Amidines. Part 13.[1] Influence of Substitution at Imino Nitrogen Atom on pK_a Values of N^1N^1-Dimethylacetamidines

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20 N^1N^1-Dimethylacetamidines containing alkyl, aralkyl, or substituted phenyl groups have been synthesized, and their pK_a values in 95.6% ethanol (azeotrope) measured. The pK_a values obtained were correlated with Hammett σ constants. The applicability of various σ values is discussed, and it is shown that for substituents at nitrogen σ° values should be used. It has also been shown that the pK_a values of amidines correlate well with the pK_a values of corresponding primary amines, and that this correlation can serve for the prediction of the pK_a of amidine. Comparison of the correlations for N^1N^1-dimethylacetamidines with those for N^1N^1-dimethylformamidines indicate that sensitivity of the amidine group to substitution at the imino nitrogen atom depends to a considerable degree on substitution at a functional carbon atom.

Although it is well known that amidines are strong bases and that their basicity depends on substitution at both the functional carbon atom and the nitrogen atoms, investigations on the quantitative relations between substitution and basicity are few. The imino nitrogen atom is the protonation site of the amidine group; therefore it might be expected that the strongest effect of substitution on basicity will be observed for this atom. Until the last decade, however, only papers dealing with substitution at the functional carbon atoms have been published.[2] [4] More recently several papers on amidines containing a substituted phenyl ring at the imino nitrogen atom have appeared.[5] [10] In all these papers it was shown that the pK_a values of amidines can be correlated with Hammett σ constants.

We have shown that amidines containing a substituted phenyl ring at the amino nitrogen atom also obey the Hammett equation,[11,12] and the assumption has been made that in the case of NN'-diphenylbenzamidines containing three substituents (one at each phenyl ring) equation (1) can be applied

$$pK_a = pK_a° - \rho_{Im}\sigma_{Im} - \rho_{Am}\sigma_{Am} - \rho_F\sigma_F \qquad (1)$$

where σ_{Im}, σ_{Am}, and σ_F are the σ constants of substituents in the phenyl rings at the imino and amino nitrogen atoms, and at the functional carbon atom, respectively.

Preliminary results obtained for several series of amidines indicated that the ρ value may depend to some extent on substitution at other sites, and thus that in this regression some additional expression depending on the character of the substituent has to be introduced.[13]

In the search for a more general relation enabling predictions of the pK_a of 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 with the pK_a values of corresponding primary amines R_xNH_2 measured in the same conditions.[1,14,15]

$$pK_{a_{amidine}} = \alpha pK_{a_{amine}} + \beta \qquad (2)$$

Thus the question arises whether the basicity of all amidines can be predicted with satisfactory accuracy on the basis of the basicity of analogous model compounds, or better on the basis of substituent constants expressed on one uniform scale, common to both substituted phenyl rings, as well as for other substituents such as alkyl or aralkyl attached to a certain atom instead of a substituted phenyl ring. None of the above hypotheses could be verified on the basis of the literature data because the reported pK_a values of amidines of different series
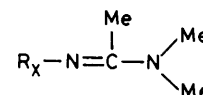
(1)	$R_X = p-C_6H_4NO_2$	(11)	$R_X = p- C_6H_4OEt$
(2)	$R_X = m-C_6H_4Br$	(12)	$R_X = p- C_6H_4OMe$
(3)	$R_X = m-C_6H_4Cl$	(13)	$R_X = p- CH_2C_6H_4Cl$
(4)	$R_X = p-C_6H_4Br$	(14)	$R_X = COPh$
(5)	$R_X = p-C_6H_4Cl$	(15)	$R_X = Bu^i$
(6)	$R_X = m-C_6H_4OMe$	(16)	$R_X = n-C_6H_{13}$
(7)	$R_X = m-C_6H_4OEt$	(17)	$R_X = Bu^n$
(8)	$R_X = Ph$	(18)	$R_X = Pr^n$
(9)	$R_X = m-C_6H_4Me$	(19)	$R_X = cyclo-C_6H_{11}$
(10)	$R_X = p-C_6H_4Me$	(20)	$R_X = Pr^i$

were measured in various solvents, *i.e.* in water,[3,7,9] in 50% ethanol,[6,8] absolute ethanol,[10-14] 50% methanol,[2] and acetonitrile.[4] It is well known that the ρ value depends to a considerable degree on the solvent.[2]

For the above reasons acquisition of pK_a values of differently substituted amidines measured under standard identical conditions appeared to be necessary. We report here the synthesis of a series of N^1N^1-dimethylacetamidines (ADM), (1)—(20) and measurements of their pK_a values in 95.6% ethanol.

Experimental

Acetamidines.—The N^1N^1-dimethylacetamidines were synthesized by Scoogins'[16] procedure by heating equimolar amounts (0.05 mol) of a primary amine with dimethylacetamide dimethyl acetal[17] for 10—20 min at 60 °C. The amidines, except for the nitro-derivatives, after evaporation of the methanol, were distilled under reduced pressure. Their b.p.s are summarized in Table 1. The yields were *ca.* 100% for aliphatic amidines and over 90% for aromatic ones. Their structures were confirmed by ¹H n.m.r. spectra recorded at 80 MHz for CDCl₃ solutions at room temperature. The numbers of protons in each group are consistent with the structures assigned. Chemical shifts are summarized in Table 1.

Purity of Acetamidines.—The dimethylacetamidines were >99% pure, and free of unchanged amines. Their purity was

Table 1. Characterization of acetamidines ADM

Compound	Formula	B.p. (°C)/p(mmHg)	$-NMe_2$	$\geqslant C-Me$	2-H	6-H	3-H	5-H	4-H	Me
							Phenyl ring at N_{lm}			
(1)	$C_{10}H_{13}N_3O_2$	a	3.03	1.93	6.72			8.05		
(2)	$C_{10}H_{13}BrN_2$	170—174/18	2.98	1.83	6.85	6.58[b]		7.06	7.00	
(3)	$C_{10}H_{13}ClN_2$	158—160/17[c]	2.97	1.84	6.70	6.56		7.08	6.86	
(4)	$C_{10}H_{13}BrN_2$	168—176/18	2.98	1.83	6.58			7.30		
(5)	$C_{10}H_{13}ClN_2$	160—163/17[d]	2.99	1.84	6.61			7.15		
(6)	$C_{11}H_{16}N_2O$	160—168/18	2.90	1.80	62.0[b]	6.20[b]		7.03	6.41	3.68
(7)	$C_{12}H_{18}N_2O$	170—176/17	2.92	1.81	6.20[b]	6.21[b]		7.03	6.42	1.32[e]
(8)	$C_{10}H_{14}N_2$	134/15[f]	2.99	1.84	6.70			7.20	6.94	
(9)	$C_{11}H_{16}N_2$	144/17	2.96	1.83	6.54	6.50		7.09	6.74	2.29
(10)	$C_{11}H_{16}N_2$	144—146/17[g]	2.98	1.83	6.58			6.99		2.27
(11)	$C_{12}H_{18}N_2O$	176/17	2.98	1.83	6.58			6.76		1.36[h]
(12)	$C_{11}H_{16}N_2O$	166/15[i]	2.97	1.83	6.60			6.77		3.73
					$=N-CH_2-$			Ph		
(13)	$C_{11}H_{15}ClN_2$	172—174/18	2.91	1.88	4.43			7.23		
(14)	$C_{11}H_{16}N_2$	136—137/14	2.93	1.89	4.49			7.28		
					H_α			H_β		H_γ
(15)	$C_8H_{18}N_2$	60/40	2.84	1.86	3.01			1.98		0.98
(16)	$C_{10}H_{22}N_2$	125/30	2.84	1.86	3.18			1.34		0.89
(17)	$C_8H_{18}N_2$	62/30	2.84	1.85	3.20			1.44		0.94
(18)	$C_7H_{16}N_2$	35/30	2.88	1.89	3.18			1.49		0.99
(19)	$C_{10}H_{20}N_2$	82—84/14	2.83	1.85	2.83			1.20—1.70		
(20)	$C_7H_{16}N_2$	46/40	2.85	1.85	j			1.06		

[a] M.p. 93—94 °C; ref. 9, 95—97 °C. [b] ±0.05. [c] Ref. 18, 96—97/0.28. [d] Ref. 9, 110—112/1. [e] Ethoxy group, $-CH_2-$, 3.94. [f] Ref. 9, 86/0.5; ref. 19, 75—76/0.005; ref. 20, 125—130/3. [g] Ref. 9, 88—90/0.6. [h] Ethoxy group, $-CH_2-$, 3.98. [i] Ref. 9, m.p. 30—32. [j] Undetectable.

Table 2. pK_a values of N^2-substituted N^1N^1-dimethylacetamidines (ADM) in 95.6% EtOH at (25 ± 0.1) °C *

Compound	pK_a	Compound	pK_a
(1)	5.69 ± 0.02	(11)	8.90 ± 0.05
(2)	7.19 ± 0.02	(12)	8.96 ± 0.08
(3)	7.25 ± 0.04	(13)	11.24 ± 0.05
(4)	7.55 ± 0.04	(14)	11.70 ± 0.05
(5)	7.65 ± 0.04	(15)	12.30 ± 0.05
(6)	8.22 ± 0.06	(16)	12.37 ± 0.07
(7)	8.26 ± 0.06	(17)	12.34 ± 0.05
(8)	8.32 ± 0.07	(18)	12.46 ± 0.07
(9)	8.41 ± 0.06	(19)	12.55 ± 0.07
(10)	8.65 ± 0.06	(20)	12.56 ± 0.05

* At ionic strength μ 0.01, using imidazole pK_a 5.95 ± 0.1 as standard.

checked by g.l.c. on a 3 m column packed with 15% silicone gum rubber GE-SE-30 on Chromosorb WAW 60—80 mesh. Analyses were made at 240 °C using nitrogen at flow rate 20 cm^3 min^{-1}, and a flame ionization detector. Retention indices of amidines and amines are given elsewhere.[21]

pK_a *Measurements.*—The pK_a values were determined by a potentiometric method from relation (3)[22] where pK_{a_i} and pK_{a_s}

$$pK_{a_i} = pH_{x_i} - pH_{x_s} + pK_{a_s} \qquad (3)$$

are the pK_a values of the compound investigated (i), and the standard (s), and pH_x are pH indications of a pH-meter at $x = \frac{1}{4}, \frac{1}{2}$, and $\frac{3}{4}$ neutralization points. As this formula is obeyed only when a well ionizable salt is formed, or if titration is carried out in the presence of neutral and completely dissociated salt in sufficient concentration, tetramethylammonium chloride was added to titration samples. Experimental details and apparatus were described in previous papers.[1,15] The glass electrode was kept for at least 24 h in the solvent before measurements, and was not used in other solvents during the measurements. As the standard, imidazole was used.[15] The pK_a values and calculated accuracy limits at confidence level of 0.95 are summarized in Table 2.

The error in the pK_a determination as discussed previously[15] does not exceed 0.05 pK_a units. The pK_a values may include a systematic error of ca. 0.1 pK_a unit contributed by the pK_a value of used standard (imidazole), but on account of its constancy it has no influence on the slope of regression lines.

Results and Discussion

Measurements Conditions.—The high reproducibility of pK_a determinations is a very important aspect of investigations of structure–basicity relations. Therefore as the most suitable standard solvent we have considered 95.6% ethanol,[15] because as the azeotrope it always contains the same amount of water, and in consequence it is easy to obtain identical results in different laboratories (not so for absolute alcohols). Moreover, amidines are soluble in it.

The potentiometric method for pK_a was chosen because minute impurities in the samples affect measurements to a much smaller degree than in other methods, and thus ensure better comparability and reproducibility of the results.

Correlations with σ Constants.—It is well known that in any kind of investigation on the relations between structure and properties of organic compounds the proper choice of σ value is crucial. In most papers on the basicity of amidines their pK_a values were correlated with ordinary σ values.[2,4,6-8] Only Passet,[5] for monosubstituted phenylacetamidines, and later Katritzky[9] for N^1N^1-dimethyl-N^2-phenylacetamidines have applied σ° values.

The proper choice of parameters can, however, be achieved

Table 3. Parameters of obtained regressions *

Series	Type of σ	pK_a°	ρ	r	s	n	Solvent	Ref.
ADM	σ°	8.32	3.08 ± 0.27	0.994	0.116	10 }	95.6% Ethanol	This work
	σ	8.29	3.00 ± 0.38	0.984	0.171	12 }		
	σ°	10.20	3.51 ± 0.49	0.993	0.190	7 }	Water	9
	σ	10.10	3.57 ± 0.36	0.996	0.139	7 }		
FDM	σ°	7.46	2.60 ± 0.28	0.990	0.125	11 }	95.6% Ethanol	15
	σ	7.39	2.52 ± 0.40	0.973	0.183	13 }		
	σ°	8.13	2.65 ± 0.25	0.998	0.091	6 }	Water	7
	σ	8.08	2.55 ± 0.22	0.998	0.081	6 }		
BPM	σ°	7.04	2.90 ± 0.38	0.990	0.159	9 }	95.6% Ethanol	1
	σ	7.00	2.66 ± 0.37	0.984	0.162	11 }		
	σ°	6.67	2.70 ± 0.30	0.992	0.128	9 }	50% Ethanol	1
	σ	6.63	2.49 ± 0.32	0.986	0.140	11 }		
	σ°	7.52	2.38 ± 0.73	0.946	0.309	9 }	50% Ethanol	8
	σ	7.45	2.34 ± 0.70	0.948	0.298	9 }		

* At a confidence level of 0.95.

only as a result of consideration of possible interactions of substituents with the reaction centre. In the case of amidines there are three possible sites to which substituent may be bonded, i.e. both nitrogen atoms (N_{Im}, N_{Am}) and the functional carbon atom (C_F).

Substituents on the phenyl ring at the amino nitrogen atom (N^1) cannot conjugate with the reaction centre. Electron-withdrawing substituents at the imino nitrogen atom (N^2) conjugate with the amidine system but as the conjugation effect of the substituent does not produce either charge formation or an electron configuration on the imino nitrogen atom which is the reaction (protonation) centre.
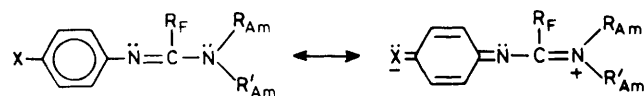

Therefore it seemed reasonable that in the case of amidines containing variable substituents at the phenyl ring on either of the nitrogen atoms the most suitable should be σ°,[23] while ordinary σ values[24] are suitable only for substituents on the phenyl ring of the functional carbon atom.

We have compared correlations of pK_a values with both σ as well as σ° values for dimethylacetamidines (ADM) described here and other amidines studied previously.[1,7,9,15] The parameters of the regressions (Table 3) indicate that correlations with σ° values are indeed of higher quality; however, it must be mentioned that correlations with σ values are still satisfactory and in some cases may be used for predictive purposes.

The ρ values obtained from the pK_a values of N^1N^1-dimethyl-N^2-phenylacetamidines (ADM) can be compared with that of N^1N^1-dimethyl-N^2-phenylformamidines (FDM) measured under the same conditions.[15] The test of parallelism for regression lines calculated for amidines containing the same substituents in both series (compounds with substituents occurring only in one of the series were neglected) disclose, that the slopes of the regression lines are undoubtedly different: ADM, ρ 3.08, r 0.994, s 0.116; FDM, ρ 2.62, r 0.991, s 0.127.

The difference in ρ values leads to the conclusion that the sensitivity of the amidine group to substitution on the phenyl ring at the imino nitrogen atom depends on substitution on the functional carbon atom. This conclusion finds good support from other data. For the same series of acetamidines and formamidines (particular compounds in the series, however, were different) the pK_a values measured in water have already been reported.[7,9] We have correlated these values with σ° constants (Table 3). In this case the slope of the regression line for acetamidines is also higher than for formamidines.
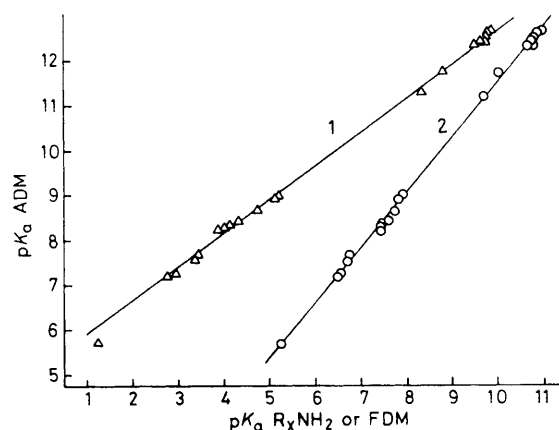
Correlations of pK_a of dimethylacetamidines (ADM) with pK_a of primary amines (R_xNH_2), line 1, and with pK_a of dimethylformamidines (FDM), line 2

Correlations with pK_a of Amines.—Additional evidence is provided by correlations 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, and thus the changes in sensitivity to substitution are more prominent. We have found it convenient to modify the equation used in the previous papers[1,14,15] as mentioned in the Introduction. In this equation the term β corresponded to the pK_a value of the non-existent, theoretical amidine containing the amine, whose pK_a value is equal to zero. The modified equation is in the form (4). In this equation the term pK_a° now has the same meaning as in the Hammett equation, and represents the pK_a of amidine containing as variable substituent R_x the unsubstituted phenyl ring.

$$pK_{a_{amidine}} = pK_{a_{amidine}}^\circ + \alpha_{Im}(pK_{a_{R_xNH_2}} - pK_{a_{PhNH_2}}) \quad (4)$$

For our series the following parameters of the modified equation are obtained:

Series	pK_a°	α_{Im}	r	s	n
ADM	8.18	0.76 ± 0.01	0.999	0.009	20
FDM	7.31	0.62 ± 0.03	0.997	0.012	20

In this case also the α_{Im} value for acetamidines is higher than for formamidines. But the most important and convincing feature is that the ratio of the slopes of the regression lines $\alpha_{ADM} : \alpha_{FDM} = 1.23$ is almost the same as $\rho_{ADM} : \rho_{FDM} = 1.18$. The results indicate that the equations derived here, in spite of some inaccuracies caused by the difference of interactions between substituents and reaction centre in amidines and anilines, are of good predictive value. The most important advantage of this treatment is that amines are used in the synthesis of amidines and are usually available.

The correlation between the pK_a values of ADM with FDM is of a higher quality than with pK_a of primary amines (Figure). However, correlation coefficients r are in both cases the same (0.999). This indicates that much more accurate pK_a predictions could be achieved if the uniform scale of substituent constants, including different types of substituents, was used. Unfortunately, in the literature only separate scales for alkyl substituents (σ^* constants) and for substituted phenyl rings (σ constants) are used.

Our results shed new light on the problem of the correlation of basicity of amidines containing two or more variable substituents at different sites with substituents constants. It is generally accepted that compounds containing several substituents at different sites obey the Hammett equation (5). This

$$\lg(K/K^\circ) = \rho_1\sigma_1 + \rho_2\sigma_2 + \cdots + \rho_n\sigma_n \qquad (5)$$

equation implies that for each series of compounds in which one variable substituent is at a given site the ρ value is identical no matter what kind of substituents are at the other sites, and the constant values $\rho_2\sigma_2 + \cdots + \rho_n\sigma_n$ for each series are included in a new K° value.

The difference between the slopes of the regression lines indicates that the pK_a values of amidines containing two substituents, one at nitrogen atom and the second at the functional carbon atom, do not obey a linear equation but a relationship of the form (6) where the coefficient μ represents

$$\lg(K/K^\circ) = \rho_1\sigma_1 + \rho_2\sigma_2 + \mu\sigma_1\sigma_2 \qquad (6)$$

the mutual interaction of substituents, and is responsible for the 'twist' of the regression line. This type of equation has already been proposed.[7,25-27] In the case of series with only one variable substituent the value $\rho_2\sigma_2$ is included in the K° value, and the observed ρ value (different for each series) is represented by $\rho_1 + \mu\sigma_2$. It seems quite probable that this equation is obeyed by reactions other than protonation of amidines.

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