SUBSTITUENT EFFECTS ON THE BASICITY OF *ortho*-, *meta*- AND *para*-SUBSTITUTED N^1,N^1-DIMETHYL-N^2-PHENYLFORMAMIDINES IN ETHANOL AND IN WATER

Ewa Daniela RACZYŃSKA

Institute of General Chemistry,
Warsaw Agricultural University, 02528 Warszawa, Poland

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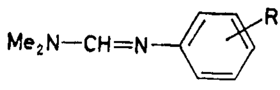
The relative δpK_a values of *ortho*-, *meta*-, and *para*-substituted N^1,N^1-dimethyl-N^2-phenylformamidines obtained in 95·6% aqueous ethanol have been compared with those in water. The comparison shows only some differences in the *ortho* substituent effects. The *meta* and *para* substituent effects in ethanol are not very different from those in water. Quantitative analysis of the experimental δpK_a values based on the Taft equation has led to separation of the total electromeric effects into the inductive and mesomeric effects. As compared to the amino group in anilines, the formamidine group is more sensitive to the transmission of the inductive than the mesomeric effects.

For systematic studies of Brönsted basicities and substituent effects on the pK_a values of about five hundred amidine compounds, 95·6% aqueous ethanol was chosen as the most suitable standard solvent[1]. The reason was good solubility of amidines and high reproducibility of pK_a determinations in contrast to the measurements in "absolute" alcohol.

However, in literature, 95·6% aqueous ethanol has not been often used for the pK_a measurements of other organic bases. The results obtained for amidines in ethanol cannot be combined with those for other compounds in general Brönsted acidity/basicity scale, or compared with the other acidity/basicity scales in solution and in the gas phase. For such comparisons pK_a values in water have usually been used. Water is considered as a primary standard solvent, and pK_a values of almost all organic acids and bases, including biologically active ones have been measured in water. For these reasons investigation of basicity of amidines in water and comparison of the results obtained in water with those found in 95·6% ethanol appeared to be necessary.

In this paper substituent effects on the basicity of *ortho*-, *meta*-, and *para*-substituted N^1,N^1-dimethyl-N^2-phenolformamidines (*I*) have been investigated in water and compared with those in 95·6% aqueous ethanol.



I

For such a consideration the relative basicities, $\delta pK_a = pK_a(H) - pK_a(R)$, are most suitable. They refer to the proton-exchange reaction (*A*), and are a direct measure of the total substituent effects on the basicity of the amidine group.

$$Me_2NCH{=}NC_6H_4R + Me_2NCH{=}\overset{(+)}{N}HPh \rightleftharpoons Me_2NCH{=}\overset{(+)}{N}HC_6H_4R + Me_2NCH{=}NPh \qquad (A)$$

The relative basicities δpK_a of *I* obtained in water and in 95·6% aqueous ethanol[1–4] are given in Table I. For all substituents studied the imino nitrogen atom (N^2) is the preferred site of protonation in solution, like in the gas phase[5]. Protonation of a basic group in substituent R (e.g. COMe, CN, and NO_2) can be excluded, as acetophenone, benzonitrile and nitrobenzene are very weak bases in solution[6–8].

The comparison of the δpK_a values for *I* in water with those in ethanol shows some differences in *ortho* substituent effects. All derivatives obey the Hammett equation with σ^0 constants in both solvents[4]. Relative basicities of *meta*- and *para*-

TABLE I

Relative basicities[a] (δpK_a) of substituted N^1,N^1-dimethyl-N^2-phenylformamidines (*I*) [$\delta pK_a = pK_a(H)-pK_a(R)$]

R	In 95·6% aq. EtOH			In H_2O		
	ortho	*meta*	*para*	*ortho*	*meta*	*para*
H		0·00			0·00	
OEt	—	0·00	−0·38	—	—	—
OMe	−0·19	0·00	−0·46	0·03	0·08	−0·37
Me	0·28	−0·18	−0·30	−0·12	−0·09	−0·30
F	—	—	0·29	—	—	0·17
Cl	1·79	0·95	0·61	1·30	1·05	0·61
Br	1·87	1·00	0·76	1·44	1·06	0·75
I	—	—	0·70	—	—	—
COMe	0·49	0·87	1·15	1·25	0·85	1·13
CF_3	—	—	1·12	—	—	1·18
CN	—	—	1·75	—	—	1·71
NO_2	2·78	1·78	2·20	2·50	1·75	2·13

[a] pK_a are taken from literature[1–4].

-substituted *I* give the same $\delta pK_a - \sigma^0$ correlation line with slopes 2·47 and 2·53 in water and 95·6% aqueous ethanol, respectively. However, relative basicities of *ortho*-substituted *I* give an additional correlation line in water (slope 2·68) and in ethanol (slope 2·54) situated below that obtained for *meta*- and *para*-substituted *I* (by about 0·5 and 1 pK_a units in water and in ethanol, respectively).

Similarly, in plots of the δpK_a values in 95·6% aqueous ethanol against those in water, the *ortho* derivatives show a separate correlation line (slope about unit), parallel to that obtained for the *meta* and *para* derivatives.

The parallelism of the correlation lines of *o-I* to those of *m*- and *p-I* indicates that, generally, steric and solvent effects in *ortho* derivatives can be considered as constant[3,4] and the changes in the δpK_a values caused by variation of the substituent in *ortho* position depend mainly on the electromeric substituent effects (inductive and mesomeric), like in *m*- and *p-I*.

For the investigation of inductive and mesomeric effects of *ortho*, *meta* and *para* substituents some qualitative and quantitative methods have been applied to the series of *I*.

In a first qualitative approximation the differences between the relative δpK_a values of *p*- and *m-I* $[\Delta\delta pK_a = \delta pK_a(p) - \delta pK_a(m)]$ can be treated as a measure of the mesomeric substituent effects[9] (Table II). The comparison of the $\Delta\delta pK_a$ values in ethanol with those in water suggests that the mesomeric as well as the inductive substituent effects[9] are in 95·6% ethanol almost the same as in water.

Quantitative analysis of the experimental δpK_a values, which leads to the separation of the inductive (I) and mesomeric (M) effects, is based on the Taft[10] equation (*1*).

$$\delta pK_a = I + M \qquad (1)$$

Combination of Eq. (*1*) and the relations for the ratio of the inductive, $\lambda = I(p)/$

TABLE II

Differences between the δpK_a values of *para*- and *meta*-substituted N^1,N^1-dimethyl-N^2-phenylformamidines (*I*), $\Delta\delta pK_a = \delta pK_a(p) - \delta pK_a(m)$

R	In 95·6% aq. EtOH	In H_2O
OMe	−0·46	−0·45
Me	−0·12	−0·21
Cl	−0·34	−0·44
Br	−0·24	−0·31
COMe	+0·28	+0·28
NO_2	+0·42	+0·38

/I(m), and mesomeric effects of substituent in *meta* and *para* positions[9], $\alpha = M(m)/M(p)$, give Eqs (*2*) and (*3*), used for estimation of the I and M effects of a substituent in *para* position[11]. The I and M effects of a substituent in *meta* position can be calculated analogously.

$$I(p) = [\delta pK_a(m) - \alpha\delta pK_a(p)] / (1/\lambda - \alpha) \quad (2)$$

$$M(p) = [\delta pK_a(p) - \lambda\delta pK_a(m)] / (1 - \lambda\alpha) \quad (3)$$

In Table III separated I and M substituent effect contributions for *p-I* are given as estimated on the basis of Eqs (*2*) and (*3*). For calculation, $\lambda = 1{\cdot}19$ and $\alpha = 0{\cdot}32$ in 95·6% aqueous ethanol, and $\lambda = 1{\cdot}16$ and $\alpha = 0{\cdot}21$ in water have been used. The obtained results indicate that good correlations of both I and M effects in ethanol with those in water exist. The slopes of these two correlation lines are not much different from unit, which is in good agreement with the conclusion of the qualitative method. The transmission of individual *meta* and *para* substituent effects to the site of protonation (the N^2 atom) is more or less the same both in 95·6% aqueous ethanol and in water.

All the studied *I* can be considered as non-conjugated systems. For such type of compounds the Taft equation (*1*) can be expressed[10] by relation (*4*),

$$\delta pK_a = \varrho_I\sigma_I + \varrho_R\sigma_R^0 \quad (4)$$

which can be derived from the Hammett equation where σ^0 constants are the sums of contributions of the inductive and mesomeric effects[9], $\sigma_p^0 = \lambda_p\sigma_I + \sigma_R^0$ and $\sigma_m^0 = \lambda_m\sigma_I + \alpha\sigma_R^0$, and the parameters ϱ_I and ϱ_R are $\varrho_I(p) = \lambda_p\varrho(p)$, $\varrho_I(m) = \lambda_m\varrho(m)$, $\varrho_R(p) = \varrho(p)$ and $\varrho_R(m) = \alpha\varrho(m)$.

Equation (*4*) was applied by Taft[10] not only to *meta* and *para* derivatives but also to *ortho* systems. Using ϱ_I and ϱ_R^0 values, taken from literature[9,12], the following values of parameters ϱ_I and ϱ_R of relation (*4*) were estimated for *o*-, *m*- and *p-I* (Table IV). The comparison of the ϱ_I and ϱ_R values found in 95·6% aqueous ethanol with those in water shows only little differences in the sensitivity of the amidine group to transmission of inductive and mesomeric substituent effects.

The ratio ϱ_R/ϱ_I for *o*-, *m*- and *p-I* (0·2, 0·3, and 0·8 in 95·6% aqueous ethanol and 0·3, 0·2, and 0·8 in water, respectively) indicate that in both solvents the formamidine group is more sensitive to the transmission of inductive than mesomeric effects, even for substituents in *para* position.

The results obtained in water for *I* can be compared with those found for ring-substituted anilines (the δpK_a values were taken from literature[8,11,13]). For anilines *ortho*- and *para*-substituted with electron-withdrawing substituents, the σ_R^- values[9], for the other anilines the σ_R^0 values[9,12] were used in Eq. (*4*). The following ϱ_I and ϱ_R values were obtained in water (Table V). All these values are greater than those found for *I*. Similarly, a ϱ value of 3·11 obtained from the $\delta pK_a - \sigma^0$ correlation for all *meta*- and *para*-substituted, non-conjugated anilines is greater than that found for

TABLE III

Inductive (I) and mesomeric (M) effect contributions to the relative basicity (δpK_a) of *para*-substituted N^1,N^1-dimethyl-N^2-phenylformamidines (*I*)

R	In 95·6% aq. EtOH		In H_2O	
	I	M	I	M
OMe	0·28	−0·74	0·24	−0·61
Me	−0·16	−0·14	−0·04	−0·26
Cl	1·45	−0·84	1·41	−0·80
Br	1·45	−0·69	1·38	−0·63
COMe	0·97	0·18	0·94	0·19
NO_2	2·07	0·13	2·00	0·13

TABLE IV

Reaction constants of dissociation of *ortho*-, *meta*-, and *para*-substituted N^1,N^1-dimethyl-N^2-phenylformamidinium ions (*I*) (Eq. (*4*))

Series	In 95·6% aq. EtOH			In H_2O		
	ϱ_I	ϱ_R	r	ϱ_I	ϱ_R	r
ortho	3·54	0·72	0·999	3·62	1·20	0·999
meta	2·70	0·83	0·997	2·61	0·53	0·9999
para	3·19	2·63	0·995	3·06	2·60	0·995

TABLE V

Reaction constants of dissociation of *ortho*-, *meta*-, and *para*-substituted anilinium ions in water (Eq. (*4*))

Series	ϱ_I	ϱ_R	r
ortho	5·10	2·50	0·979
meta	3·00	1·04	0·997
para	3·48	3·30	0·996

m- and *p*-*I* in water ($\varrho = 2{\cdot}47$). It means that, generally, the amino group in anilines is more sensitive to inductive and mesomeric effects of substituents than the amidine group in *I*. The ratio ϱ_R/ϱ_I for *ortho*-, *meta*-, and *para*-substituted anilines is 0·5, 0·3 and 0·9, respectively. The comparison of these values with those obtained for *I* in water also shows that the amino nitrogen atom in anilines is more sensitive to mesomeric effects than the imino nitrogen atom (site of protonation) in *I*.

The ϱ_I and ϱ_R values for anilines (Table V) somewhat differ from those found by Taft[10], because in the latter case "corrected" σ constants[9] were used in evaluation of ϱ constants.

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