

Amidines. Part 28.¹ Influence of Substitution at the Amidino Carbon Atom on the Sensitivity to Substitution at the Imino Nitrogen Atom. pK_a Values of N^1N^1 -Dimethylbenzamidines

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Three series (63 compounds) of N^1N^1 -dimethylamidines (*p*-methoxy-, *p*-nitro-, and *p*-chloro-benzamidines), each containing the same set of substituents R_x at the imino nitrogen atom, have been synthesized and their pK_a values in 95.6% ethanol (azeotrope) measured. The pK_a values were correlated with σ and σ^0 constants as well as with the pK_a values of the corresponding primary amines R_xNH_2 . It is shown that the sensitivity of the amidine group to substitution at the imino nitrogen atom depends on the substituent in the phenyl ring at the amidino carbon atom. A linear correlation between the slope of the correlation line and the Hammett-type constants of substituents at the phenyl ring at the amidino carbon atom has been found.

It has been found that in the case of series of amidines containing one variable substituent at any of three sites, at the amino and imino nitrogen atoms and at the amidino carbon atom, their pK_a values obey the Hammett equation.²⁻¹⁰ It has been also shown that the ρ value for N^1N^1 -dimethylacetamidines is higher than that of N^1N^1 -dimethylformamidines containing the same set of variable substituents.¹¹ Thus the hypothesis has been proposed that the ρ value for substitution at one site depends on polar effects of substituent at the second site, and that the pK_a values of amidines containing two substituents, one at the imino nitrogen atom and the second at the functional carbon atom, obey equation (1) where σ_{Im} and σ_F are constants of the substituents on the phenyl ring at the imino nitrogen atom and the functional carbon atom, respectively. The term μ represents the mutual interaction of substituents at the imino nitrogen atom and at the amidino carbon atom. This equation ensures that if the substituent at one of these sites is not varied in the series a linear correlation will be obtained.

$$pK_a = pK_a^0 - \rho_{Im}\sigma_{Im} - \rho_F\sigma_F - \mu\sigma_{Im}\sigma_F \quad (1)$$

However, correlations of pK_a values with σ values obtained for series of benzamidines with variable substituents at the phenyl ring at the amidino carbon atom,¹² namely N^1N^1 -pentamethylene-*N*²-*p*-tolyl- (BPM,*p*-Me) and N^1N^1 -pentamethylene-*N*²-*p*-chlorophenyl-benzamidines (BPM,*p*-Cl), as well as for benzamidines with variable substituents at the imino nitrogen atom,¹³ namely N^1N^1 -dimethyl- (H-BDM), N^1N^1 -*p*-trimethyl- (*p*-Me-BDM), and N^1N^1 -dimethyl-*p*-chloro-benzamidines (*p*-Cl-BDM) did not provide sufficient support for this hypothesis.

The differences between the ρ_F values for N^1N^1 -pentamethylenebenzamidines were so small (1.95 ± 0.23 for BPM,*p*-Me and 1.85 ± 0.13 for BPM,*p*-Cl) that it was concluded that both ρ_F values may be taken as equal.¹² The differences between the ρ_{Im} values for the series of N^1N^1 -dimethylbenzamidines (3.22 ± 0.42 for H-BDM, 3.00 ± 0.36 for *p*-Me-BDM, and 3.02 ± 0.31 for *p*-Cl-BDM) were also smaller than the confidence intervals.¹³

Lately we have shown¹⁴ that the ρ_{Im} for N^1N^1 -dimethylamidines, derivatives of aliphatic carboxylic acids (form-, acet-, propion-, isobuty-, and pival-amidines) containing variable substituents at the imino nitrogen atom, can be correlated with the σ^* values of the alkyl substituent at the amidino carbon atom [equation (2)]. But amidines containing a

phenyl ring at this site (benzamidines) did not fit this correlation.¹⁴

$$\rho_{Im} = \rho_{Im}^0 + \mu\sigma^*_F \quad (2)$$

The results obtained for amidines with alkyl substituents at the amidino carbon atom indicated that there is probably some relation between the σ values of the substituent at the phenyl ring at one site and the ρ value for substitution at the second site, but in the case of the said benzamidines the differences between the substituent effects were too small to be observed.

Therefore in this work we have synthesized two series of benzamidines, each containing the same set of 25 substituents R_x at the imino nitrogen atom and an invariant substituent Z at the phenyl ring at the functional carbon atom. For comparative purposes we have also synthesized 13 N^1N^1 -dimethyl-*p*-chlorobenzamidines (which were not studied previously).¹³ Their pK_a values have been measured under the same conditions as for the series of amidines,⁹⁻¹⁴ i.e. in 95.6% ethanol.

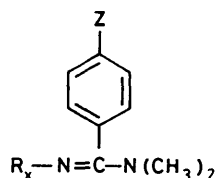
Experimental

Synthesis of Benzamidines.— N^1N^1 -Dimethylbenzamidines were synthesized by Scoggins¹⁵ procedure, by heating dimethylbenzamide dimethyl acetal (1.8 mmol) with a corresponding primary amine (1.5 mmol) for 4 h at 60 °C (*p*-methoxybenzamidines) or ca. 24 h at 60 °C (*p*-nitrobenzamidines).

Structures and Purity of Benzamidines.—The structures of the amidines obtained were confirmed by ¹H n.m.r. spectra (80 MHz; CDCl₃; room temperature). Chemical shifts are given elsewhere.¹⁶

The amidines were over 95% pure, and free of unchanged amine. The purity of *p*-methoxybenzamidines was checked by g.l.c. on a 3 m column packed with 15% silicone gum rubber GE SE-30 on Chromosorb W AW 60–80 mesh. Analyses were made at 280 °C using nitrogen at a flow rate of 25 cm³ min⁻¹, and a flame ionization detector. Retention indices are given elsewhere.¹⁷ The purity of *p*-nitrobenzamidines was checked by a ¹H n.m.r. method.

pK_a Measurements.—The pK_a values, as previously, were determined by the potentiometric method from relationship (3)¹⁸ where pK_a , and pK_a , are the pK_a values of the compound



OMe	NO ₂	Cl	R _x
(1)	(26)		<i>p</i> -C ₆ H ₄ NO ₂
(2)	(27)	(51)	<i>m</i> -C ₆ H ₄ NO ₂
(3)	(28)		<i>m</i> -C ₆ H ₄ Br
(4)	(29)	(52)	<i>m</i> -C ₆ H ₄ Cl
(5)	(30)	(53)	<i>p</i> -C ₆ H ₄ I
(6)	(31)	(54)	<i>p</i> -C ₆ H ₄ Br
(7)	(32)		<i>p</i> -C ₆ H ₄ Cl
(8)	(33)		<i>m</i> -C ₆ H ₄ OCH ₃
(9)	(34)	(55)	<i>m</i> -C ₆ H ₄ OC ₂ H ₅
(10)	(35)		C ₆ H ₅
(11)	(36)	(56)	<i>m</i> -C ₆ H ₄ CH ₃
(12)	(37)		<i>p</i> -C ₆ H ₄ CH ₃
(13)	(38)	(57)	<i>p</i> -C ₆ H ₄ OC ₂ H ₅
(14)	(39)		<i>p</i> -C ₆ H ₄ OCH ₃
(15)	(40)		<i>p</i> -CH ₂ C ₆ H ₄ Cl
(16)	(41)		CH ₂ C ₆ H ₅
(17)	(42)	(58)	<i>m</i> -CH ₂ C ₆ H ₄ OCH ₃
(18)	(43)		<i>p</i> -CH ₂ C ₆ H ₄ CH ₃
(19)	(44)	(59)	allyl
(20)	(45)	(60)	Bu ⁱ
(21)	(46)		C ₆ H ₁₃
(22)	(47)	(61)	Bu ⁿ
(23)	(48)	(62)	Pr ⁿ
(24)	(49)		cyclohexyl
(25)	(50)	(63)	Pr ⁱ

Z	Series	
OCH ₃	N ¹ ,N ¹ -dimethyl- <i>p</i> -methoxybenzamides	(<i>p</i> -MeO-BDM)
NO ₂	N ¹ ,N ¹ -dimethyl- <i>p</i> -nitrobenzamides	(<i>p</i> -NO ₂ -BDM)
Cl	N ¹ ,N ¹ -dimethyl- <i>p</i> -chlorobenzamides	(<i>p</i> -Cl-BDM)

$$pK_a = pH_{xi} - pH_{xs} + pK_a \quad (3)$$

investigated (i) and the standard (s), and pH_x are indications of a pH-meter at $x = 1/4, 3/8, 1/2, 5/8,$ and $3/4$ neutralization points.

For pK_a values below 3.5 corrections for hydrogen ions concentration¹⁹ were taken into account.

Samples of the investigated amidine (0.15 mmol) dissolved in 0.1M-tetramethylammonium chloride in ethanol (15 cm³) were titrated with 0.15M-HCl in ethanol. As standard, imidazole (pK_a 5.94 in 95.6% ethanol²⁰) was used. Discussion on errors and experimental details, securing the reproducibility as well as the reliability of the measured pK_a values, is given in previous papers.⁹⁻¹¹ The pK_a values and calculated confidence intervals at a significance level of 0.05 are summarized in Table 1. The pK_a values may include a systematic error (below 0.1 pK_a units) 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.—For the reasons discussed previously¹⁴ only correlations obtained for series of compounds containing the same set of substituents at a given site can be compared. To make possible such a comparison between *p*-nitro-, *p*-methoxy-, and the previously studied *p*-chloro-benzamides¹³ we have synthesized and measured the pK_a values of some *p*-chlorobenzamides (51)—(63).

We have correlated the pK_a values of the studied amidines with both σ and σ^0 values.^{21,22} Regression parameters are summarized in Table 2.

Consideration of the interaction of substituents with the protonation centre (imino nitrogen atom) led to the conclusion¹¹ that for amidines containing substituents on the phenyl ring at the imino nitrogen atom σ^0 constants should be the most suitable. The regression parameters obtained (Table 2) indicate that for all the studied series (as for other series of amidines¹¹⁻¹⁴) correlation with σ^0 values is of higher quality. However, correlations with ordinary σ values are still satisfactory, as indicated by the correlation coefficient r and Exner's Ψ function.²³ The correlations obtained for *p*-nitrobenzamides are of lower quality than that for *p*-methoxy- and *p*-chloro-benzamides.

The correlations provide strong support for the hypothesis that the substituent at the phenyl ring at the functional (amidino) carbon atom exerts an influence on the ρ_{im} value. The ρ_{im} value for *p*-methoxybenzamides (3.53 ± 0.32) is undoubtedly different from that for *p*-nitrobenzamides (1.89 ± 0.38).

Linear Correlations with the pK_a Values of Amines.—As in previous papers we have correlated the pK_a values of the amidines with the pK_a values of the corresponding primary amines measured under the same conditions.^{9,24} Parameters of the regressions [equation (4)] are summarized in Table 3.

$$pK_a(\text{amidine}) = pK_a^0(\text{amine}) + \alpha_{im}[pK_a(R_xNH_2) - pK_a(PhNH_2)] \quad (4)$$

The correlations of pK_a values of amidines with the pK_a values of the corresponding primary amines are of very good quality, as indicated by the correlation coefficient r and Exner's Ψ function. The parameters of these equations can be used for fairly accurate prediction of the pK_a values of amidines of various series, containing alkyl, aryl, or aralkyl substituents at the imino nitrogen atom. The changes of the α_{im} values, following the changes of the σ values of the substituents on the phenyl rings at the functional carbon atom are not so evident (except for *p*-nitrobenzamides) as in the case of the ρ_{im} values obtained for *N*²-phenylbenzamides.

Dual Parameter Correlations.—Comparing *p*-OMe- and *p*-NO₂-BDM with the previously studied¹³ *p*-Cl-, H-, and *p*-Me-BDM one can see that the ρ_{im} value increases with the decrease of the σ value of the substituent on the phenyl ring at the amidino carbon atom.

We have found that the ρ_{im} values of these series correlate with the σ values of the substituents on the phenyl ring at the amidino carbon atom [equation (2)].

As there is a strong conjugation between the amidino group and the substituent on the phenyl ring at the amidino carbon atom, the correlation with σ value was of only satisfactory quality (r 0.951, Ψ 0.400).

A better correlation is obtained if for the nitro group the σ^- value is used instead of σ . Parameters of obtained correlations are summarized in Table 4. This indicates that for the nitro group at this site, σ^- should be used instead of σ . However for

Table 1. pK_a values of N^2 -substituted N^1N^1 -dimethyl- p -methoxybenzamidines (p -OMe-BDM), p -nitrobenzamidines, (p -NO₂-BDM), and p -chlorobenzamidines (p -Cl-BDM) in 95.6% EtOH at $(25 \pm 1)^\circ\text{C}$ *

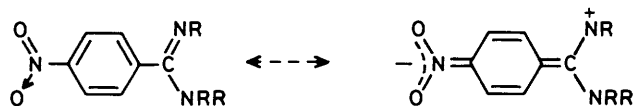
p -OMe-BDM		p -NO ₂ -BDM		p -Cl-BDM	
Compound	pK_a	Compound	pK_a	Compound	pK_a
(1)	5.28 ± 0.01	(26)	2.55 ± 0.11	(51)	4.97 ± 0.03
(2)	5.71 ± 0.03	(27)	3.03 ± 0.11	(52)	5.77 ± 0.03
(3)	6.96 ± 0.06	(28)	3.19 ± 0.11	(53)	6.13 ± 0.06
(4)	6.79 ± 0.03	(29)	3.28 ± 0.16	(54)	6.08 ± 0.05
(5)	6.95 ± 0.02	(30)	3.34 ± 0.07	(55)	6.81 ± 0.09
(6)	7.18 ± 0.01	(31)	3.41 ± 0.06	(56)	7.02 ± 0.04
(7)	7.15 ± 0.03	(32)	3.69 ± 0.04	(57)	7.53 ± 0.01
(8)	7.91 ± 0.06	(33)	4.15 ± 0.09	(58)	9.37 ± 0.03
(9)	8.16 ± 0.03	(34)	4.10 ± 0.15	(59)	9.78 ± 0.03
(10)	8.39 ± 0.16	(35)	4.14 ± 0.17	(60)	10.19 ± 0.04
(11)	8.21 ± 0.03	(36)	4.12 ± 0.12	(61)	10.32 ± 0.02
(12)	8.79 ± 0.08	(37)	4.35 ± 0.05	(62)	10.32 ± 0.02
(13)	8.68 ± 0.06	(38)	4.55 ± 0.12	(63)	10.42 ± 0.03
(14)	8.83 ± 0.06	(39)	4.66 ± 0.04		
(15)	9.99 ± 0.03	(40)	5.78 ± 0.05		
(16)	10.37 ± 0.03	(41)	5.86 ± 0.05		
(17)	10.42 ± 0.05	(42)	5.87 ± 0.02		
(18)	10.52 ± 0.04	(43)	5.99 ± 0.05		
(19)	10.59 ± 0.04	(44)	6.02 ± 0.02		
(20)	11.06 ± 0.02	(45)	6.15 ± 0.07		
(21)	11.25 ± 0.02	(46)	6.09 ± 0.05		
(22)	11.06 ± 0.04	(47)	6.24 ± 0.04		
(23)	11.35 ± 0.04	(48)	6.20 ± 0.06		
(24)	11.39 ± 0.03	(49)	6.00 ± 0.05		
(25)	11.23 ± 0.11	(50)	6.11 ± 0.04		

* At ionic strength μ 0.01, using imidazole pK_a 5.94 as standard.**Table 2.** Parameters of regressions* with substituent constants

Series	Type of σ	pK_a^0	ρ_{im}	s	r	Ψ	F	n
p -OMe-BDM	σ	8.07	3.40 ± 0.49	0.225	0.975	0.240	231	14
	σ^0	8.15	3.53 ± 0.32	0.144	0.992	0.141	599	12 ^a
p -NO ₂ -BDM	σ	4.07	1.88 ± 0.38	0.174	0.952	0.329	117	14
	σ^0	4.09	1.89 ± 0.38	0.171	0.962	0.299	125	12 ^a
p -Cl-BDM	σ	6.80	2.86 ± 0.32	0.147	0.984	0.190	375	14
	σ^0	6.83	2.87 ± 0.24	0.108	0.993	0.130	704	12 ^a

* At a confidence level of 0.95. ^a Without p -OEt and m -OEt derivatives.**Table 3.** Parameters of regressions with pK_a values of primary amines [equation (3)]*

Series	pK_a^0	α_{im}	s	r	Ψ	F	n
p -OMe-BDM	7.79	0.60 ± 0.05	0.024	0.982	0.198	588	24
p -NO ₂ -BDM	3.94	0.41 ± 0.03	0.014	0.989	0.155	973	24
p -Cl-BDM	6.62	0.62 ± 0.04	0.264	0.991	0.137	1 254	24

* At a confidence level 0.95; without m -NO₂ derivatives.

this group on the phenyl ring at the imino nitrogen atom σ^0 was the best choice.

The regression provides evidence for the conclusion that the sensitivity of the amidino group to substitution at the imino nitrogen atom depends on the substituent on the phenyl ring at the amidino carbon atom and also that for prediction of the pK_a values of amidines equation (1) should be used.

On account of the similar mesomeric effects of the chlorine

atom and the methyl group the ρ value for p -Me-BDM is almost identical to that for p -Cl-BDM. However, the inductive effects of the methyl group and chlorine atom in the *para* position are opposite and the difference between their σ values is 0.4σ units. A similar effect was observed in the case of series of amidines containing variable substituents at the amidino carbon atom and a *p*-methyl or *p*-chloro substituent on the imino nitrogen atom.¹²

We have calculated parameters for equation (1) on the basis of the pK_a values of all five series (p -OMe-, p -NO₂-, p -Cl-, H-, p -Me-BDM; total 50 compounds) using σ^0 values for substituents on the phenyl ring at the imino nitrogen atom and σ values for substituents on the phenyl ring at the amidino carbon atom. For NO₂ on the phenyl ring at the amidino carbon atom we have used σ^- . Parameters of obtained regressions are summarized in Table 5.

Table 4. Parameters of regressions with ρ_{Im} value with σ constants [equation (2)]^a

ρ_{Im}^0	μ	s	r	Ψ	F	n
3.06	-1.40 ± 0.84	0.264	0.951	0.400	28	5
3.17	-1.58 ± 0.43	0.100	0.996	0.124	254	4 ^b
3.10	-0.97 ± 0.51	0.160	0.962	0.354	37	5 ^c
3.20	-1.07 ± 0.27	0.063	0.997	0.119	290	4 ^{b,c}

^a At a confidence level of 0.95. ^b Without *p*-Me-BDM series. ^c For series *p*-NO₂-BDM σ^- values used.

Table 5. Parameters of regressions of pK_a values of amidines with σ^0 values of substituents at phenyl ring at imino nitrogen atom and σ values of substituents at phenyl ring at amidino carbon atom^a

pK_a	ρ_{Im}	ρ_{F}	μ	s_{Im}	s_{F}	s_{μ}	R	Ψ	n
7.22	3.06 ± 0.30	3.75 ± 0.28	-1.40 ± 0.73	0.149	0.139	0.363	0.984	0.184	50 ^b
7.18	2.86 ± 0.32	3.44 ± 0.25		0.159	0.124		0.979	0.209	50 ^c
7.33	3.09 ± 0.18	2.60 ± 0.11	-0.97 ± 0.28	0.089	0.055	0.139	0.995	0.105	50 ^{b,d}
7.29	2.85 ± 0.23	2.39 ± 0.12		0.114	0.060		0.990	0.148	50 ^{c,d}

^a At a confidence level of 0.95. ^b According to equation (1). ^c According to equation (5). ^d σ^- value for NO₂ group at phenyl ring at amidino carbon atom.

For comparison in Table 5 we have shown regression parameters for equation (5), without the cross-term $\mu\sigma_{\text{Im}}\sigma_{\text{F}}$. The

$$pK_a = pK_a^0 - \rho_{\text{Im}}\sigma_{\text{Im}} - \rho_{\text{F}}\sigma_{\text{F}} \quad (5)$$

term μ has a negative value. It indicates that the increase of the electron density at the C=N double bond, caused by the polar effect of a substituent on the phenyl ring at the amidino carbon atom, increases the sensitivity of the amidino group to the effect of substituents on the imino nitrogen atom. This implies that on the other hand electron-donating substituents at the imino nitrogen atom increase the sensitivity of the amidino group to substitution at the amidino carbon atom.

All the correlations have predictive value, but the best results are obtained for equation (1) taking into account the mutual interactions between substituents and when σ^- for the NO₂ group on the phenyl ring at the amidino carbon atom is used instead of σ .

Acknowledgements

This research was supported by project RP.II.10 from the Polish Ministry of Sciences and Higher Education.

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Received 10th December 1987; Paper 7/2168