General Structure–Basicity Relations for Trisubstituted Acetamidines

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An equation enabling prediction of the pK_a values in ethanol for trisubstituted acetamidines containing substituents at both nitrogen atoms is derived, and its parameters are compared with those obtained previously for trisubstituted formamidines. The effect of the methyl group at the amidine carbon atom is discussed.

The pK_a values of trisubstituted acetamidines containing a substituted phenyl ring at the imino and/or amino nitrogen atoms obey the Hammett equation,[1–3] and the basicity of N^1N^2-diarylacetamidines can be predicted with satisfactory accuracy on the basis of equation (1) where pK_a° is the pK_a of

$$pK_a = pK_a^\circ - \rho_{Im}\sigma_{Im}^\circ - \rho_{Am}\sigma_{Am}^\circ \quad (1)$$

N^1N^2-diphenylacetamidine (pK_a for N^1-methyl-N^1N^2-diphenylacetamidine in ethanol 6.96 ± 0.01), and σ_{Im}° and σ_{Am}° are the σ° constants[4] of substituents on phenyl rings at the imino and the amino nitrogen atoms, respectively. The values of the ρ_{Im}° and ρ_{Am}° parameters in ethanol are 2.9 ± 0.2 and 1.4 ± 0.2, respectively.

The application of equation (1) to the study of tautomeric and acid–base equilibria for tautomerizing *NN'*-diarylacetamidines had led to a prediction of both the pK_T and pK_a values of individual tautomers which are not experimentally accessible.[5]

The possibility of correlation of the pK_a values of acetamidines containing any substituent R_x (alkyl, aryl, or aralkyl) at the imino nitrogen atom with the pK_a values of the corresponding primary amines R_xNH_2 measured under the same conditions[2] shed new light on the problem of the derivation of general relations predicting the pK_a values of amidines. A study of a series of N^2-phenylacetamidines[6] PhN=CMe–NR_yR_z (APh) containing substituents R_y and R_z at the amino nitrogen atom showed that their pK_a values can be correlated with the pK_a values of corresponding secondary amines R_yR_zNH measured under the same conditions.

The good correlations of the pK_a values of acetamidines with those of the corresponding amines indicate that the basicity of trisubstituted acetamidines with substituents at both nitrogen atoms can be predicted with satisfactory accuracy by equation (2), in which pK_a° is the pK_a value of N^1-methyl-N^1N^2-diphenylacetamidine, and ΔpK_a (PA) and ΔpK_a° (SA) are the differences of the pK_a values of primary R_xNH_2 and $PhNH_2$, and of secondary amines R_yR_zNH and MePhNH, respectively. Such correlation [equation (2)] is of higher diagnostic value

$$pK_a = pK_a^\circ + \alpha_{Im}\Delta pK_a\,(PA) + \alpha_{Am}\Delta pK_a\,(SA) \quad (2)$$

than the correlation with σ° constants [equation (1)], because the range of pK_a values considered is twice as large as that for substituted phenyl groups, and thus the sensitivity to substitution is more marked.

For the calculation of the parameters of equation (2) the pK_a values of recently studied N^1N^1-dimethylacetamidines[2] (ADM), N^1-methyl-N^1N^2-diphenylacetamidines[3] (ADPhM), and N^2-phenylacetamidines[6] (APh) can be used, because they were measured under the same conditions in 95.6% ethanol (azeotrope). Moreover all acetamidines have the same structure (*E*) as shown by ^1H and ^{13}C n.m.r. spectra.[6–8]

The parameters of equation (2) have been calculated by the least-squares method at a significance level of 0.05. In the case of trisubstituted acetamidines (ATS) the pK_a values of some amidines strongly deviated from earlier correlations.[3,6] If these points were neglected for the remaining 41 compounds the following parameters of equation (2) were obtained and compared with those found previously for trisubstituted formamidines[9] (FTS):

Series	pK_a°	α_{Im}	α_{Am}	r
ATS	6.78	0.76 ± 0.02	0.23 ± 0.02	0.993
FTS	5.09	0.62 ± 0.01	0.36 ± 0.02	0.994

In both cases the strongest effect of substitution on basicity is observed for the imino nitrogen atom, confirming the earlier conclusion that this atom is the protonation site of the amidine group.

The correlations obtained are of very good quality, as indicated by the correlation coefficients. To illustrate the value of equation (2) the pK_a values were calculated for a few trisubstituted acetamidines, and compared with those measured in ethanol (Table 1). The errors in the predicted pK_a values do not exceed 0.2 pK units.

Comparison of the parameters for the regressions obtained for acetamidines ATS with those for formamidines FTS indicates that the sensitivity of the amidine group to substitution at the nitrogen atoms depends to a considerable degree on substitution at the functional carbon atom, and thus for each series of trisubstituted amidines which have a different substituent at this atom the different parameters of equation (2) can be obtained. The difference between the slopes of the regressions can be explained by the effect of mutual interaction of the substituent at the functional carbon atom with that at both nitrogen atoms, or by other effects of substituents at the amidine carbon atom.

For the amidines studied the α_{Im} value for acetamidines is 1.21 times higher than for formamidines but the α_{Am} value is 0.64 times smaller. It means that the replacement of the hydrogen atom at the amidine carbon atom in formamidines by the methyl group increases the transmission of substituent effects at the imino nitrogen atom to the site of protonation but decreases the transmission of the substituents effects at the amino nitrogen atom. This can be explained by the hyperconjugation effect of the methyl group on the imino nitrogen atom [structure (**c**)]. Additional hyperconjugation decreases the contribution of the conjugation of the amino with the imino nitrogen atom [structure (**b**)].

In the case of formamidines the contribution of structure (**e**) is considerably higher. For that reason α_{Am} for formamidines ($\alpha_{Am} = 0.6\ \alpha_{Im}$) is higher than for acetamidines ($\alpha_{Am} = 0.3\ \alpha_{Im}$). Moreover, in the case of acetamidines there are two structures (**b**) and (**c**) which produce a higher contribution of the sp^3

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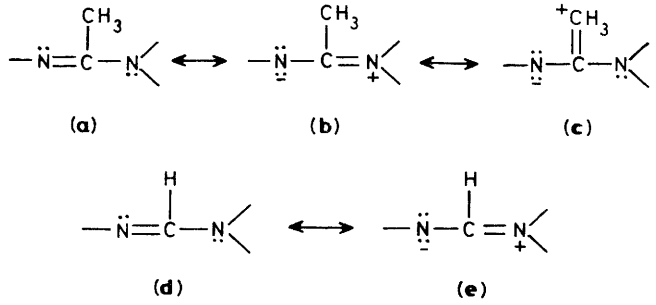
Table 1. Comparison of the pK_a values of trisubstituted acetamidines ATS (R_xN=CMe–NR_yR_z) calculated on the basis of equation (2) with that measured in 95.6% ethanol

Substituents			pK_a	
R_x	R_y	R_z	Calculated	Measured
Pr^n	Me	Me	12.42 ± 0.23	12.46 ± 0.07[a]
CH_2Ph	Me	Me	11.74 ± 0.22	11.70 ± 0.05[a]
p-C_6H_4Me	Me	Me	8.64 ± 0.13	8.65 ± 0.06[a]
p-C_6H_4Cl	Me	Me	7.64 ± 0.13	7.65 ± 0.04[a]
Ph	Pr^n	Pr^n	8.15 ± 0.14	8.16 ± 0.03[b]
Ph	$(CH_2)_5$		8.18 ± 0.14	8.03 ± 0.02[b]
Ph	Et	Ph	6.90 ± 0.04	6.99 ± 0.02[b]
p-C_6H_4Me	Me	Ph	7.24 ± 0.04	7.34 ± 0.03[c]
p-C_6H_4Br	Me	Ph	6.22 ± 0.04	6.10 ± 0.03[c]
m-C_6H_4Cl	Me	*p*-C_6H_4OMe	6.18 ± 0.06	6.05 ± 0.02[c]

[a] Ref. 2. [b] Ref. 6. [c] Ref. 3.



electron configuration on the imino nitrogen atom than structure (**e**) in the case of formamidines, and thus the α_{Im} value for ATS is higher than for FTS. This conclusion is supported by other data. For the Hammett equation, the ρ_{Im} value for N^1N^1-dimethylacetamidines (3.08 ± 0.27) is also higher than for formamidines[2] (2.60 ± 0.28), but is smaller than for anilines[6] (3.64 ± 0.26) for which the electron configuration on the nitrogen atom approaches closer to the sp^3 configuration.

Comparison of other literature data such as ^1H and ^{13}C n.m.r. results for acetamidines with those for formamidines confirms the effect of the methyl group.

For formamidines containing electron-accepting (aryl) groups at the imino nitrogen atom the contribution of structure (**e**) is so high that the alkyl groups at the amino nitrogen atom are not equivalent, and separate signals of equal intensity are observed in ^{13}C n.m.r. spectra at room temperature,[8] *e.g.* for the methyl groups in N^1N^1-dimethylformamidines (FDM) two signals at δ 35 ± 1 and 40 ± 1 p.p.m. are observed. For acetamidines the contribution of structure (**b**) is smaller, and thus for alkyl groups one sharp signal, even for the strong electron-accepting *p*-$C_6H_4NO_2$ group at the imino nitrogen atom, is observed in ^1H and ^{13}C n.m.r. spectra,[2,6–8] *e.g.* the methyl groups in ADM are equivalent and give one sharp signal at δ 38.0 ± 0.1 p.p.m.

Comparison of the additivity parameters of the amidine group –N=CR–NR_yR_z applied in the case of acetamidines to predict chemical shifts of a ring proton at the imino nitrogen atom[7] (Table 2), and those of a ring carbon[8] (Table 3) with those for formamidines indicates that substitution at the amidine carbon atom by the methyl group causes an upfield shift of the *ortho* and *para* hydrogen atoms (Table 2) and a downfield shift of *ortho* and an upfield shift of *para* carbon atoms (Table 3).

For the influence of structure on ^1H chemical shifts in amidines for a series of formamidines R_xN=CH–NMe_2 (FDM)[10] a linear correlation of the ^1H chemical shifts for methyl groups at the amino nitrogen atom with that for the

Table 2. Comparison of the additivity parameters of the –N=CR–NMe_2 group[a]

Series	d_o	d_m	d_p	γ
ADM	−0.62	−0.10	−0.44	0.58
FDM	−0.34	−0.08	−0.34	0.63

[a] For calculating chemical shifts of protons in a phenyl ring at the imino nitrogen atom for *para* derivatives from the equation: $\delta_2 = 7.266 + d_o(R^1) + \gamma(R^1)d_m(R^4)$, and for *meta* derivatives from equations: $\delta_2 = 7.266 + d_o(R^1) + d_o(R^3)$, $\delta_4 = 7.266 + d_o(R^3) + d_p(R^1)$, and $\delta_5 = 7.266 + d_m(R^1) + d_m(R^3)$.[7]

Table 3. Comparison of the additivity parameters (substituent-induced chemical shifts, SCS) of the –N=CR–NR_yR_z group[a]

Series	C-1	*ortho*	*meta*	*para*
ADM	23.7	−6.0	0.2	−7.1
FDM	23.5	−7.4	0.4	−6.2
APM[b]	23.6	−6.2	0.2	−7.2
FPM[c]	23.6	−7.5	0.4	−6.2
AOPM[d]	22.9	−6.6	0.3	−7.5
FOPM[e]	22.9	−7.4	0.5	−5.6
ADPhM	23.2	−6.3	0.3	−6.7
FDPhM[f]	22.9	−7.3	0.5	−5.2

[a] For calculating chemical shifts of carbons in a phenyl ring at the imino nitrogen atom from the equation: $\delta(C_i) = 128.5 + \Sigma\Delta\delta_{jk}(X_j)$ where $\Delta\delta_{jk}$ is the additivity parameters (SCS) of substituent X_j at position *k* (C-1, *o*, *m*, and *p*) with respect to C_i as in ref. 8. [b] N^1N^1-Pentamethyleneacetamidines. [c] N^1N^1-Pentamethyleneformamidines. [d] N^1N^1-3-Oxapentamethyleneacetamidines. [e] N^1N^1-3-Oxapentamethyleneformamidines. [f] N^1-Methyl-N^1N^2-diphenylformamidines.

hydrogen atom at the functional carbon atom is observed (slope 0.68 ± 0.15, *r* 0.895, *n* 23) but for acetamidines R_xN=CMe–NMe_2 (ADM)[2] a scatter diagram for the ^1H chemical shifts in methyl groups at the amino nitrogen atom and that at the functional carbon atom is obtained (Figure 1). In the case of ^{13}C n.m.r. spectra for different series of formamidines containing substituted phenyl groups at the imino nitrogen atom[8] the chemical shifts of the functional carbon atom can be correlated with the σ constants[11] of substituents in the phenyl ring (Figure 2), and linear regressions are obtained (for FDM slope 0.74 ± 0.14, *r* 0.963, *n* 13; for FPM slope 0.36 ± 0.18, *r* 0.875, *n* 9; for FOPM slope 0.50 ± 0.27, *r* 0.930, *n* 6; and for FHM slope 0.68 ± 0.28, *r* 0.960, *n* 6). In the case of acetamidines ADM the chemical shifts of the functional carbon atom do not correlate with the σ constants (*r* 0.621, *n* 8). Hyperconjugation by the methyl group causes the modes of transmission of the inductive and mesomeric effects of

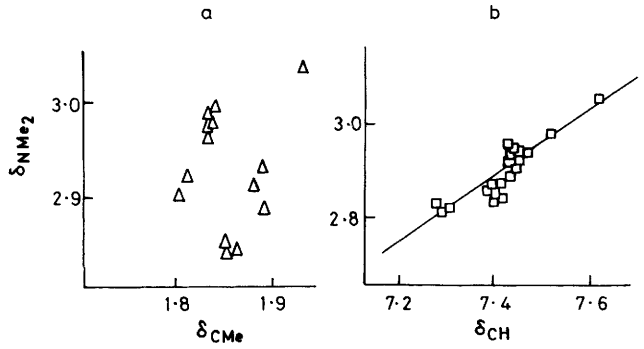


Figure 1. Chemical shifts of hydrogen atoms at the functional carbon atom *versus* chemical shifts of hydrogen atoms in methyl groups at the amino nitrogen atom; *a*, for acetamidines ADM (R_xN=CMe–NMe_2) (△); *b*, for formamidines FDM (R_xN=CH–NMe_2) (□), according to data from refs. 2 and 10, respectively

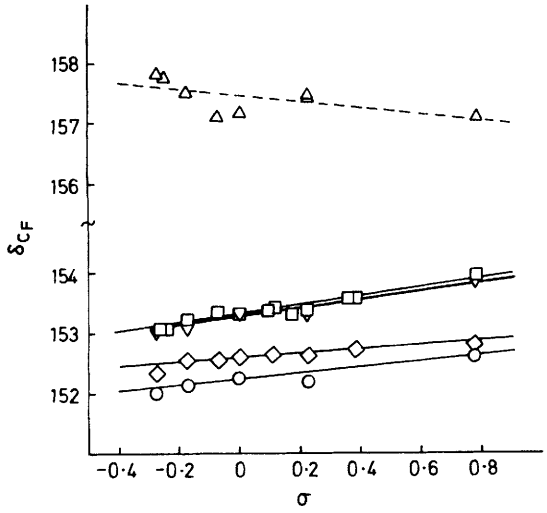


Figure 2. Chemical shifts of the functional carbon atom[8] *versus* σ constants[11] of substituents at phenyl ring at the imino nitrogen atom for formamidines: FDM (□), FPM (◇) FOPM (○), FHM (▽), and acetamidines ADM (△)

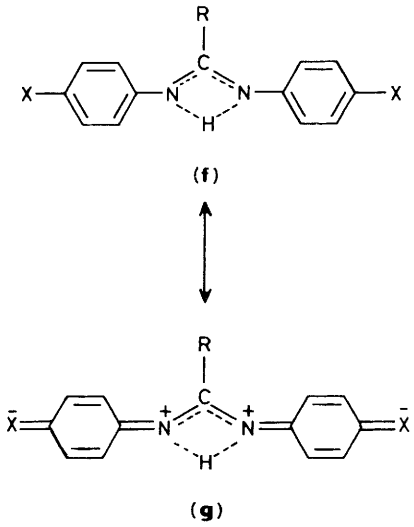
substituents at the phenyl ring on the imino nitrogen atom to be different than for formamidines. The parameters of the equation $\Delta\delta(C_F) = -10\sigma_I - 0.58\sigma_R^+$ (r 0.975) found for acetamidines ADM indicate that the resonance contribution is six times higher than the inductive.

The reactions of acetamidines with 1,3,5-trinitrobenzene, and with 1,3-dinitronaphthalene in which the product of structure (**c**) prevails,[13] are additional confirmation of hyperconjugation by the methyl group at the amidine carbon atom.

For predicting the basicity of tautomeric mixtures of symmetrical *NN'*-disubstituted amidines for which tautomerization is very fast equation (3) can be used in which pK_a° is the

$$pK_a = pK_a^\circ + (\alpha_{Im} + \alpha_{Am})\Delta pK_a\ (PA) \qquad (3)$$

pK_a of the *NN'*-diphenylamidine as mentioned in ref. 9. The sum of α_{Im} and α_{Am} values obtained is the same for acetamidines (0.99 ± 0.04) and formamidines (0.99 ± 0.03). It means that the sensitivity of the amidine group to substitution at both nitrogen atoms in tautomerizing symmetrical *NN'*-disubstituted formamidines and acetamidines is the same as in primary amines, and thus their $\Delta pK_a = \Delta pK_a$ (PA). Moreover the interaction of the substituent with the reaction centre is possible. Electron-withdrawing substituents at the nitrogen atoms in amidines can conjugate with the amidine system, and the conjugation effect produces a similar formation of charge and variation of electron configuration on the nitrogen atoms as for amines.



The parameters α_{Im} and α_{Am} can be treated as some kind of transmission factor denoted by π.[14] In the case of symmetrical *NN'*-disubstituted formamidines and acetamidines it can be assumed that the transmission of the polar effect of substituents at nitrogen atoms for protonation of amino and amidino groups (**f**) are similar.

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