Amidines. Part 15.[1] Influence of Substitution at Imino and Amino Nitrogen Atoms on pK_a Values of N^1-Methyl-N^1N^2-diarylacetamidines

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A series of 19 unreported N^1-methyl-N^1N^2-diarylacetamidines containing two different substituents at the phenyl rings have been synthesized and their pK_a values in 95.6% ethanol (azeotrope) measured. The pK_a values have been correlated with σ° constants of the two substituents. The influence of substitution at either of the nitrogen atoms on basicity and on the regression coefficient is discussed, and it is shown that the pK_a values of N^1N^2-diarylamidines can be predicted with satisfactory accuracy on the basis of the dual-substituent (planar) Hammett equation.

The basicity of compounds containing the amidine ($-\mathrm{N{=}\overset{|}{C}{-}N}\!<$) group depends on substitution at three sites, at the functional carbon atom, at the imino, and at the amino nitrogen atoms; therefore accurate predictions of the basicity of compounds containing this group is possible only if the influence of substituents at all these sites is known. Until recently this question was investigated only occasionally. The first published papers dealt with substitution at the functional carbon atom;[2–4] later several papers concerning substitution at the imino nitrogen atom appeared.[5–10]

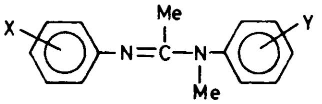
In our laboratory it was shown that amidines containing a substituted phenyl ring at the amino nitrogen atom obey the Hammet equation;[11,12] therefore it was concluded that the pK_a values of NN'-diarylamidines containing two different substituents at the two phenyl rings obey equation (1) where σ_{Im} and σ_{Am} are the σ constants of substituents on phenyl rings at the imino and amino nitrogen atoms, respectively. Consequently amidines containing three variable substituents should obey equation (2) where σ_F is the σ constant of a substituent in the phenyl ring at the functional carbon atom.

$$pK_a = pK_a^\circ - \rho_{\mathrm{Im}}\sigma_{\mathrm{Im}} - \rho_{\mathrm{Am}}\sigma_{\mathrm{Am}} \qquad (1)$$

$$pK_a = pK_a^\circ - \rho_{\mathrm{Im}}\sigma_{\mathrm{Im}} - \rho_{\mathrm{Am}}\sigma_{\mathrm{Am}} - \rho_F\sigma_F \qquad (2)$$

Both equations imply that for different series of amidines in which the phenyl ring with a variable substituent is at the same site the ρ values should be identical. However obtained, ρ_{Im} and ρ_{Am} values for N^1-methyl-N^1N^2-diaryl-formamidines[11] and -benzamidines[12] appeared to be different, thus indicating that they may depend on substitution at the amidine carbon atom. Recently, comparing correlations of pK_a values of N^1N^1-dimethyl-formamidines[13] and -acetamidines[14] with σ° constants as well as with pK_a values of the corresponding amines we found that the sensitivity of the amidine group to substitution at the imino nitrogen atom (ρ_{Im} and α_{Im} values) depends to a considerable degree on substitution at the amidine carbon atom.[14] The assumption that it is independent of substitution at that site may cause considerable error. As a consequence, the question arose whether the ρ_{Im} and ρ_{Am} values depend to any considerable extent on substitution at the second nitrogen atom, and in consequence whether for the prediction of the pK_a values of amidines containing substituted phenyl rings at the nitrogen atoms, equation (1) should be used, or rather an equation with a term taking into account the mutual interaction of the substituents.

For this reason we have synthesized a series of N^1-methyl-N^1N^2-diarylacetamidines (ADPhM) (1)—(19) containing two different substituents at the two phenyl rings and measured their pK_a values in 95.6% ethanol.



	X	Y		X	Y
(1)	*p*-OMe	*p*-OMe	**(11)**	H	H
(2)	*p*-OMe	H	**(12)**	H	*p*-Br
(3)	*p*-OMe	*m*-Cl	**(13)**	H	*m*-Cl
(4)	*p*-Me	*p*-Me	**(14)**	*p*-Br	*p*-Me
(5)	*p*-Me	H	**(15)**	*p*-Br	H
(6)	*p*-Me	*m*-Cl	**(16)**	*p*-Br	*p*-Br
(7)	*m*-Me	*p*-OMe	**(17)**	*m*-Cl	*p*-OMe
(8)	*m*-Me	H	**(18)**	*m*-Cl	H
(9)	H	*p*-OMe	**(19)**	*m*-Cl	*m*-Cl
(10)	H	*p*-Me			

Experimental

Synthesis of Acetamidines.—The N^1-methyl-N^1N^2-diarylacetamidines (1)—(19) were synthesized, similarly to benzamidines,[12] by reaction of substituted *N*-methylanilines with substituted *N*-phenylacetimidoyl chlorides. The structures of amidines were confirmed by ^{1}H n.m.r. spectra recorded at 80 MHz for $CDCl_3$ solutions at room temperature. The number of protons in each group are consistent with the structures assigned. Chemical shifts are summarized in Table 1.

Purity of Acetamidines.—The acetamidines were 95% pure, and free of unchanged amines. Their purity was checked by g.l.c. at 280 °C as described earlier.[14] Retention indices are summarized in Table 1.

pK_a Measurements.—pK_a Values were determined by potentiometric titration in 95.6% ethanol (azeotrope) at 25.0 ± 0.1 °C in the presence of tetramethylammonium chloride,[14] and calculated from relation (3)[15] 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 $x = 1/4$, $1/2$, and $3/4$ neutralization points.

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

As the standard, imidazole (pK_a 5.95 in 95.6% ethanol[14]) was used. Discussion of experimental details securing the reproducibility as well as the reliability of measured pK_a values is given in previous papers.[13,14,16] The pK_a values and

Table 1. Characterization of obtained N^1-methyl-N^1N^2-diarylacetamidines (**1**)—(**19**)

<table>
<tr><th rowspan="3">Acetamidine</th><th rowspan="3">Formula</th><th rowspan="3">M.p. (°C)</th><th rowspan="3">Retention index</th><th colspan="14">^{1}H N.m.r. spectra assignments (δ)</th></tr>
<tr><th rowspan="2">$>$C–Me</th><th rowspan="2">N–Me</th><th colspan="6">Phenyl ring at N_{Am}</th><th colspan="6">Phenyl ring at N_{Im}</th></tr>
<tr><th>H-2</th><th>H-6</th><th>H-3</th><th>H-5</th><th>H-4</th><th>Me</th><th>H-2</th><th>H-6</th><th>H-3</th><th>H-5</th><th>H-4</th><th>Me</th></tr>
<tr><td>(1)</td><td>$C_{17}H_{20}N_2O_2$</td><td>[a]</td><td>2 474 ± 1</td><td>1.64</td><td>3.34</td><td colspan="2">7.11</td><td colspan="2">6.88</td><td></td><td>3.75</td><td colspan="2">6.43</td><td colspan="2">6.43</td><td></td><td>3.75</td></tr>
<tr><td>(2)</td><td>$C_{16}H_{18}N_2O$</td><td>[a]</td><td>2 211 ± 2</td><td>1.65</td><td>3.35</td><td colspan="2">7.18[b]</td><td colspan="2">7.18[b]</td><td>7.18[b]</td><td></td><td colspan="2">6.51</td><td colspan="2">6.51</td><td></td><td>3.70</td></tr>
<tr><td>(3)</td><td>$C_{16}H_{17}ClN_2O$</td><td>[a]</td><td>2 415 ± 3</td><td>1.68</td><td>3.36</td><td colspan="2">7.21</td><td colspan="2">7.21</td><td>7.21</td><td></td><td colspan="2">6.55</td><td colspan="2">6.55</td><td></td><td>3.75</td></tr>
<tr><td>(4)</td><td>$C_{17}H_{20}N_2$</td><td>97—98</td><td>2 147 ± 2</td><td>1.68</td><td>3.39</td><td colspan="2">7.16</td><td colspan="2">7.13</td><td></td><td>2.38</td><td colspan="2">6.73</td><td colspan="2">7.06</td><td></td><td>2.31</td></tr>
<tr><td>(5)</td><td>$C_{16}H_{18}N_2$</td><td>75—77</td><td>2 059 ± 3</td><td>1.64</td><td>3.35</td><td colspan="2">7.26[b]</td><td colspan="2">7.26[b]</td><td>7.26[b]</td><td></td><td colspan="2">6.70</td><td colspan="2">7.06</td><td></td><td>2.26</td></tr>
<tr><td>(6)</td><td>$C_{16}H_{17}ClN_2$</td><td>[a]</td><td></td><td>1.66</td><td>3.33</td><td colspan="2">7.26</td><td colspan="2">7.26</td><td>7.26</td><td></td><td colspan="2">6.70</td><td colspan="2">7.08</td><td></td><td>2.26</td></tr>
<tr><td>(7)</td><td>$C_{17}H_{20}N_2O$</td><td>48—51</td><td>2 283 ± 0</td><td>1.65</td><td>3.35</td><td colspan="2">7.14</td><td colspan="2">6.89</td><td></td><td>3.81</td><td>6.55</td><td>6.61</td><td></td><td>7.15</td><td>6.79</td><td>2.30</td></tr>
<tr><td>(8)</td><td>$C_{16}H_{18}N_2$</td><td>40—43</td><td>2 041 ± 2</td><td>1.64</td><td>3.35</td><td colspan="2">7.23[b]</td><td colspan="2">7.23[b]</td><td>7.23[b]</td><td></td><td>6.56</td><td>6.61</td><td></td><td>7.16</td><td>6.79</td><td>2.28</td></tr>
<tr><td>(9)</td><td>$C_{16}H_{18}N_2O$</td><td>[a]</td><td>2 196 ± 5</td><td>1.65</td><td>3.36</td><td colspan="2">7.18</td><td colspan="2">6.94</td><td></td><td>3.81</td><td colspan="2">6.84</td><td colspan="2">7.30[b]</td><td>7.00[b]</td><td></td></tr>
<tr><td>(10)</td><td>$C_{16}H_{18}N_2$</td><td>[a]</td><td>2 117 ± 0</td><td>1.68</td><td>3.36</td><td colspan="2">7.08</td><td colspan="2">7.11</td><td></td><td>2.35</td><td colspan="2">6.79</td><td colspan="2">7.24</td><td>7.00[b]</td><td></td></tr>
<tr><td>(11)</td><td>$C_{15}H_{16}N_2$</td><td>[a]</td><td>1972 ± 0</td><td>1.68</td><td>3.41</td><td colspan="2">7.28</td><td colspan="2">7.28</td><td>7.28</td><td></td><td colspan="2">6.83</td><td colspan="2">7.28</td><td>7.06[b]</td><td></td></tr>
<tr><td>(12)</td><td>$C_{15}H_{15}BrN_2$</td><td>56—59</td><td>2 252 ± 3</td><td>1.68</td><td>3.34</td><td colspan="2">7.06</td><td colspan="2">7.28</td><td></td><td></td><td colspan="2">6.76</td><td colspan="2">7.26</td><td>7.01[b]</td><td></td></tr>
<tr><td>(13)</td><td>$C_{15}H_{15}ClN_2$</td><td>[a]</td><td>2 156 ± 3</td><td>1.70</td><td>3.38</td><td colspan="2">7.23</td><td colspan="2">7.23</td><td>7.23</td><td></td><td colspan="2">6.80</td><td colspan="2">7.26</td><td>7.06[b]</td><td></td></tr>
<tr><td>(14)</td><td>$C_{16}H_{17}BrN_2$</td><td>114—115</td><td>2 358 ± 3</td><td>1.64</td><td>3.35</td><td colspan="2">7.10</td><td colspan="2">7.10</td><td></td><td>2.35</td><td colspan="2">6.70</td><td colspan="2">7.20</td><td></td><td></td></tr>
<tr><td>(15)</td><td>$C_{15}H_{15}BrN_2$</td><td>109—110</td><td>2 231 ± 3</td><td>1.65</td><td>3.35</td><td colspan="2">7.28</td><td colspan="2">7.28</td><td>7.28</td><td></td><td colspan="2">6.68</td><td colspan="2">7.26</td><td></td><td></td></tr>
<tr><td>(16)</td><td>$C_{15}H_{14}Br_2N_2$</td><td>65—67</td><td>2 565 ± 3</td><td>1.65</td><td>3.34</td><td colspan="2">7.09</td><td colspan="2">7.31</td><td></td><td></td><td colspan="2">6.66</td><td colspan="2">7.36</td><td></td><td></td></tr>
<tr><td>(17)</td><td>$C_{16}H_{17}ClN_2O$</td><td>37—39</td><td>2 387 ± 2</td><td>1.64</td><td>3.31</td><td colspan="2">7.11</td><td colspan="2">6.90</td><td></td><td>3.81</td><td>6.84</td><td>6.68</td><td></td><td>7.18</td><td>[c]</td><td></td></tr>
<tr><td>(18)</td><td>$C_{15}H_{15}ClN_2$</td><td>39—41</td><td>2 165 ± 4</td><td>1.61</td><td>3.30</td><td colspan="2">7.26</td><td colspan="2">7.26</td><td>7.26</td><td></td><td>6.85</td><td>6.69</td><td></td><td>7.20</td><td>7.00</td><td></td></tr>
<tr><td>(19)</td><td>$C_{15}H_{14}ClN_2$</td><td>46—48</td><td>2 311 ± 4</td><td>1.68</td><td>3.31</td><td colspan="2">7.23</td><td colspan="2">7.23</td><td>7.23</td><td></td><td>6.77</td><td>6.64</td><td></td><td>7.16</td><td>6.94</td><td></td></tr>
</table>

[a] Oil. [b] ±0.05 p.p.m. [c] Uncertain.

calculated confidence intervals at the 0.95 significance level are summarized in Table 2. The error in pK_a determinations as discussed previously[13] 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 the standard, but it has no influence on the regression coefficient.

Results and Discussion

In investigations on the relation between structure and properties of organic compounds the proper choice of σ values is very often a crucial point. The proper choice of parameters can be achieved as a result of consideration of possible interactions of substituents with the reaction centre. Thus we have shown[14] that in the case of amidines containing variable substituents on the phenyl rings at either of the nitrogen atoms σ° values should be used, while ordinary σ values are suitable only for substituents on the phenyl ring at the amidine carbon atom.

In this study N^1N^2-diarylacetamidines containing a methyl group at the amino nitrogen atom were chosen as they do not display tautomerism. Pairs of substituents for which σ° constants are not collinear as indicated by the correlation coefficient of the linear relationship between them ($r = 0.014$) were selected. These conditions ensure that the correlations of pK_a with substituent constants represent the influence of substitution at either of the nitrogen atoms on the basicity of acetamidines.

As the main question in this work was the influence of the substituent at one of the nitrogen atoms on the sensitivity to substitution at the second nitrogen, we have correlated the pK_a values with σ° constants[17] using two relations, the above mentioned equation (1), and equation of a 'twisted plane' (4) discussed previously[14] similar to those proposed in the literature.[18–20] Both equations ensure that if the substituent at one of the sites is invariable a linear correlation will be obtained. But in the first case the slopes of all the regression lines are identical, and in the second the regression lines are not parallel, and their slopes depend on the σ value of the invariant substituent, and on the term μ representing the mutual interaction of substituents.

$$\mathrm{p}K_a = \mathrm{p}K_a^\circ - \rho_{\mathrm{Im}}\sigma_{\mathrm{Im}} - \rho_{\mathrm{Am}}\sigma_{\mathrm{Am}} - \mu\sigma_{\mathrm{Im}}\sigma_{\mathrm{Am}} \qquad (4)$$

The first attempts at correlations indicated that for some unknown reason the pK_a value of N^1-methyl-N^1N^2-bis-(p-methoxyphenyl)acetamidine (**1**) strongly deviates from both correlations. It should be mentioned that distinct deviation from correlation was observed in the case of other previously studied N^1N^2-diphenylamidines containing two p-methoxyphenyl rings.[11,12,21]

Thus, neglecting the pK_a value of this compound, for the remaining 18 acetamidines at a significance level of 0.95 the following parameters have been found by the least-squares method:

for the planar equation (1)

$$\mathrm{p}K_a = 6.90 - (2.88 \pm 0.18)\sigma^\circ_{\mathrm{Im}} - (1.42 \pm 0.16)\sigma^\circ_{\mathrm{Am}} \qquad (5)$$
$$s_o = 0.019, \quad s_{\mathrm{Im}} = 0.086, \quad s_{\mathrm{Am}} = 0.083$$
$$r = 0.995, \quad s = 0.070$$

for the twisted plane equation (4)

$$\mathrm{p}K_a = 6.91 - (2.94 \pm 0.15)\sigma^\circ_{\mathrm{Im}} - (1.46 \pm 0.13)\sigma^\circ_{\mathrm{Am}} - (0.87 \pm 0.67)\sigma^\circ_{\mathrm{Im}}\sigma^\circ_{\mathrm{Am}} \qquad (6)$$
$$s_o = 0.015, \quad s_{\mathrm{Im}} = 0.071, \quad s_{\mathrm{Am}} = 0.062, \quad s_\mu = 0.310$$
$$r = 0.997, \quad s = 0.058$$

Table 2. pK_a Values of N^1-methyl-N^1N^2-diarylacetamidines in 95.6% EtOH at (25 ± 0.1) °C *

Compound	pK_a	Compound	pK_a
(**1**)	7.17 ± 0.02	(**11**)	6.96 ± 0.01
(**2**)	7.58 ± 0.02	(**12**)	6.48 ± 0.02
(**3**)	6.89 ± 0.03	(**13**)	6.45 ± 0.03
(**4**)	7.41 ± 0.03	(**14**)	6.29 ± 0.03
(**5**)	7.34 ± 0.03	(**15**)	6.10 ± 0.03
(**6**)	6.78 ± 0.03	(**16**)	5.77 ± 0.02
(**7**)	7.44 ± 0.03	(**17**)	6.05 ± 0.02
(**8**)	7.07 ± 0.03	(**18**)	5.90 ± 0.02
(**9**)	7.24 ± 0.04	(**19**)	5.40 ± 0.03
(**10**)	7.19 ± 0.04		

* At ionic strength $\mu \doteq 0.01$, using imidazole, pK_a 5.95, as a standard.

The pK_a°, ρ_{Im}, and ρ_{Am} parameters of both equations (5) and (6) are identical within the confidence intervals, and the 'cross term' of equation (6) is highly uncertain, as the confidence interval amounts to > 75% of the μ value. This leads to the conclusion that the pK_a values of N^1-methyl-N^1N^2-diarylacetamidines (ADPhM) are best explained by the planar equation (5). It means that the influence of substituents on the phenyl ring at one of the nitrogen atoms on the sensitivity to the effects of substituents on the second nitrogen atom is negligible.

The influence of substitution at the amino nitrogen atom can be visualized by a comparison of the ρ_{Im} value of N^1-methyl-N^1N^2-diarylacetamidines (ADPhM), and the previously studied[14] N^1N^1-dimethylacetamidines (ADM). Substituent effects are more prominent if observed over a large interval of substituent constants as discussed in the case of amidines containing both aryl, alkyl, and aralkyl groups at the nitrogen atom.[13,14,16,22] In order to ensure reliable results we have calculated regression lines (ρ_{Im}) for ADPhM with an unsubstituted phenyl ring at the amino nitrogen atom ($\sigma^\circ_{\mathrm{Am}} = 0$), and for ADM taking into account only compounds containing the same substituents in both series. By the least-squares method the following parameters have been obtained ($n = 6$):

$$\text{ADPhM:} \quad \rho_{\mathrm{Im}} = 2.92 \pm 0.23, r = 0.998, s = 0.082$$

$$\text{ADM:} \quad \rho_{\mathrm{Im}} = 2.84 \pm 0.21, r = 0.999, s = 0.075$$

The test of parallelism discloses that the slopes of both regression lines cannot be treated as different.

The identity of the slopes of regression lines (ρ_{Im}) in the case of such different substituents at the amino nitrogen atom as phenyl and methyl provides further support for the conclusion on the applicability of equation (5). The difference between the measured pK_a values, and those predicted from equation (5) for the acetamidines [except (**1**)] does not exceed 0.15 pK units, and for 12 compounds is smaller than 0.05 pK units. However, the differences between ρ values obtained for amidines containing different substituents at the amidine carbon atom, *i.e.* formamidines, acetamidines, and benzamidines, indicate that the equation for amidines with two variable substituents, one of which is at the functional carbon atom, should contain the cross-term discussed above.

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Received 8*th May* 1984; *Paper* 4/727