the amino nitrogen atom, respectively.

$$pK_{a_1} = pK_{a_1}^o - \rho_{Im}\sigma_X^o \qquad (6)$$

$$pK_{a_2} = pK_{a_2}^o - \rho_{Am}\sigma_X^o \qquad (7)$$

On the plot (Figure) the pK_a values of the tautomers B_1 and B_2 are represented by the two intersecting straight lines 1 and 2, respectively. The intersection point of these lines refers to the microscopic pK_{a_H} value of unsubstituted amidine where R_x =

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B1 B2

H, and can be obtained, according to equation (2), by direct measurements of the pK_{a_m} value of the unsubstituted amidine.

The relationship for the prediction of measured pK_{a_m} values of *N*-arylamidines is obtained by replacing K_{a_1} and K_{a_2} in equation (1) by the terms obtained from equations (6) and (7).

$$pK_{a_m} = -\log[K^{\circ}_{a_1}\,10^{\rho_{\mathrm{Im}}\sigma^{\circ}_{X}} + K^{\circ}_{a_2}\,10^{\rho_{\mathrm{Am}}\sigma^{\circ}_{X}}] \qquad (8)$$

Using the uniform scale of σ° constants the equations (6)—(8) can be modified as follows. The pK_a of both tautomers should obey equations (9) and (10), respectively, where σ°_{H} is the σ° constant of hydrogen atoms in the uniform scale σ°.

$$pK_{a_1} = pK_{a_H} - \rho_{\mathrm{Im}}(\sigma^{\circ}_{X} - \sigma^{\circ}_{H}) \qquad (9)$$

$$pK_{a_2} = pK_{a_H} - \rho_{\mathrm{Am}}(\sigma^{\circ}_{X} - \sigma^{\circ}_{H}) \qquad (10)$$

By a similar procedure to that used for equation (8), the relationship for the prediction of pK_{a_m} value of any *N*-monosubstituted amidine is obtained.

$$pK_{a_m} = pK_{a_H} - \log[10^{\rho_{\mathrm{Im}}(\rho^{\circ}_{X} - \sigma^{\circ}_{H})} + 10^{\rho_{\mathrm{Am}}(\sigma^{\circ}_{X} - \sigma^{\circ}_{H})}] \qquad (11)$$

On the Figure the measured pK_{a_m} values are represented by the curve m; two asymptotes overlap with the straight lines 1 and 2, and m passes below the intersection point of these lines at a distance equal to log 2 [according to equation (2)].

As ρ_{Im} is different from ρ_{Am},[9,12–14] the relationship between pK_{a_m} and σ° constants cannot be treated as a straight-line equation. For this reason, the conclusion reported in several papers,[15,16] and even in a monograph,[17] maintaining that the measured pK_{a_m} values of *N*-monosubstituted amidines obey the Hammett equation, is incorrect, since an erroneous assumption was made.

pK_T *of* N-*Arylamidines*.—The tautomeric equilibrium constant, defined as $pK_T = -\log(B_1)/(B_2)$, is determined by the difference in the pK_a values of both tautomers.

$$pK_T = pK_{a_1} - pK_{a_2} \qquad (12)$$

For an unsubstituted amidine where R_x = H, the pK_T is equal to 0.

Tautomerization of amidine is a very fast reaction.[18,19] For this reason the microscopic constants (pK_{a_1} and pK_{a_2}) of single tautomers, and thus the pK_T value, are not experimentally accessible. However, the pK_T values can be estimated by application of the basicity method on the basis of some general equations between pK_T and parameters of structure, or on the basis of the pK_a values of certain model compounds.

The relationship between pK_T and substituent constants can be derived from equations (6), (7), and (12). After rearrangement the Hammett equation (13) is obtained, where $pK^{\circ}_T = pK^{\circ}_{a_1} - pK^{\circ}_{a_2}$ and $\rho_T = \rho_{\mathrm{Im}} - \rho_{\mathrm{Am}}$.

$$pK_T = pK^{\circ}_T - \rho_T\sigma^{\circ}_X \qquad (13)$$

On uniform scale of σ° constants the relationship (13) can be expressed as follows:

$$pK_T = -\rho_T(\sigma^{\circ}_X - \sigma^{\circ}_H) \qquad (14)$$

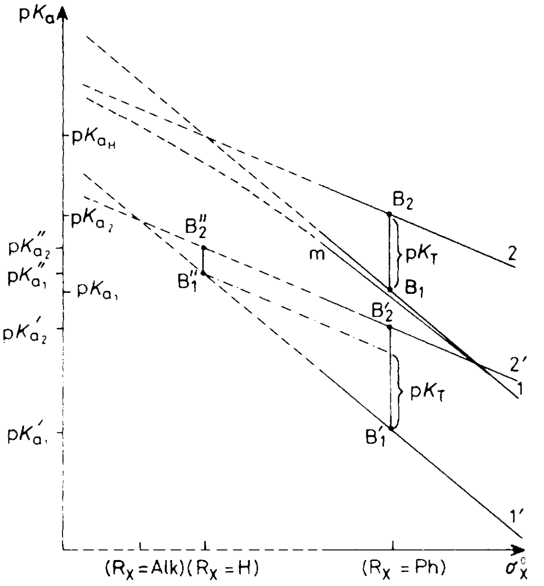


Figure. Plot of pK_a *vs.* σ°_X for *N*-monosubstituted amidines. Calculation of pK_T on the basis of the pK_a values of 4 model derivatives: B'_1, B'_2, B''_1, and B''_2 [equation (15)].

Equation (14) has the advantage that it contains neither pK°_T nor $pK^{\circ}_{a_1}$ and $pK^{\circ}_{a_2}$, which, as mentioned above, are not experimentally accessible and need to be estimated. Moreover, equation (14) can be used for the prediction of pK_T values of any *N*-monosubstituted amidine.

The ρ_{Im} and ρ_{Am} values can be taken from investigation of the corresponding series of trisubstituted amidines, since substitution at the nitrogen atom has no significant influence on these values.[9,12,13] But as substitution at a functional carbon atom has considerable influence,[9,10,20,21] one should be careful to use only ρ_{Im} and ρ_{Am} values obtained for amidines with the same substituents at the functional carbon atom.

When investigation of a series is impossible, the method of Katritzky *et al.*[6,7] can be used, with certain modifications. First, as model compounds the alkylated (methylated) derivatives should be used, *e.g.* compounds containing the same substituent at the functional carbon atom. It was observed that replacement of the hydrogen atom at the amidine carbon atom by methyl, substituted phenyl, or other groups causes considerable changes in pK_a and ρ values.[9,10,20,21] Secondly, the pK_T value should be estimated on the basis of the pK_a values of two pairs of corresponding model compounds. Only in the case of *N,N'*-disubstituted amidines can one pair of alkylated derivatives be used for prediction of the pK_T values, since replacement of the hydrogen atom in both tautomers by an alkyl group does not influence the difference in their pK_a values (*e.g.* pK_T).

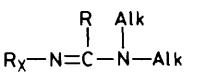
According to the modified method, the pK_T value can be calculated from the pK_a values of the alkylated derivatives B'_1 and B'_2 (*i.e.* R_x = Ph), and of the corresponding pair B''_1 and B''_2.

The pK_a values of the compounds B'_1 and B'_2 should obey equation (5). According to the assumption described above, the straight lines 1' and 2', which represent the pK_a values of compounds B'_1 and B'_2, should be parallel to the straight lines 1 and 2, respectively (Figure). If the substituent R_x is the same alkyl group as substituent Alk in both B'_1 and B'_2, then compounds B'_1 and B'_2 are identical, and thus the lines 1' and 2' intersect at the point which refers to the pK_a of this amidine. If R_x = H, the compounds B'_1 and B'_2 have the same structure as the compounds B''_1 and B''_2 respectively. Thus the points which

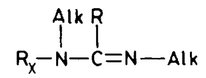
Table. pK_T Values in ethanol (azeotrope) predicted for *N*-monosubstituted amidines on the basis of the pK_a of the corresponding methyl derivatives B'_1, B'_2, B''_1, and B_2'' [equation (15)], and of the Hammett equation [equation (14)]

			pK_a in 95.6% ethanol				pK_T		
R	Alk	R_x	B'_1	B'_2	B''_1	B''_2	eq. (15)	eq. (14)	%B_1[a]
H	Me	*p*-C_6H_4OMe	7.91[b]	8.96[c]	11.33[e]	10.52[f] + log 2 = 10.82	−1.6	−1.6	97.5
		p-C_6H_4Me	7.75[b]	8.84[c]			−1.6	−1.7	98
		m-C_6H_4Me	7.63[b]	8.74[c]			−1.6	−1.8	98
		Ph	7.45[b]	8.66[d]			−1.7	−1.9	98.5
		p-C_6H_4Cl	6.84[b]	8.33[c]			−2.0	−2.2	99
		m-C_6H_4Cl	6.50[b]	8.16[c]			−2.2	−2.3	99.5
		m-$C_6H_4NO_2$	5.67[g]	7.69[c]			−2.5	−2.7	100
		p-$C_6H_4NO_2$	5.27[b]	7.55[c]			−2.8	−2.9	100
Me	Me	*p*-C_6H_4OMe	8.96[h]	11.41[i]	12.81[g]	12.35[j] + log 2 = 12.65	−2.6	−2.1	99.5
		p-C_6H_4Me	8.65[h]	11.28[i]			−2.8	−2.3	100
		m-C_6H_4Me	8.41[h]	11.18[i]			−2.9	−2.4	100
		Ph	8.32[h]	11.09[k]			−2.9	−2.5	100
		p-C_6H_4Cl	7.65[h]	10.75[i]			−3.3	−2.9	100
		m-C_6H_4Cl	7.25[h]	10.57[i]			−3.5	−3.1	100
		m-$C_6H_4NO_2$	6.38[g]	10.08[i]			−3.9	−3.7	100
		p-$C_6H_4NO_2$	5.69[h]	9.93[i]			−4.4	−3.8	100

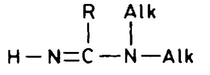
[a] Calculated from the equation p$K_T = -\log(x/1 - x)$ where x is the molar fraction of B_1. [b] As in ref. 11. [c] Calculated from eq. (5) using as pK_a^o the pK_a of N^1,N^2-dimethyl-N^2-phenylformamidine, equal to 8.66[d], and $\rho_{Am} = 1.36$.[14] [d] Calculated from eq. (3) using as pK_a^o the pK_a of N^1-methyl-N^1,N^2-diphenylformamidine, equal to 5.29,[22] $\alpha_{1m} = 0.62$,[10] and as $\Delta pK_{a_{PA}}$ the difference in the pK_a values of methylamine (9.55[23]) and aniline (4.12[11]). [e] As in ref. 9. [f] Calculated from eq. (4) using as pK_a^o the pK_a of *N*,*N'*-diphenylformamidine, equal to 5.38,[24] $\alpha_{1m} = 0.62$,[10] $\alpha_{Am} = 0.35$,[22] and $\Delta pK_{a_{PA}}$[d]. [g] As in ref. 24. [h] As in ref. 10. [i] Calculated from eq. (5) using as pK_a^o the pK_a of N^1,N^2-dimethyl-N^2-phenylacetamidine, equal to 11.09[j], and $\rho_{Am} = 1.42$.[13] [j] Calculated from eq. (4) using as pK_a^o the pK_a of *N*,*N'*-diphenylacetamidine, equal to 6.97,[5] $\alpha_{1m} = 0.76$,[10] $\alpha_{Am} = 0.23$,[24] and $\Delta K_{a_{PA}}$[d]. [k] Calculated from eq. (3) using as pK_a^o the pK_a of N^1-methyl-N^1,N^2-diphenylacetamidine, equal to 6.96,[13] $\alpha_{1m} = 0.76$,[10] and $\Delta pK_{a_{PA}}$[d].


$R_X{-}N{=}\overset{R}{C}{-}\overset{Alk}{N}{-}Alk$

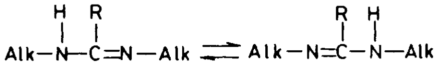
B'_1


$R_X{-}\overset{Alk}{N}{-}\overset{R}{C}{=}N{-}Alk$

B'_2


$H{-}N{=}\overset{R}{C}{-}\overset{Alk}{N}{-}Alk$

B''_1


$Alk{-}\overset{H}{N}{-}\overset{R}{C}{=}N{-}Alk \rightleftharpoons Alk{-}N{=}\overset{R}{C}{-}\overset{H}{N}{-}Alk$

B''_2

refer to the pK_a of B''_1 and B''_2 are placed on the lines 1′ and 2′, respectively.

As shown (Figure), the difference between the pK_a values of tautomers B_1 and B_2 (pK_T) is not equal to the difference in the pK_a values of compounds B'_1 and B'_2, as was assumed in the original method of Katritzky *et al.*,[6,7] but can be obtained by subtraction of the difference in the pK_a values of compounds B''_1 and B''_2 from the difference in the pK_a values of compounds B'_1 and B'_2 [equation (15)], where pK''_{a_2} is the microscopic pK_a of

$$pK_T = pK'_{a_1} - pK'_{a_2} + pK''_{a_2} - pK''_{a_1} \qquad (15)$$

symmetrically substituted *N*,*N'*-dialkylamidine (B''_2). Thus it is about log 2 higher than the measured pK_a.[5]

Therefore, the pK_T values determined for some *N*-monosubstituted acetamidines[6,7] as the difference in the pK_a values of one pair of model compounds are incorrect. The pK_T values presented in the paper[7] need to be reduced. Using a similar analysis to that above it can be easily shown that the correction to pK_T is equal to the difference of the pK_a of N^1,N^1-dimethylacetamidine and of amino-tautomer of *N*-methylacetamidine. In the case of compounds studied in the original paper,[6] an additional erroneous assumption was made, in that compounds containing different substituents at the functional carbon atom were used as models, and thus the error in pK_T determination cannot be estimated.

The pK_a values of individual tautomers can be obtained on the basis of equations (1) and (12), and the estimated pK_T and the measured pK_{a_m} of tautomeric mixture.

The above presented methods have been applied to the prediction of pK_T values for several *N*-aryl-formamidines and -acetamidines. The pK_a values have been estimated (Table) on the basis of the pK_a values of corresponding methyl derivatives B'_1, B'_2, B''_1, and B''_2 [equation (15)], and calculated from the Hammett equation [equation (14)], using $\rho^o = 1.49$,[9] $\sigma_T = 1.24$ for formamidines ($\rho_{Im} = 2.60$,[10] $\rho_{Am} = 1.36$[14]), and $\sigma_T = 1.66$ for acetamidines ($\rho_{Im} = 3.08$,[10] $\rho_{Am} = 1.42$[13]), and can be seen to be similar. The error in the pK_T prediction does not exceed 0.5 pK_T units. Moreover, the results obtained provide confirmation of literature qualitative and quantitative conclusions[2-4,6,7,25] that *N*-arylamidines exist predominantly as the imino-tautomer B_1, and thus the concentration of the amino-tautomer B_2 can be undetectable.

Acknowledgements

The author is indebted to Professor T. M. Krygowski for enjoyable discussions, and to Professor J. Oszczapowicz for encouragement and useful discussions.

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Received 7th June 1985; *Paper* 5/967