Amidines. Part 24.[1] Influence of Alkyl Substituents at the Amidino Carbon Atom on the Sensitivity to Substitution at the Imino Nitrogen Atom. pK_a Values of N^1N^1-Dimethylamidines

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Three series of N^1N^1-dimethylamidines, propionamidines, isobutyramidines, and pivalamidines, each containing the same set of 25 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. Regression parameters for the series studied were compared with those for N^1N^1-dimethyl-formamidines and -acetamidines. It is shown that the sensitivity of the amidine group to substitution at the imino nitrogen atom depends on the polar effects of substituents at the amidino carbon atom. A good linear correlation between the slope of the correlation line and the σ^* value of the substituent at the amidino carbon atom is found.

The basicity of amidines depends on substitution at three sites, at both nitrogen atoms and the amidino carbon atom. The site of protonation is the imino nitrogen atom. Thus, as expected, substitution at this site exerts the strongest influence on the pK_a value of amidines. It was shown[2-11] that the pK_a values of amidines containing a substituent at the imino nitrogen atom obey the Hammett equation (1). It was also found that the pK_a

$$pK_a = pK_a^0 - \rho_{Im}\sigma_{Im} \qquad (1)$$

values of amidines containing a substituent R_x (alkyl, aryl, or aralkyl) at the imino nitrogen atom can be correlated with the pK_a values of the corresponding primary amines R_xNH_2 measured under the same conditions, and that equation (2) thus

$$pK_{a_{amidine}} = pK_a^0_{amidine} + \alpha_{Im}(pK_{a_{R_xNH_2}} - pK_{a_{PhNH_2}}) \qquad (2)$$

obtained may be used for prediction of the pK_a values of amidines.[10-13] In equation (2) pK_a^0 has the same meaning as in the Hammett equation.

It is known that the pK_a values of amidines containing a substituent at the amidino carbon atom obey the Hammett equation.[14-16] Thus amidines containing two substituents, one at the imino nitrogen atom and the other at the amidino carbon atom, might obey the dual substituent linear regression (3) where σ_{Im} and σ_F are constants of substituents on the phenyl rings at the nitrogen atom and the functional carbon atom, respectively.

$$pK_a = pK_a^0 - \rho_{Im}\sigma_{Im} - \rho_F\sigma_F \qquad (3)$$

But recently, when comparing correlations of pK_a values of N^1N^1-dimethyl-formamidines and -acetamidines with σ^0 values as well as with the pK_a values of the corresponding primary amines, we have found that the regression coefficients [ρ_{Im} and α_{Im}, equations (1) and (2)] depend to a considerable degree on substitution at the amidine carbon atom.[13] The hypothesis has been formed that the pK_a values of amidines containing two variable substituents at these sites obey equation (4). This

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

equation ensures that if the substituent at one of these sites is not varied a linear correlation will be obtained. The slope of the

correlation line depends on the σ value of the substituent and on the term μ representing the mutual interaction of substituents. For series of amidines with variable substituents at the imino nitrogen atom the value $\rho_F\sigma_F$ is included in the pK_a^0 value for the series and the observed ρ_{Im} value is equal to the sum $\rho_{Im} + \mu\sigma_F$.

However it appeared that in the case of benzamidines changes in the ρ_{Im} or ρ_F values caused by substitution of a methyl group for a chlorine atom at the *para*-position of phenyl ring can be neglected, and that for prediction of their pK_a values a dual parameter linear equation (3) can be used.[17,18]

Thus the questions arose whether it is possible to find one common equation for amidines containing substituents at amidine carbon atom, how far the equation (4) can be applied for prediction of the pK_a values of amidines, and what is the value of the term μ?

For this reason we have synthesized three series of N^1N^1-dimethylamidines containing alkyl substituents of increasing

Compound	R_x	Compound	R_x
(1), (26), (51)	p-C$_6$H$_4$NO$_2$	(14), (39), (64)	p-C$_6$H$_4$OCH$_3$
(2), (27), (52),		(15), (40), (65)	p-CH$_2$C$_6$H$_4$Cl
(76), (81)	m-C$_6$H$_4$NO$_2$	(16), (41), (66)	CH$_2$C$_6$H$_5$
(3), (28), (53)	m-C$_6$H$_4$Br	(17), (42), (67),	
(4), (29), (54)	m-C$_6$H$_4$Cl	(78)	m-CH$_2$C$_6$H$_4$OCH$_3$
(5), (30), (55),		(18), (43), (68),	
(77)	p-C$_6$H$_4$I	(79)	p-CH$_2$C$_6$H$_4$CH$_3$
(6), (31), (56)	p-C$_6$H$_4$Br	(19), (44), (69),	
(7), (32), (57)	p-C$_6$H$_4$Cl	(80), (82)	allyl
(8), (33), (58)	m-C$_6$H$_4$OCH$_3$	(20), (45), (70)	isobutyl
(9), (34), (59)	m-C$_6$H$_4$OC$_2$H$_5$	(21), (46), (71)	n-hexyl
(10), (35), (60)	C$_6$H$_5$	(22), (47), (72)	n-butyl
(11), (36), (61)	m-C$_6$H$_4$CH$_3$	(23), (48), (73)	n-propyl
(12), (37), (62)	p-C$_6$H$_4$CH$_3$	(24), (49), (74)	cyclohexyl
(13), (38), (63)	p-C$_6$H$_4$OC$_2$H$_5$	(25), (50), (75)	isopropyl

R_z	Series	
CH$_2$CH$_3$	N^1N^1-dimethylpropionamidines	(PrpDM)
CH(CH$_3$)$_2$	N^1N^1-dimethylisobutyramidines	(iBtrDM)
C(CH$_3$)$_3$	N^1N^1-dimethylpivalamidines	(PivDM)
CH$_3$	N^1N^1-dimethylacetamidines	(ADM)
H	N^1N^1-dimethylformamidines	(FDM)

Table 1. Characterization of N^1N^1-dimethylamidines

(a) N^2-Phenyl derivatives

Columns under **^{1}H Chemical shift (δ)**: the amidine carbon bears either a CH (N=C–N | CH) or a CH$_3$ (N=C–N–C | CH$_3$); the remaining columns (H-2, H-6, H-3, H-5, H-4, CH$_3$, CH$_2$) refer to the phenyl ring at N^2.

Compound	Formula	B.p. (°C/mmHg)	NMe$_2$	CH	CH$_3$	H-2	H-6	H-3	H-5	H-4	CH$_3$	CH$_2$
(1)	$C_{11}H_{15}N_3O_2$	*h*	3.06	2.33	1.05	6.78		8.14				
(2)	$C_{11}H_{15}N_3O_2$	*i*	3.15	2.39	1.08	7.60	7.20		7.30	8.06		
(3)	$C_{11}H_{15}BrN_2$	175—177/14	3.13	2.37	1.04	7.11	6.86		7.26	7.34		
(4)	$C_{11}H_{15}ClN_2$	158—162/12	3.09	2.34	1.03	6.89	6.70		7.10	7.21		
(5)	$C_{11}H_{15}IN_2$	194—200/16	3.03	2.23	1.01	6.51		7.51				
(6)	$C_{11}H_{15}BrN_2$	175—178/12	3.05	2.29	1.01	6.61		7.33				
(7)	$C_{11}H_{15}ClN_2$	160—162/12	3.03	2.28	1.01	6.68		7.20				
(8)	$C_{12}H_{18}N_2O$	188—192/16	3.09	2.35	1.08	6.45	6.49		7.35	6.68	3.88[a]	
(9)	$C_{13}H_{20}N_2O$	180—185/14	3.10	2.38	1.06	6.46	6.50		7.34	6.69	1.40[a]	4.13[a]
(10)	$C_{11}H_{16}N_2$	126—128/12	3.05	2.30	1.04	6.75		7.30		6.98		
(11)	$C_{12}H_{18}N_2$	140—143/12	3.06	2.35	1.03	6.74	6.66		7.21	6.99	2.35	
(12)	$C_{12}H_{18}N_2$	140—144/12	3.00	2.29	1.01	6.58		7.00			2.29	
(13)	$C_{13}H_{20}N_2O$	188—190/16	3.10	2.35	1.03	6.84		7.00			1.40[a]	4.13[a]
(14)	$C_{12}H_{18}N_2O$	180—182/16	3.04	2.29	1.03	6.67		6.83			3.80[a]	
(15)	$C_{12}H_{17}ClN_2$	157—160/12	3.05	2.44	1.05	7.49[c]		7.49[c]				4.63[b]
(16)	$C_{12}H_{18}N_2$	140—145/12	3.08	2.48	1.05	7.51[c]		7.51[c]		7.51[c]		4.68[b]
(17)	$C_{13}H_{20}N_2O$	185—187/12	3.06	2.46	1.08	d		d		d	3.91[a]	4.65[b]
(18)	$C_{13}H_{20}N_2$	150—155/12	3.04	2.50	1.06	7.39[c]		7.39[c]			2.38	4.64[b]
(26)	$C_{12}H_{17}N_3O_2$	*j*	3.08	2.94[c]	1.12	6.63		8.04		7.98		
(27)	$C_{12}H_{17}N_3O_2$	*k*	3.03	3.03[c]	1.16	7.50	7.23		7.33	7.00		
(28)	$C_{12}H_{17}BrN_2$	180—182/15	2.95	3.00[c]	1.13	6.83	6.60		7.04	6.93		
(29)	$C_{12}H_{17}ClN_2$	170/17	2.99	3.00[c]	1.16	6.70	6.50		7.11			
(30)	$C_{12}H_{17}IN_2$	185/12	2.98	3.00[c]	1.14	6.49		7.51				
(31)	$C_{12}H_{17}BrN_2$	174/17	3.00	3.00[c]	1.14	6.59		7.31				
(32)	$C_{12}H_{17}ClN_2$	188—190/15	3.00	3.00[c]	1.12	6.59		7.15				
(33)	$C_{13}H_{20}N_2O$	166—170/13	3.00	3.00[c]	1.14	6.24	6.30		7.11	6.33	3.75[a]	
(34)	$C_{14}H_{22}N_2O$	186/15	2.96	2.98[c]	1.11	6.20	6.26		7.09	6.46	1.33[a]	3.98[a]
(35)	$C_{12}H_{18}N_2$	147—148/19[e]	2.98	2.99[c]	1.11	6.66		7.18		6.91		
(36)	$C_{13}H_{20}N_2$	150—152/13	3.00	3.00[c]	1.14	6.55	6.48		7.11	6.69	2.30	
(37)	$C_{13}H_{20}N_2$	156—158/17	2.99	3.05[c]	1.14	6.60		7.04			2.30	
(38)	$C_{14}H_{22}N_2O$	188—190/15	2.96	3.01[c]	1.12	6.59		6.79			1.35[a]	3.99[a]
(39)	$C_{13}H_{20}N_2O$	182—184/18	2.99	3.08[c]	1.16	6.64		6.78			3.75[a]	
(40)	$C_{13}H_{19}ClN_2$	186—190/20	2.91	3.00[c]	1.20	7.24[c]		7.24[c]				4.53[b]
(41)	$C_{13}H_{20}N_2$	160—163/15	2.90	3.03[c]	1.23	7.31[c]		7.31[c]		7.31[c]		4.59[b]
(42)	$C_{14}H_{22}N_2O$	190—192/15	2.91	3.05[c]	1.18	d	d		d	d	3.78[a]	4.49[b]
(43)	$C_{14}H_{22}N_2$	176—180/18	2.89	2.98[c]	1.21	7.18[c]		7.18[c]			2.30	4.60[b]
(51)	$C_{13}H_{19}N_3O_2$	*l*	2.75		1.34	6.64		8.10				
(52)	$C_{13}H_{19}N_3O_2$	*m*	2.68		1.34	7.48	7.13		7.33	7.93		
(53)	$C_{13}H_{19}BrN_2$	176—180/20	2.61		1.33	6.80	6.61		7.06	6.89		
(54)	$C_{13}H_{19}ClN_2$	160—164/14	2.61		1.31	6.61	6.45		7.08	6.82		
(55)	$C_{13}H_{19}IN_2$	184—192/14	2.60		1.30	6.43		7.45				
(56)	$C_{13}H_{19}BrN_2$	168—170/14	2.61		1.33	6.54		7.28				
(57)	$C_{13}H_{19}ClN_2$	162—164/13	2.56		1.29	6.56		7.10				
(58)	$C_{14}H_{22}N_2O$	166/22	2.55		1.28	6.15	6.20		7.03	6.31	3.71[a]	
(59)	$C_{15}H_{24}N_2O$	176—180/14	2.59		1.30	6.24	6.24		7.04	6.40	1.35[a]	4.01[a]
(60)	$C_{13}H_{20}N_2$	120/10	2.54		1.29	6.63		7.15		6.90		
(61)	$C_{14}H_{22}N_2$	142—144/12	2.56		1.30	6.48	6.36		6.95	6.59	2.26	
(62)	$C_{14}H_{22}N_2$	142/10	2.53		1.29	6.59		6.99			2.26	
(63)	$C_{15}H_{24}N_2O$	174/10	2.55		1.31	6.61		6.81			1.36[a]	4 00[a]
(64)	$C_{14}H_{22}N_2O$	170/10	2.53		1.30	6.59		6.75			3.75[a]	
(65)	$C_{14}H_{21}ClN_2$	174—180/14	2.81		1.25	7.26[d]		7.26[c]				4.46[b]
(66)	$C_{14}H_{22}N_2$	144—146/10	2.81		1.28	7.31[c]		7.31[c]		7.31[c]		4.56[b]
(67)	$C_{15}H_{24}N_2O$	174—180/12	2.78		1.25	d	d		d	d	3.80[a]	4.53[b]
(68)	$C_{15}H_{24}N_2$	158—162/12	2.78		1.25	7.16[c]		7.16[c]			2.33	4.50[b]
(76)	$C_{10}H_{13}N_3O_2$	*n*	3.01	1.91		7.51	7.15		7.31	7.80		
(77)	$C_{10}H_{13}IN_2$	190—196/16	3.04	1.89		6.43		7.28				
(78)	$C_{12}H_{18}N_2O$	188—194/14	3.00	1.92		d	d		d	d	3.86[a]	4.55[b]
(79)	$C_{12}H_{18}N_2$	144—148/12	2.98	2.00		7.21[c]		7.21[c]			2.34	4.52[b]
(81)	$C_9H_{11}N_3O_2$	202—204/13[g]	3.05	*f*		7.59	7.33		7.35	7.80		

[a] Alkoxy. [b] Benzyl. [c] ±0.1. [d] Multiplet δ 6.7—7.3. [e] Ref. 24, 75—78/1. [f] N=CH–N: δ 7.78. [g] Ref. 25, 198—200/12; ref. 26, 111—113/0.0005. [j] M.p. 85—86 °C. [k] M.p. 72—74 °C. [l] M.p. 78—79 °C. [m] M.p. 65—66 °C. [n] M.p. 88—90 °C.

Table 1 (*continued*)

(b) N^2-Alkyl derivatives

			NMe₂	N=C-N CH	N=C-N C CH₃	α	β	γ	δ	ε	ζ
								Alkyl group at N²			
(19)	C₈H₁₆N₂	74/20	3.24	2.24	1.15	3.91	5.93	5.20			
(20)	C₉H₂₀N₂	80/16	3.26	2.20	1.11	3.18	1.78	0.84			
(21)	C₁₁H₂₄N₂	107—108/16	3.28	2.22	1.08	3.25	a	a	a	a	0.88
(22)	C₉H₂₀N₂	86—90/16	3.23	2.23	1.13	3.13	b	b	0.92		
(23)	C₈H₁₈N₂	72—75/15	3.24	2.21	1.11	3.11	1.58	0.91			
(24)	C₁₁H₂₂N₂	105—108/13	3.25	2.25	1.08	3.25	b	b	b		
(25)	C₈H₁₈N₂	55/16	3.34	2.25	1.11	3.66	1.04				
(44)	C₉H₁₈N₂	80—82/17	2.84	3.05ᶜ	1.20	4.01	5.94	5.10			
(45)	C₁₀H₂₂N₂	77—78/15	2.81	3.04ᶜ	1.19	3.10	1.79	0.92			
(46)	C₁₂H₂₆N₂	122—123/16	2.74	3.00ᶜ	1.19	3.24	a	a	a	a	0.83
(47)	C₁₀H₂₂N₂	86—86/16	2.79	3.01ᶜ	1.20	3.29	a	a	0.93		
(48)	C₉H₂₀N₂	73/17	2.78	3.01ᶜ	1.19	3.23	1.48	0.90			
(49)	C₁₂H₂₄N₂	120—122/17	2.75	3.04ᶜ	1.20	3.30	b	b	b		
(50)	C₉H₂₀N₂	80—82/35	2.78	3.10ᶜ	1.20	3.75	1.05				
(69)	C₁₀H₂₀N₂	81/18	2.74		1.18	3.95	5.88	5.11			
(70)	C₁₁H₂₄N₂	82/18	2.73		1.16	3.08	1.85	0.86			
(71)	C₁₃H₂₈N₂	114—120/16	2.73		1.15	3.25	a	a	a	a	0.86
(72)	C₁₁H₂₄N₂	88/16	2.74		1.18	3.28	a	a	0.92		
(73)	C₁₀H₂₂N₂	76—78/18	2.73		1.15	3.21	1.50	0.89			
(74)	C₁₃H₂₆N₂	124—128/23	2.71		1.11	3.41	b	b	b		
(75)	C₁₀H₂₂N₂	64/18	2.75		1.15	3.86	1.12				
(80)	C₇H₁₄N₂	68/19	2.94	2.09		3.94	5.90	5.21			
(82)	C₆H₁₂N₂	50/20	2.85	d		3.88	5.90	5.18			

ᵃ Multiplet, δ 1.20—1.60. ᵇ Multiplet, δ 1.20—1.80. ᶜ ±0.1. ᵈ N=CH–N: δ 7.28.

inductive effect such as ethyl, isopropyl, and t-butyl at the amidine carbon atom and measured their pK_a values in 95.6% ethanol. Compounds of each series contained the same set of 25 substituents R_x at the imino nitrogen atom. For comparative purposes we have also synthesized a few formamidines (**81**) and (**82**) and acetamidines (**76**)—(**80**) which were not studied previously.[10,13]

Experimental

Synthesis of Propionamidines, Acetamidines, and Formamidines.—The N^1N^1-dimethyl-propionamidines (**1**)—(**25**), -acetamidines (**76**)—(**80**), and -formamidines (**81**) and (**82**) were synthesized by Scoggins'[19] procedure by heating equimolar amounts of primary amine R_xNH_2 with the dimethyl acetal of the corresponding dimethylamide.[20,21] The amidines after evaporation of methanol evolved in the reaction were distilled under reduced pressure in a microscale apparatus.

Synthesis of Pivalamidines and Isobutyramidines.—The N^1N^1-dimethyl-pivalamidines (**51**)—(**75**) and -isobutyramidines (**26**)—(**50**) were synthesized by reaction of primary amines R_xNH_2 with a chloroform solution of NN-dimethylchloropivaliminium chloride, or NN-dimethylchloroisobutyriminium chloride respectively. Chloroiminium chloride solutions were obtained by reaction of the corresponding dimethylamide in CHCl₃ with an equimolar amount of oxalyl chloride at low temperature.[22]

The amidines after evaporation of chloroform, extraction by ether from the basified reaction mixture, and evaporation of ether were distilled under reduced pressure in a microscale apparatus.

Structures and Purity of Amidines.—The structures of the amidines obtained were confirmed by ¹H n.m.r. spectra (80 MHz; CDCl₃; room temperature). Chemical shifts are summarized in Table 1.

The amidines were over 95% pure, and free of unchanged amine. Their purity 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 240 °C using nitrogen at a flow rate of 40 cm³ min⁻¹, and a flame ionization detector. Retention indices of amidines are given elsewhere.[23]

pK_a *Measurements.*—The pK_a values were determined by potentiometric titration in 95.6% ethanol (azeotrope) at 25 ± 0.1 °C and calculated from relation (5)[27] where pK_{a_i} and pK_{a_s} are the pK_a values of the investigated compound (i) and the standard (s), and pH_x are the pH values at the $x = 1/4, 3/8, 1/2, 5/8,$ and $3/4$ neutralization points. As standard, imidazole (pK

$$pK_{a_i} = pH_{x_i} - pH_{x_s} + pK_{a_s} \qquad (5)$$

5.94 in 95.6% ethanol[28]) was used. Discussion of experimental details securing the reproducibility as well as the reliability of the measured pK_a values is given in previous papers.[10,11,13] The pK_a values and confidence intervals calculated at a significance level of 0.95 are summarized in Table 2. The error in pK_a determination, as discussed previously,[10] does not exceed 0.05 pK_a units. The pK_a values may include a systematic error of *ca.* 0.1 pK_a units contributed by the pK_a value of the standard, but on account of its constancy it has no influence on the regression coefficients.

Results and Discussion

Correlations with σ Constants.—The reliability of any conclusions based on comparison of the ρ values depends on both the number of compounds in the series as well as on the range of substituent effects. But there is another substantial factor to which not enough attention is paid, that is the comparability of the series. As the regression line very seldom goes through all the experimental points, and usually is only the

Table 2. pK_a Values of N^2-substituted $N^1 N^1$-dimethyl-propionamidines (PrpDM), -isobutyramidines (iBtrDM), -pivalamidines (PivDM), -acetamidines (ADM), and -formamidines (FDM) in 95.6% EtOH at $(25 \pm 0.1)\,^{\circ}C^a$

Compound	PrpDM pK_a	Compound	iBtrDM pK_a	Compound	PivDM pK_a	Compound	ADM pK_a
(1)	5.65 ± 0.03	(26)	5.52 ± 0.03	(51)	5.18 ± 0.04	(76)	6.38 ± 0.03
(2)	6.06 ± 0.06	(27)	6.14 ± 0.03	(52)	5.86 ± 0.03	(77)	7.53 ± 0.02
(3)	7.13 ± 0.03	(28)	7.03 ± 0.01	(53)	6.81 ± 0.03	(78)	11.60 ± 0.03
(4)	7.15 ± 0.07	(29)	7.10 ± 0.01	(54)	7.01 ± 0.06	(79)	11.64 ± 0.03
(5)	7.36 ± 0.01	(30)	7.54 ± 0.07	(55)	7.17 ± 0.01	(80)	11.75 ± 0.03
(6)	7.43 ± 0.07	(31)	7.41 ± 0.02	(56)	7.20 ± 0.01		
(7)	7.55 ± 0.02	(32)	7.51 ± 0.02	(57)	7.19 ± 0.09		FDM
(8)	8.13 ± 0.03	(33)	8.12 ± 0.01	(58)	7.91 ± 0.02		
(9)	8.16 ± 0.01	(34)	8.15 ± 0.01	(59)	7.93 ± 0.03	(81)	5.58 ± 0.01
(10)	8.30 ± 0.03	(35)	8.22 ± 0.02	(60)	8.03 ± 0.04	(82)	10.18 ± 0.01
(11)	8.38 ± 0.07	(36)	8.41 ± 0.03	(61)	8.24 ± 0.03		
(12)	8.44 ± 0.08	(37)	8.63 ± 0.02	(62)	8.43 ± 0.01		
(13)	8.89 ± 0.03	(38)	8.93 ± 0.01	(63)	8.63 ± 0.05		
(14)	8.94 ± 0.03	(39)	8.89 ± 0.03	(64)	8.62 ± 0.02		
(15)	11.11 ± 0.09	(40)	11.13 ± 0.07	(65)	9.96 ± 0.02		
(16)	11.41 ± 0.04	(41)	11.36 ± 0.04	(66)	10.30 ± 0.05		
(17)	11.48 ± 0.09	(42)	11.31 ± 0.05	(67)	10.28 ± 0.02		
(18)	11.66 ± 0.05	(43)	11.72 ± 0.06	(68)	10.54 ± 0.04		
(19)	11.59 ± 0.04	(44)	11.88 ± 0.05	(69)	10.65 ± 0.04		
(20)	11.96 ± 0.06	(45)	11.93 ± 0.09	(70)	10.76 ± 0.03		
(21)	12.11 ± 0.09	(46)	11.95 ± 0.09	(71)	10.98 ± 0.09		
(22)	12.13 ± 0.03	(47)	12.22 ± 0.09	(72)	10.91 ± 0.03		
(23)	12.20 ± 0.09	(48)	12.33 ± 0.07	(73)	10.94 ± 0.03		
(24)	12.28 ± 0.05	(49)	12.16 ± 0.09	(74)	10.91 ± 0.03		
(25)	12.30 ± 0.09	(50)	12.26 ± 0.06	(75)	10.88 ± 0.05		

^{a} At ionic strength μ 0.01, using imidazole pK_a 5.94 as standard.

Table 3. Parameters of regressions* with substituent constants [equation (1)]

Series	Type of σ	pK_a^0	ρ_{Im}	r	Ψ	s	n
FDM	σ	7.39	2.53 ± 0.33	0.9790	0.2202	0.1522	14
	σ^0	7.45	2.63 ± 0.21	0.9935	0.1252	0.0956	12†
ADM	σ	8.27	2.91 ± 0.34	0.9835	0.1957	0.1546	14
	σ^0	8.33	2.97 ± 0.25	0.9931	0.1288	0.1112	12†
PrpDM	σ	8.19	3.01 ± 0.34	0.9843	0.1908	0.1561	14
	σ^0	8.24	3.07 ± 0.22	0.9949	0.1105	0.0983	12†
iBtrDM	σ	8.21	3.11 ± 0.29	0.9890	0.1595	0.1338	14
	σ^0	8.26	3.14 ± 0.23	0.9946	0.1140	0.1040	12†
PivDM	σ	7.97	3.15 ± 0.37	0.9827	0.2003	0.1714	14
	σ^0	8.04	3.23 ± 0.27	0.9932	0.1276	0.1198	12†

* At a confidence level of 0.95. † Without p- and m-OEt derivatives.

Table 4. Parameters of regressions^a with pK_a values of primary amines [equation (2)]

Series	pK_a^0	α_{Im}	r	Ψ	s	n
FDM	7.29	0.62 ± 0.02	0.9969	0.0816	0.0104	24^b
	7.34	0.69 ± 0.10	0.9788	0.2226	0.0434	13^c
	6.24	0.82 ± 0.05	0.9974	0.0799	0.0198	11^d
ADM	8.16	0.75 ± 0.02	0.9983	0.0609	0.0094	24^b
	8.21	0.82 ± 0.08	0.9896	0.1566	0.0361	13^c
	7.44	0.89 ± 0.12	0.9833	0.2014	0.0549	11^d
PrpDM	8.07	0.73 ± 0.02	0.9981	0.0651	0.0097	24^b
	8.12	0.82 ± 0.09	0.9862	0.1801	0.0417	13^c
	7.78	0.78 ± 0.07	0.9934	0.1268	0.0301	11^d
iBtrDM	8.06	0.74 ± 0.03	0.9971	0.0798	0.0120	24^b
	8.14	0.87 ± 0.07	0.9929	0.1291	0.0313	13^c
	7.96	0.75 ± 0.22	0.9312	0.4030	0.0976	11^d
PivDM	7.73	0.58 ± 0.04	0.9870	0.1679	0.0200	24^b
	7.90	0.88 ± 0.10	0.9851	0.1869	0.0462	13^c
	7.40	0.63 ± 0.15	0.9545	0.3295	0.0651	11^d

^{a} At a confidence level of 0.95. ^{b} Without m-NO_2 derivatives. ^{c} Only N^2-phenyl derivatives. ^{d} Only N^2-alkyl and N^2-benzyl derivatives.

'line of the best fit' it is obvious that addition or substraction of some experimental points may alter the slope of a regression line.

Therefore we have studied series of amidines containing the same set of substituents at the imino nitrogen atom. To make possible comparison of correlations obtained for propionamidines, isobutyramidines, and pivalamidines with the previously studied formamidines[10] and acetamidines[13] we have synthesized and measured the pK_a values of a few acetamidines (76)—(80) and formamidines (81) and (82).

We have correlated the pK_a values of the amidines studied with both σ and σ^0 values.[29,30] Regression parameters are summarized in Table 2.

Consideration of the interaction of substituents with the protonation centre (imino nitrogen atom) led to the conclusion[13] that for amidines containing substituents at the phenyl ring on the imino nitrogen atom σ^0 should be most suitable. The regression parameters obtained (Table 3) indicate that for all studied series (as for other series of amidines[10,13,18])

correlations with σ^0 values are of higher quality; however correlations with ordinary σ values are still satisfactory, as indicated by the correlation coefficients r and Exner's[31] Ψ function.

The correlations provide evidence for an earlier conclusion that substituents at the functional (amidino) carbon atom exert an influence on the ρ_{Im} value.[13] Comparing the ADM, PrpDM, iBtrDM, and PivDM series one readily sees that the ρ value increases with the number of methyl groups at the α-carbon atom at the functional carbon atom. Indeed there is a good linear correlation between the ρ values and the number of methyl groups. This indicates that the ρ value may depend on the inductive effect of an alkyl substituent at the amidino carbon atom.

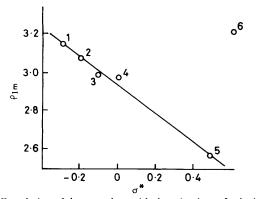We have found that the ρ_{Im} values of these series and also the

Figure. Correlation of the ρ_{Im} values with the σ^* values of substituents at the amidino carbon atom. 1, PivDM; 2, iBtrDM; 3, PrpDM; 4, ADM; 5, FDM; 6, BDM series

FDM series can be correlated with the σ^* values[32] of alkyl substituents[18] at the amidino carbon atom [equation (6)]. But

$$\rho_{Im} = \rho_{Im}^0 + \mu\sigma_F^* \qquad (6)$$

amidines containing a phenyl ring at this site (benzamidines BDM[18]) do not fit this correlation as shown in the Figure. In equation (6) ρ_{Im} is the observed ρ value for series of amidines containing various substituents at the phenyl ring on the imino nitrogen atom, and a fixed substituent at the amidino carbon atom. ρ_{Im}^0 Is the ρ_{Im} value for the ADM series (σ^* of CH_3 group = 0).

Using the least-squares method at a significance level of 0.95 the parameters for equation (6) are displayed in equation (7).

$$\rho_{Im} = (2.99 \pm 0.02) - (0.76 \pm 0.08)\sigma_F^*$$
$$r = 0.998, \ \Psi = 0.074, \ s_a = 0.0250, \ n = 5 \qquad (7)$$

The regression provides strong support for the conclusions that the sensitivity of the amidino group to substitution at the imino nitrogen atom depends on substitution at the amidino carbon atom and that for prediction of the pK_a values of amidine derivatives of aliphatic carboxylic acids an equation of type (4) should be used.

The term μ has a negative value. It indicates that the increase of the electron density at the C=N double bond, caused by the inductive effect of a substituent at the amidino carbon atom, increases the sensitivity of the amidino group to the effect of substituents at the imino nitrogen atom.

We have calculated parameters for equation (4) using the pK_a values of all 5 series (FDM, ADM, PrpDM, iBtrDM, and PivDM; total 60 compounds).

$pK_a = 8.04 - (2.99 \pm 0.20)\sigma^\circ{}_{Im} - (0.93 \pm 0.27)\sigma_F^* - (0.76 \pm 0.72)\sigma_{Im}^0\sigma_F^*$
$r = 0.973, \ \Psi = 0.239, \ s_{Im} = 0.0980, \ s_F = 0.1357, \ s_\mu = 0.3576, n = 60$

The correlation does have a predictive value. The difference between the pK_a values obtained experimentally and those calculated from equation (6) in 80% of cases does not exceed 0.3 pK_a units, and in 92% of cases does not exceed 0.35 pK_a units.

The best results are obtained for isobutyramidines, where the mean deviation is *ca.* 0.03 pK_a units. For other amidines, except those with alkoxy and *p*-nitro derivatives, it does not exceed 0.2 pK_a. The largest deviations are observed in the case of the *m*- and *p*-alkoxy derivatives: *p*-OMe-FDM −0.44; *m*-OMe-ADM 0.48; and *m*-OMe-PrpDM 0.31 pK_a.

It has to be mentioned that deviations of the pK_a values from the regression for alkoxyphenyl derivatives of amidines were

already observed in other cases,[33] and therefore they call for some attention.

A considerable deviation from the correlation between the ρ_{Im} values and the σ^* values of substituents at the amidino carbon atom observed for benzamidines (*cf.* Figure, BDM) indicates that a general equation for prediction of the pK_a values of both types of amidines, containing alkyl as well as aryl substituents at the amidine carbon atom, should contain additional terms. The most probable reason is that the σ^* values represent only inductive effects, while in the case of benz-amidines the resonance effects may be also involved. This question can be answered only as a result of investigation of properly chosen series of benzamidines.

Correlation with the pK_a *Values of Amines.*—We have correlated the pK_a values of the amidines studied with the pK_a values of the corresponding primary amines measured under the same conditions (the pK_a value of allylamine 8.95 $\pm$ 0.04, the pK_a values of other amines were already reported.[10]) Parameters of the regressions [equation (2)] are summarized in Table 4.

On account of the wider range of the pK_a values of amidines and larger numbers of experimental points, correlations with the pK_a values of corresponding primary amines are of higher quality than with the σ^0 values, as indicated by the correlation coefficients 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 certain series. However the changes of the α_{Im} values, following the changes of the σ^* values of the substituent at the functional carbon atom are not so evident as in the case of the ρ_{Im} values obtained for N^2-phenylamidines, and thus give no basis for deriving a general equation for prediction of the pK_a values of amidines containing any kind of substituent at the functional carbon atom. This is most probably due to the different influence of substitution at this site on N-alkyl- and N-aryl-amidines. As can be seen from Table 4 the α_{Im} values for N^2-alkylamidines seem to decrease with an increase of the σ^* value of the substituent at the amidino carbon atom, whereas for N^2-phenylamidines it is increasing, as expected on the basis of correlations with σ values.

Acknowledgements

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