Amidines. Part 31.[1] pK_a Values of N^1,N^1-Dialkyl-N^2-phenylformamidines in Water–Ethanol Solutions

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The pK_a values of three series (30 compounds in all) of N^1,N^1-dialkyl-N^2-phenylformamidines ($XC_6H_4N{=}CH{-}NRR$) have been measured in water–ethanol mixtures. The obtained pK_a values of the amidines have been correlated with Hammett-type substituent constants and the pK_a values of the corresponding primary amines determined in the same solvent. The applicability of various σ values is discussed and it is shown that, in each case, for substituents on the phenyl ring at the amino nitrogen atom σ° values should be used. It is found that the slopes of regression lines for correlations with Hammett-type constants depend on the substituents at the amino nitrogen atom, as well as on the solvent.

The basicity of compounds containing the amidino $-N{=}\overset{|}{C}-N<$ group is attracting much attention on account of their biological activity[2–4] since it is known that this governs many of the chemical and biological properties of these compounds.

Quantitative relations between the basicity of various series of amidines and their structural parameters have been discussed in several papers. It was shown that the pK_a values of amidines containing a substituted phenyl ring at the functional carbon atom,[5–8] at the imino nitrogen atom[9–16] or at the amino nitrogen atom[1,17–19] obey the Hammett equation (1).

$$\mathrm{p}K_a = \mathrm{p}K_a^\circ - \rho\sigma \qquad (1)$$

It was also found that pK_a values of amidines containing substituents of any kind at either of the two nitrogen atoms correlate with the pK_a values of the corresponding amines.[14–16] For amidines containing variable substituents at the imino nitrogen atom the correlations are in the form of eqn. (2)

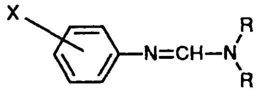
$$\mathrm{p}K_a(\text{amidine}) = \mathrm{p}K_a^\circ + \alpha[\mathrm{p}K_a(\text{amine}) - \mathrm{p}K_a(\text{aniline})] \qquad (2)$$

where the term pK_a° has the same meaning as in the Hammett equation.

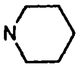
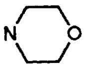
Most of the data were obtained in non-aqueous solvents because all compounds in the series were soluble enough to obtain reliable pK_a values only in these solvents. However, for biologically active compounds the most important consideration is the possibility of predicting their pK_a values in aqueous solutions. Thus the question arose of how far the relations obtained for non-aqueous solvents can be applied for this purpose.

It is well known that the ρ value depends on the structure of compound and on the solvent. But in the case of the pentamethylenebenzamidine[20] series containing variable substituents at the imino nitrogen atom it was found that the α values [eqn. (2)] in 98.5% and in 50% aqueous ethanol were almost the same. Thus it seemed that the α value may be approximately constant also for other series of amidines and that this correlation may be applied for prediction of the pK_a values of amidines in one solvent on the basis of the α values measured in another. As this could afford a way to predict pK_a values in aqueous solutions on the basis of pK_a values in ethanol we thought it necessary to find out whether the α values are approximately the same for other series of amidines and for other solvents.

Table 1 Compounds investigated



FDM	FPM	FOPM	X
1	**15**	**23**	*p*-NO_2
2			*m*-NO_2
3			*m*-Br
4	**16**	**24**	*m*-Cl
5			*p*-I
6			*p*-Br
7	**17**	**25**	*p*-Cl
8	**18**	**26**	*m*-OMe
9			*m*-OEt
10	**19**	**27**	H
11	**20**	**28**	*m*-Me
12	**21**	**29**	*p*-Me
13			*p*-OEt
14	**22**	**30**	*p*-OMe

NRR	Series
NMe_2	N^1,N^1-Dimethyl-N^2-phenylformamidines (FDM)
	N^1,N^1-Pentamethylene-N^2-phenylformamidines (FPM)
	N^1,N^1-(3-Oxa-pentamethylene)-N^2-phenylformamidines (FOPM)

Therefore we have undertaken an investigation on the dependence of correlation parameters [eqns. (1) and (2)] on the solvent. In this work we have synthesized three series of N^1,N^1-dialkyl-N^2-phenylformamidines containing various substituents on the phenyl ring at the imino nitrogen atom and measured their pK_a values in ethanol–water mixtures.

Experimental

Synthesis of Formamidines.—The studied N^1,N^1-dialkylformamidines (Table 1) were obtained in our laboratory by heating equimolar amounts of dimethylformamide dimethylacetal, *N*-formylpiperidine dimethylacetal, or *N*-formylmorpholine dimethylacetal, respectively, with the appropriate primary amine accordingly to Scoggins' procedure.[21]

Table 2 pK_a values of N^1,N^1-dimethyl-N^2-phenylformamidines (FDM) in binary ethanol–water solutions[a,b] at (25 ± 0.1) °C

Compound	Ethanol (w/w%) in the binary mixture			
	80	50	30	0
1	4.88 ± 0.01	5.81 ± 0.05	6.32 ± 0.06	6.71 ± 0.03
2	5.12 ± 0.01	6.04 ± 0.01	6.94 ± 0.06	7.29 ± 0.03
3	6.05 ± 0.01	7.04 ± 0.04	7.60 ± 0.05	8.08 ± 0.04
4	6.07 ± 0.02	6.95 ± 0.06	7.58 ± 0.05	7.97 ± 0.02
5	6.36 ± 0.02	7.18 ± 0.02	7.84 ± 0.04	—
6	6.38 ± 0.01	7.27 ± 0.03	7.91 ± 0.06	8.10 ± 0.02
7	6.37 ± 0.02	7.37 ± 0.02	7.89 ± 0.02	8.46 ± 0.03
8	7.01 ± 0.02	7.56 ± 0.04	8.31 ± 0.05	8.60 ± 0.03
9	7.06 ± 0.01	7.75 ± 0.04	8.46 ± 0.03	8.87 ± 0.04
10	7.19 ± 0.08	7.59 ± 0.02	8.66 ± 0.08	9.00 ± 0.07
11	7.22 ± 0.02	8.07 ± 0.02	8.65 ± 0.02	9.11 ± 0.03
12	7.40 ± 0.02	8.15 ± 0.04	8.78 ± 0.01	9.21 ± 0.02
13	7.43 ± 0.01	8.22 ± 0.02	8.74 ± 0.02	9.24 ± 0.04
14	7.47 ± 0.01	8.25 ± 0.02	8.83 ± 0.06	9.35 ± 0.05

[a] At ionic strength μ = 0.01; using imidazole[1] (pK_a: 6.26 for 95.6%; 5.98 for 80%; 6.45 for 50%; 6.8 for 30%; 7.15 for 0%) as a standard. [b] pK_a values in 95.6% ethanol are given in ref. 19.

Table 3 pK_a values of N^1,N^1-pentamethylene-N^2-phenylformamidines (FPM) in binary ethanol–water solutions[a] at (25 ± 0.1) °C

Compound	Ethanol (w/w%) in the binary mixture			
	95.6	80	50	30
15	5.83 ± 0.03	4.85 ± 0.05	5.78 ± 0.03	—
16	6.83 ± 0.02	5.93 ± 0.02	6.85 ± 0.01	7.47 ± 0.04
17	7.14 ± 0.03	6.37 ± 0.03	7.16 ± 0.01	7.76 ± 0.05
18	7.75 ± 0.02	6.95 ± 0.01	7.66 ± 0.02	8.07 ± 0.07
19	7.83 ± 0.02	7.06 ± 0.02	7.86 ± 0.07	—
20	7.91 ± 0.02	7.15 ± 0.03	7.91 ± 0.02	8.40 ± 0.08
21	8.08 ± 0.03	7.38 ± 0.04	8.13 ± 0.07	—
22	8.25 ± 0.03	7.56 ± 0.05	8.17 ± 0.03	—

[a] *cf.* Footnotes to Table 2.

Table 4 pK_a values of N^1,N^1(3-oxapentamethylene)-N^2-phenylformamidines (FOPM) in binary ethanol–water solutions[a] at (25 ± 0.1) °C

Compound	Ethanol (w/w%) in the binary mixture			
	95.6	80	50	30
23	5.67 ± 0.05	4.45 ± 0.01	4.97 ± 0.05	—
24	5.99 ± 0.04	5.14 ± 0.02	5.92 ± 0.03	6.51 ± 0.05
25	6.27 ± 0.03	5.55 ± 0.04	6.39 ± 0.08	6.92 ± 0.04
26	6.77 ± 0.02	5.95 ± 0.01	6.86 ± 0.02	7.16 ± 0.02
27	6.76 ± 0.01	6.09 ± 0.02	6.96 ± 0.04	—
28	6.99 ± 0.03	6.17 ± 0.03	7.02 ± 0.02	7.48 ± 0.03
29	7.02 ± 0.01	6.31 ± 0.01	7.10 ± 0.02	—
30	7.07 ± 0.03	6.34 ± 0.03	7.12 ± 0.03	—

[a] *cf.* Footnotes to Table 2.

Structure and Purity of Formamidines.—Most of the compounds have been described previously.[22] The structures of unreported compounds were confirmed by their ^{1}H NMR spectra (80 MHz; CDCl$_3$; room temperature). Chemical shifts in the ^{1}H NMR spectra are in good agreement with additivity parameters derived earlier for amidines,[23] and the numbers of protons in each group are consistent with the structures assigned.

The amidines were over 95% pure, and free of unchanged amines, as determined by gas chromatography. Only starting amides were detected as impurities. Purity was checked by a GLC method 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 a flow rate of 25 cm^3 min^{-1} and a flame ionization detector. Retention indices of amidines are given elsewhere.[24] Additional evidence of purity was provided by the titration volumes and the shapes of the titration curves, as there is considerable difference in the pK_a values between each amidine and the corresponding amine.

pK_a *Measurements.*—The detailed measurement procedure, as well as precautions ensuring the reproducibility of the obtained results, are given in preceding papers.[1,15]

Obtained pK_a values were corrected according to the known relation[25] [eqn. (3)] where the pH value is measured at the $\frac{1}{2}$ neutralization point, pK_{a_i} and pK_{a_s} are the pK_a values of the compound investigated (i) and the standard (s).

$$\mathrm{p}K_{a_i} = \mathrm{p}H_i - \mathrm{pH}_s + \mathrm{p}K_{a_s} \qquad (3)$$

As the standard for pK_a determination, imidazole was used because its pK_a values in water–ethanol mixtures were known.[26] The obtained pK_a values with confidence intervals calculated at a significance level of 0.05 are summarized in Tables 2–4.

The pK_a values in aqueous solutions for N^1,N^1-pentamethylene- and for N^1,N^1-(3-oxapentamethylene)-N^2-phenylformamidines (FPM and FOPM series) were not determined because their solubility in water is too low for potentiometric determinations.

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 change 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 values of the standard (imidazole) in water–ethanol mixtures but, on account of its constant value, it has no influence on the regression coefficients.

Results and Discussion

Linear Correlations with σ Constants.—It was previously shown[1,15,16] that, in the case of amidines containing variable substituents at the phenyl ring on either nitrogen atom, the most suitable should be the σ° values[27,28] while ordinary σ values[29] are suitable only for substituents on the phenyl ring at the functional carbon atom. In the literature, however, ordinary σ values were applied for substitution at the imino nitrogen atom.[11,12,30] We have compared correlations of pK_a values of all studied formamidines with both σ and σ° values. As the correlation line seldom goes through all experimental points, and is usually only a line of the best fit, the parameters of correlation may depend to a certain degree on the set of substituents in the series. Therefore, whenever applicable, we have used the same set of substituents for correlations with σ values as for correlations with σ° values.

The parameters of the regressions (Table 5) indicate that in each case studied correlations with σ° values are indeed of higher quality, however, correlations with σ values are still satisfactory, as indicated by the correlation coefficient r and Exner's ψ function.[31]

Comparing correlations obtained for the same series in various solutions we have found that the pK_a° values for all series studied goes, for each amidine in the series, through a minimum at *ca.* 80% ethanol. However, the ρ values change with the composition of the binary solvent, in a different way for each series studied. As is seen (Table 5) for amidines containing the dimethylamino group (FDM series) it undoubtedly goes through a minimum for solutions containing *ca.* 50% ethanol, and for aqueous solutions it is lower than for 95.6% ethanol. For amidines containing the pyrrolidino group (FPM series) in

Table 5 Parameters of regressions[a] of pK_a values with Hammett-type substituent constants [eqn. (1)]

Series	% EtOH (w/w)	Type of σ	pK_a°	ρ	r	ψ	n
FDM	95.6	σ°	7.77	2.62 ± 0.21	0.993	0.126	12[b]
		σ	7.71	2.52 ± 0.33	0.979	0.221	14
		σ	7.71	2.56 ± 0.33	0.984	0.194	12[b]
	80	σ°	7.06	2.66 ± 0.22	0.993	0.127	12[b]
		σ	7.00	2.56 ± 0.33	0.979	0.218	14
		σ	7.00	2.60 ± 0.32	0.985	0.188	12[b]
	50	σ°	7.81	2.38 ± 0.23	0.991	0.149	12[b]
		σ	7.77	2.32 ± 0.27	0.983	0.196	14
		σ	7.76	2.33 ± 0.28	0.985	0.186	12[b]
	30	σ°	8.49	2.40 ± 0.26	0.989	0.158	12[b]
		σ	8.42	2.28 ± 0.35	0.972	0.256	14
		σ	8.43	2.35 ± 0.35	0.978	0.228	12[b]
	0	σ°	8.90	2.48 ± 0.26	0.990	0.155	11[b]
		σ	8.86	2.37 ± 0.33	0.978	0.226	13
		σ	8.86	2.42 ± 0.34	0.983	0.206	11[b]
FPM	98.5	σ°	8.71	2.65 ± 0.28	0.993	0.135	9[b,c]
		σ	8.65	2.39 ± 0.29	0.989	0.165	10
	95.6	σ°	7.78	2.40 ± 0.28	0.993	0.135	8
		σ	7.75	2.37 ± 0.38	0.987	0.184	8
	80	σ°	7.03	2.68 ± 0.28	0.995	0.118	8
		σ	6.98	2.66 ± 0.37	0.990	0.160	8
	50	σ°	7.77	2.42 ± 0.25	0.995	0.120	8
		σ	7.73	2.30 ± 0.37	0.988	0.176	8
FOPM	98.5	σ°	7.75	2.38 ± 0.37	0.985	0.195	9[b,c]
		σ	7.72	2.14 ± 0.46	0.961	0.306	11[c]
	95.6	σ°	6.78	1.52 ± 0.41	0.966	0.299	8
		σ	6.75	1.51 ± 0.40	0.966	0.299	8
	80	σ°	6.02	1.97 ± 0.29	0.990	0.167	8
		σ	5.99	1.95 ± 0.34	0.985	0.199	8
	50	σ°	6.85	2.23 ± 0.43	0.982	0.221	8
		σ	6.81	2.19 ± 0.54	0.971	0.276	8

[a] At a confidence level of 0.95. [b] Without OEt-derivatives. [c] Based on the data from ref. 22.

Table 6 Parameters of regressions of pK_a values of N^1,N^1-dialkyl-N^2-phenylformamidines with pK_a values of corresponding substituted anilines [eqn. (2)]

Series	% EtOH	α	r	ψ	n
FDM	95.6	0.69 ± 0.10	0.979	0.223	13
	80	0.69 ± 0.19	0.930	0.403	12
	50	0.67 ± 0.11	0.970	0.264	14
	30	0.84 ± 0.15	0.964	0.288	14
	0	0.77 ± 0.13	0.971	0.262	13
FPM	95.6	0.65 ± 0.10	0.988	0.180	8
	80	0.77 ± 0.28	0.954	0.353	7
	50	0.68 ± 0.15	0.977	0.248	8
	30	0.57 ± 0.27	0.927	0.445	7
FOPM	95.6	0.41 ± 0.13	0.953	0.350	8
	80	0.57 ± 0.27	0.927	0.445	7
	50	0.61 ± 0.20	0.952	0.354	8

95.6% ethanol the ρ value is almost the same as in 50% ethanol and it seems to go through a maximum at *ca* 80% ethanol. In the case of amidines containing the morpholino group (FOPM series) the influence of the binary solvent composition on ρ is the most significant. The ρ value for 50% ethanol is definitely higher than for 95.6% solution. The differences between the slopes of regression lines are in some cases within calculated confidence intervals, but a parallelism test for regression lines reveals that the slopes of regression lines are undoubtedly different.

We have also calculated correlations with the pK_a values of corresponding primary amines [eqn. (2)] measured in the same solvents (Table 6), because, in the case of N^1,N^1-pentamethylenebenzamidines,[20] the α value for solutions in rectified spirit was the same as for 50% ethanol, thus suggesting that it might be the same in other solvents. Present results indicate that the identity of α values for series of benzamidines was just coincidental. We have found that for N^1,N^1-pentamethyleneformamidines the α values in these two solvents are also identical, but this is not true for other series and for other solutions. The changes in the α values with the composition of binary water–ethanol mixtures, similarly for changes in the ρ values, are not alike for all these series. The question as to whether these changes may be related to certain solvent parameters, and which of the two equations [(1) or (2)] is more suitable for the purpose, requires further studies on appropriate series of amidines and other solvents.

The results obtained shed some light on the question of the influence of substituents at one site in the amidino group on sensitivity to substitution at other sites.[1,8,16] The differences between the ρ values provide evidence for the assumption that substituents at the amino nitrogen atom exert an influence on the sensitivity of the amidine group to substitution at the imino nitrogen atom. It should be noticed that such influence was also found by the results of *ab initio* calculations[32,33] for some model amidines.

Thus it can be assumed that in the equation for prediction of pK_a values of amidines in the series containing two variable substituents at the two nitrogen atoms, an additional term should be introduced. This term, similar to that explaining interaction between substituents at the imino nitrogen atom and the amidino carbon atom, should take account of this influence.

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References

1 Part 30, J. Oszczapowicz, W. Krawczyk and P. Łyżwiński, *J. Chem. Soc., Perkin Trans. 2*, 1990, 311.

2 R. J. Grout, in *The Chemistry of Amidines and Imidates*, ed. S. Patai, p. 255–281.

3 F. Lund and L. Tybring, *Nature, New Biology*, 1972, **236**, 135.

4 I. Buśko-Oszczapowicz and J. Cieślak, *Acta Pol. Pharm.*, 1973, **32**, 43.

5 H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

6 M. Charton, *J. Org. Chem.*, 1965, **30**, 969.

7 L. L. Popova, I. D. Sadekov and W. J. Minkin, *Reacts. Sposobnost Org. Soed. (Tartu)*, 1968, **5**, 682; 1969, **6**, 47.

8 J. Oszczapowicz and W. Krawczyk, *J. Chem. Soc., Perkin Trans. 2*, 1989, 21.

9 B. V. Passet, G. N. Kul'bitskii, N. A. Kalashnikova and T. Voropaeva, *Zh. Org. Khim.*, 1972, **8**, 1246.

10 J. Ševčik, *Chem. Zvesti*, 1972, **26**, 49.

11 J. Vaes, F. Faubert and Th. Zeegers-Huyskens, *Can. J. Chem.*, 1975, **53**, 604.

12 J. Ševčik, *Acta Univ. Palackianae, Olomouc, Fac. Rerum Nat.*, 1976, **49**, 53.

13 M. J. Cook, A. R. Katritzky and S. Nadji, *J. Chem. Soc., Perkin Trans. 2*, 1976, 211.

14 J. Oszczapowicz and R. Orliński, *Pol. J. Chem.*, 1980, **54**, 1901.

15 J. Oszczapowicz and E. Raczyńska, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1643.

16 J. Oszczapowicz and K. Ciszkowski, *J. Chem. Soc., Perkin Trans. 2*, 1987, 663.

17 J. Oszczapowicz, J. Osek and R. Orliński, *Pol. J. Chem.*, 1980, **54**, 1191.

18 J. Oszczapowicz, E. Raczyńska and R. Orliński, *Pol. J. Chem.*, 1981, **55**, 2031.

19 J. Oszczapowicz and E. Raczyńska, *Pol. J. Chem.*, 1983, **57**, 419.

20 J. Oszczapowicz, E. Raczyńska and T. Pawlik, *Pol. J. Chem.*, 1984, **58**, 117.

21 M. W. Scoggins, *J. Chrom. Sci.*, 1975, **13**, 146.

22 J. Oszczapowicz, R. Orliński and H. Walczyńska, *Pol. J. Chem.*, 1979, **53**, 2531.

23 J. Oszczapowicz, E. Raczyńska and J. Osek, *Magn. Reson. Chem.*, 1986, **24**, 9.

24 J. Osek, J. Oszczapowicz and W. Drzewiński, *J. Chromatogr.*, 1986, **351**, 177.

25 G. Charlot and B. Trémillon, *Les Reaction Chimiques dans les Solvants et les Sels Fondus*, Gauthier-Villars, Paris, 1963, p. 40.

26 J. Oszczapowicz and P. Łyżwiński, *Talanta*, submitted.

27 M. Sjöstrom and S. Wold, *Chem. Scr.*, 1976, **9**, 200.

28 O. Exner in *Correlation Analysis in Chemistry, Recent Advances*, eds. N. B. Chapman and J. Shorter, Plenum Press, New York, 1978.

29 D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

30 B. Fernández, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1371.

31 O. Exner, *Collect. Czech. Chem. Commun.*, 1966, **31**, 3222.

32 J. Oszczapowicz, C. U. Regelman and G. Häfelinger, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1551.

33 G. Häfelinger, J. Oszczapowicz and F. K. H. Kuske, manuscript in preparation.

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