Amidines. Part 30.[1] Influence of Substitution at Amino Nitrogen Atom on pK_a Values of N^2-Phenylacetamidines and N^2-Phenylformamidines

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A series of N^2-phenylacetamidines and N^2-phenylformamidines (22 compounds) containing variable substituents at amino nitrogen atom have been synthesized, and their pK_a values in 95.6% ethanol (azeotrope) measured. The pK_a values obtained for N^1-methyl-N^1,N^2-diphenylacetamidines were correlated with Hammett type constants. Applicability of various σ values is discussed and it is shown that for substituents on the phenyl ring at amino nitrogen atom σ^0 values should be used. It is also shown that the pK_a values of amidines correlate well with the pK_a values of corresponding secondary amines, and that this correlation can serve in the prediction of the pK_a of amidine.

Comparison of the correlations obtained for studied acetamidines and formamidines indicates that sensitivity of the amidino group to substitution at the amino nitrogen atom depends to a certain degree on the substituent at the functional carbon atom.

The basicity of compounds containing the amidine $-N=\overset{|}{C}-N<$ group depends on the substitution at the three sites: at the functional carbon atom and at both nitrogen atoms. It was previously known that the pK_a values of amidines containing substituted phenyl ring at the functional carbon atom[2–5] or at the imino nitrogen atom[1,5–11] obey the Hammett equation (1).

$$pK_a = pK_a^0 - \rho\sigma \qquad (1)$$

In the search for more general relationships which will enable prediction of pK_a for any amidine it was found recently that the pK_a values of amidines containing any substituent R^x, alkyl, aryl, or aralkyl at the imino nitrogen atom, can be correlated [equation (2)] with the pK_a values of corresponding primary amines R_xNH_2 (PA) measured in the same conditions.[5,11,12]

$$pK_a(\text{amidine}) = \alpha\, pK_a(\text{PA}) + \beta \qquad (2)$$

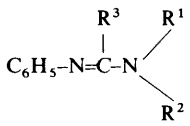
Preliminary results[13] obtained for a series of trisubstituted formamidines (C_6H_5–N=CH–NR^1R^2) containing variable substituents at the amino nitrogen atom indicated that their pK_a values can be correlated [equation (3)] with the pK_a of corresponding secondary amines R^1R^2NH (SA).

$$pK_a(\text{amidine}) = \alpha\, pK_a(\text{SA}) + \beta \qquad (3)$$

It has also been shown that the ρ values for substitution at the imino nitrogen atom depends on polar effects of substituent at the amidino carbon atom,[5,11,14] and that for prediction of pK_a values of amidines carrying two substituents, one at the imino nitrogen atom and the second at the functional carbon atom equation (4) is applicable[11] where σ_{Im} and σ_F are substituent constants for the phenyl ring at the imino nitrogen atom and the functional carbon atom respectively.

$$pK_a = pK_a^0 - \rho_{Im}\sigma_{Im} - \rho_F\sigma_F - \mu\sigma_{Im}\sigma_F \qquad (4)$$

Good correlations of pK_a values with σ constants obtained for symmetrically N,N^2-disubstituted amidines[1,15] indicate that amidines containing a substituted phenyl ring at the amino nitrogen atom should also obey the Hammett equation, but ρ values obtained for propionamidines[1] and acetamidines[1] led to the conclusion, that the influence of substituent at the amidino carbon atom on the ρ_{Am} value is different from that on the ρ_{Im} value.



$R^3 = CH_3$: N^2-phenylacetamidines (A2Ph)
$R^3 = H$: N^2-phenylformamidines (F2Ph)

R^1	R^2	(A2Ph)	(F2Ph)	R^1R^2NH
CH_3	p-C_6H_4–NO_2	(1)	—	(23)
CH_3	m-C_6H_4–NO_2	(2)	—	(24)
CH_3	m-C_6H_4–Cl	(3)	(13)	(25)
CH_3	p-C_6H_4–Cl	(4)	(14)	(26)
CH_3	C_6H_5	(5)	(15)	(27)
CH_3	p-C_6H_4–Me	(6)	(16)	(28)
CH_3	p-C_6H_4–OMe	(7)	(17)	(29)
CH_3	p-C_6H_4–OEt	(8)	(18)	(30)
CH_3	$CH_2C_6H_5$	(9)	(19)	(31)
–$(CH_2)_2$–O–$(CH_2)_2$–		(10)	(20)	(32)
–$(CH_2)_5$–		(11)	(21)	(33)
–$(CH_2)_4$–		(12)	(22)	(34)

Thus, the questions arose as to what extent the ρ and α values for substitution at amino nitrogen atom depend on polar effects of substituent at the amidino carbon atom, and whether the relation (3) can be applied to every series of amidines containing any substituents at the amino nitrogen atom.

Therefore for the present work we synthesized the series of N^2-phenylacetamidines (A2Ph) containing various substituents at the amino nitrogen atom and measured their pK_a values in 95.6% ethanol. For comparative purposes we have also synthesized some N^2-phenylformamidines (F2Ph) which were not studied previously.[13]

Experimental

Amidines.—The N^1-methyl-N^1,N^2-diphenylacetamidines and N^1-methyl-N^1,N^2-diphenylformamidines were synthesized from N-phenylacetimidoyl or N-phenylformimidoyl chloride respectively and the corresponding secondary amines by analogy to the known procedure.[16]

Some of the compounds have been described previously [(**3**), (**5**), (**6**), and (**7**);[17] (**15**), (**17**), (**18**), (**20**), (**21**), and (**22**)[13]]. The structures of unreported compounds were confirmed by ^1H NMR spectra recorded at 80 MHz for $CDCl_3$ solutions at room temperature. Chemical shifts are in good agreement with additivity parameters derived by us for amidines,[18] and the number of protons in each group is consistent with the structures assigned.

Purity of Acetamidines.—The amidines studied were over 95% pure, and free of unchanged amines, only starting amides were detected as the impurities.

Purity was checked by GLC on a 1 m column packed with 15% silicone gum rubber GE SE-30 on Chromosorb WAW 60–80 mesh.

Analyses were made at 280 °C using nitrogen at flow rate 25 $cm^3\ min^{-1}$, and a flame ionization detector. Retention indices of amidines are given elsewhere.[19]

pK_a Measurements.—The pK_a values were determined by potentiometric titration in 95.6% ethanol at 25.0 ± 0.1 °C using Mera ELWRO model N517 pH-meter and combined glass electrode type ERH-11. For the sake of higher stability the electrode was left for at least 24 h in 0.15 mol dm^{-3} solution of HCl in ethanol before use. After every 20 measurements the electrode was refilled with a fresh solution of tetramethylammonium chloride in 95.6% ethanol. The titrant was prepared by saturation of 95.6% ethanol with dry gaseous HCl until the required concentration (0.15 mol dm^{-3}) was attained and standardized by potentiometric titration of Na_2CO_3 samples.

The measurement procedure applied in previous papers[1,5,11] was considerably modified in order to increase the precision of the determination. The whole titration procedure (addition of the titrant, data collection, calculations and corrections) was controlled by means of a microcomputer connected 'on-line' to the pH-meter and dispenser, and operated by a program designed in our laboratory for that purpose.

Samples of the base investigated (0.15 mmol) dissolved in a solution of tetramethylammonium chloride in ethanol (15 cm^3; 0.01 mol dm^{-3}) were titrated with an ethanolic solution of HCl (0.15 mol dm^{-3}) while the sample was mixed by the flow of dry nitrogen (freed from acidic impurities such as CO_2 by being passed through NaOH). The titrant was added in 40 mm^3 portions by means of the dispenser (UNIPAN, model 344A) at a rate of about 5–6 injections per min. The pH-meter indications were recorded after their stabilization up to 0.01 pH units (about 10 s after each addition of the titrant). Each addition of the titrant was done immediately after the pH read-out. Total time of titration did not exceed 7 min. Short titration times enabled us to diminish errors caused by the solvolysis of amidine.

For each titration 25–40 experimental points were accumulated. The end-point was found by means of the maximum of the second derivative of the titration curve.

The pK_a values were determined by fitting the parameters of equation (5) to the points of experimental titration curve contained between 0.2 and 0.8 neutralization degree (plateau, 15–25 points) by the method of simplexes.[20] Iterations were made up to a step of 0.005 pK units.

$$pH_j = pK_a + \log [x_j/(1 - x_j)] \quad (5)$$

where pH_j are uncorrected pH values indicated by the pH-meter at the x_j degree of neutralization.

Obtained pK_a values were corrected according to the known relation [equation (6)].[21] As the standard for pK_a determination imidazole was used where the pH value is measured at the 1/2

$$pK_{ai} = pH_i - pH_s + pK_{as} \quad (6)$$

neutralization point, pK_{ai} and pK_{as} are the pK_a values of the compound investigated (i) and the standard (s).

As these formulae are obeyed only in the case when, as a result of titration, a well ionizable salt is formed or if titration is carried out in the presence of neutral and completely dissociated salt in sufficient concentration,[21] tetramethylammonium chloride was added to the titrated samples.

The pK_a values were determined for two identical samples of each compound. Prior to and after every two measurements the standard solution of imidazole was titrated to check the accuracy of the results.

Obtained pK_a values close to the pK_a value of the solvent itself (in this case about 2.3) require correction for concentration of H^+ ions formed as a result of solvent autoprotolysis.[22,23] Therefore, for compounds where the apparent pK_a values were below 3.5, the real pK_a values were calculated by use of equation (7) where pK_a^B and pK_a^A are the pK_a values of the titrated base (B) and standard (A). $[SH^+]_B$ and $[SH^+]_A$ are the concentrations of solvated protons in solution of titrated base or standard respectively. c_B and c_A are the starting concentrations of titrated base and standard, V_0 is the starting volume of titrated solution, V is the volume of added titrant, x is the titration degree, and K_S is a solvent autoprotolysis constant.

$$pK_a^B - pK_a^A = \log \left\{ \frac{[SH^+]_A^2 c_A V(1-x) - [SH^+]_A(K_S - [SH^+]_A^2)(V_0 + V)}{[SH^+]_B^2 c_B V(1-x) - [SH^+]_B(K_S - [SH^+]_B^2)(V_0 + V)} \cdot \frac{(K_S - [SH^+]_B^2)(V_0 + V) + c_B V_0 x [SH^+]_B}{(K_S - [SH^+]_A^2)(V_0 + V) + c_A V_0 x [SH^+]_A} \right\} \quad (7)$$

Obtained pK_a values with confidence intervals at a significance level of 0.05 are summarized in Table 1.

Discussion of Errors.—The error of potentiometric titration using this procedure as estimated should not exceed 0.05 pK_a units. Errors caused by the ionic strength changes from μ = 0.01 to 0.018 occurring during titration are much smaller and can be neglected. Determined pK_a values may include a systematic error contributed by the pK_a value of the standard (imidazole) but, on account of its constancy, it has no influence on the regression coefficients.

Results and Discussion

Linear Correlations with σ Constants.—In any investigation of relationships between the structure and properties of organic compounds the proper choice of σ constants is crucial. As previously discussed[14] for the case of amidines containing variable substituents at the phenyl ring on either of the nitrogen atoms the most suitable should be the σ^0 values[24,25] while ordinary σ values[26] are suitable only for substituents on the phenyl ring at the functional carbon atom. However pK_a values have also been correlated with ordinary σ values in papers concerning the basicity of amidines.[3,4,7,8]

We have compared correlations of pK_a values of acetamidines (A2Ph) and formamidines (F2Ph) with both σ, as well as σ^0 values. The parameters of the regressions (Table 2) indicate that correlations with σ^0 values are, indeed of higher quality, however, correlations with σ values are still satisfactory, as indicated by the correlation coefficient r and Exner's[27] ψ function.

The ρ values for substitution at the amino nitrogen atom, (acetamidines 1.44 ± 0.05 and formamidines 0.84 ± 0.20) are,

Table 1. pK_a[a] values of N^1-methyl-N^1,N^2-diphenylacetamidines (A2Ph), N^1-methyl-N^1,N^2-diphenylformamidines (F2Ph), and secondary amines (SA) in 95.6% ethanol at (25 + 0.1) °C.[a]

Compound	A2Ph	Compound	F2Ph	Compound	SA
(1)	5.83 ± 0.09	–	–	(23)	*d*
(2)	6.00 ± 0.09	–	–	(24)	*d*
(3)	6.52 ± 0.04	(13)	5.00 ± 0.04	(25)	*d*
(4)	6.68 ± 0.02	(14)	5.15 ± 0.03	(26)	2.42 ± 0.04[c]
(5)	7.00 ± 0.02	(15)	5.29 ± 0.05[b]	(27)	2.99 ± 0.01[c]
(6)	7.22 ± 0.02	(16)	5.46 ± 0.03	(28)	3.96 ± 0.02
(7)	7.37 ± 0.03	(17)	5.50 ± 0.06[b]	(29)	4.47 ± 0.02
(8)	7.34 ± 0.03	(18)	5.72 ± 0.06[b]	(30)	3.89 ± 0.02
(9)	9.83 ± 0.02	(19)	7.07 ± 0.01	(31)	7.99 ± 0.03
(10)	9.25 ± 0.03	(20)	6.57 ± 0.05[b]	(32)	7.06 ± 0.04
(11)	10.50 ± 0.04	(21)	7.42 ± 0.03[b]	(33)	8.95 ± 0.02
(12)	10.60 ± 0.03	(22)	8.12 ± 0.04[b]	(34)	9.20 ± 0.03

[a] Measured at ionic strength $\mu = 0.01$; [b] According to ref. 13; [c] Corrected (see text); [d] Below the pK_a of the solvent.

Table 2. Parameters of regressions[a] with substituent constants [equation (1)]

Series		pK_a	ρ	r	ψ	n
A2Ph	σ	7.00	1.43 ± 0.08	0.9986	0.0616	8
A2Ph	σ^0	7.02	1.44 ± 0.05	0.9994	0.0401	8
F2Ph	σ	5.31	0.78 ± 0.14	0.9954	0.1233	5
F2Ph	σ^0	5.32	0.84 ± 0.20	0.9917	0.1665	5

[a] At a confidence level of 0.95.

Table 3. Parameters of regressions[a] of pK_a values of amidines with pK_a of corresponding amines [equation (4)].

Series	*vs.*	pK_a^0	α	r	ψ	n
A2Ph	SA	6.81	0.60 ± 0.06	0.994	0.121	9
F2Ph	SA	5.19	0.40 ± 0.08	0.975	0.255	9

[a] At a confidence level of 0.95.

as expected, lower than those for imino nitrogen atom substitution (N^1,N^1-dimethylacetamidines[14] 3.08 ± 0.27 and N^1,N^1-dimethylformamidines[14] 2.60 ± 0.28), because in this case substituents are at a greater distance from the imino nitrogen atom being the protonation centre.

The ρ_{Am} value obtained for acetamidines (A2Ph) can be compared with the ρ_{Am} value of formamidines (F2Ph). The test of parallelism for regression lines calculated for amidines containing the same set of substituents in both series disclose, that the slopes of regression lines are undoubtedly different.

Differences between the ρ values evidently show that the substituent at the functional carbon atom also exerts an influence on the sensitivity of the amidine group to substitution at the amino nitrogen atom. This influence on both nitrogen atoms is not the same, as indicated by the ratio $\rho_{Im}:\rho_{Am} = 2.13$ in the case of acetamidines and 3.12 in the case of formamidines.

This difference is even more evident from comparison of the ρ values for each nitrogen atom. Replacement of a hydrogen atom at the functional carbon atom by a methyl group (acetamidines *vs.* formamidines) causes 1.7-fold increase of the ρ_{Am} value, but only 1.2-fold increase of the ρ_{Im} value.

The results obtained lead to the conclusion that for the prediction of the pK_a values of amidines in series containing two variable substituents, one at the amino nitrogen atom and the second at the functional carbon atom, an equation similar to (4) containing the additional term μ should probably be used.

Linear Correlations with pK_a Values of Amines.—Additional evidence is provided by correlations with the pK_a values of corresponding secondary amines obtained for extended series of acetamidines and formamidines containing alkyl and aralkyl substituents. Such correlations are of higher diagnostic value because the range of considered pK_a values is twice as large as that with substituted anilines.

We have found it convenient to modify equation (3) used in previous paper.[13] In equation (8) the term pK_a now has the same meaning as in the Hammett equation.

$$pK_a(\text{amidine}) = pK_a + \alpha[pK_a(\text{amine}) - pK_a(N\text{-methylaniline})] \quad (8)$$

Parameters of this equation for the series studied are summarized in Table 3. It can be seen that the α_{Am} value also depends on substitution at the amidino carbon atom, for A2Ph series it is considerably higher than for F2Ph.

In correlations with the pK_a values of amines the α_{Am} values are also more susceptible to polar effects of substituents at the amidino carbon atom than the α_{Im} values as is shown by the change in the ratio $\alpha_{Im}:\alpha_{Am}$, for acetamidines: 1.27 and formamidines: 1.55.

As the equations derived here are of good predictive value they provide strong support for an earlier assumption[13] that the pK_a values of trisubstituted amidines of any kind may be predicted on the basis of the pK_a values of the two corresponding amines. The most important advantage of such a treatment is that both amines are used in the synthesis of amidine and are thus usually available.

The question remains concerning the quantitative relationship between the constant of a substituent at the amidino carbon atom and the ρ_{Am} and α_{Am} values; further studies on the appropriate series of compounds are required.

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