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Concerning the Basicity of 4-Dimethylaminoquinazoline Derivatives

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Summary. Two series of selected 4-N,N-dimethylamino-2-phenylquinazoline and 2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline derivatives obtained in the reaction of substituted N-phenylbenzimidoyl chlorides or N^1,N^1-diethyl-N^2-phenylchlorocarboxyamidines with N,N-dimethylcyanamide in the presence of $TiCl_4$ were examined in order to detect the protonation centre. The untypical correlations between pK_a and σ were supported by MNDO calculations and single crystal X-ray diffraction data and point to a protonation of the ring-N-atoms with delocalization of the positive charge into the N,N-dimethylamino group.

Keywords. 4-N,N-Dimethylaminoquinazolines; UV/Vis spectroscopy; X-Ray structure determination; pK_a values, pK_a *vs.* σ correlation.

Introduction

The basicity of 4-aminoquinazolines still remains a controversial question [1]. In principle, there are three or even four potential protonation sites in compounds such as 2,4-diaminoquinazolines. These are the two endocyclic nitrogen atoms with free electron pairs and the exocyclic amine nitrogen atoms. The identification of the site most susceptible to protonation is a very important problem because some quinazoline derivatives exhibit a biological activity due to their acid-base interactions. A similar problem we have met earlier studying the basicity of 4-N,N-dimethylamino-2-phenylquinazolines substituted in *meta* and *para* positions of the 2-phenyl ring with electron donating and withdrawing groups [2]. This time we have examined two groups of selected 6- or 7-substituted 4-N,N-dimethylamino-2-phenylquinazoline and 2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline derivatives. We have determined the influence of the phenyl ring substituents in the quinazoline system on the basicity of the parent system. We have also tried to explain the electron effects of large substituents in the position 4 of the quinazoline which in our opinion leads to an untypical correlation between pK_a values and σ parameters.

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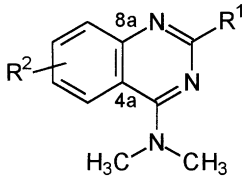
Results and Discussion

Two series of 4-N,N-dimethylamino-2-phenylquinazoline and 2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline compounds substituted at positions 6 and 7 (**1**–**14**) were synthesized according to a known method [3, 4] by reacting N-phenylbenzimidoyl chlorides or N^1,N^1-diethyl-N^2-phenylchlorocarboxyamidines with N,N-dimethylcyanamide in the presence of $TiCl_4$ as the catalyst.

The pK_a dissociation constants of **1**–**14** were determined in 10^{-5} *M* solutions using the spectrophotometric method (see Experimental) [5]. Due to the low solubilities of the title compounds in water, their pK_a values were measured in a 50% solution of aqueous methanol at 20.0±0.1°C. Our studies show that the nature of the substituent in position 6 or 7 of the quinazoline ring in 4-N,N-dimethylamino-2-R^1-quinazoline derivatives greatly affects the pK_a values. Donor substituents cause an increase in basicity compared with the pK_a of **1** (R^2 = H), and electron withdrawing substituents cause a decrease in basicity. The pK_a values were correlated with appropriate *Hammett* σ constants [6]. According to *Charton's* suggestions who has examined the application of different substituent constants in aromatic systems [7] and to our earlier studies [8,9] we have used the original *Hammett* σ_m and σ_p constants.

The application of σ_p constants for 6-substituted derivatives and σ_m constants for 7-substituted compounds gives satisfactory results (Fig. 1; Table 1, entries 1 and 3).

It should be mentioned that these correlations are not consistent with *Charton's* results on 6- and 7-substituted quinolines [7], our earlier research on the basicity of isoquinolines [9], and investigations on electron interactions in monosubstituted alternating systems [10]. To our knowledge, this is the first stated case where a reversed electron effect transfer takes place in a bicyclic benzo-fused heteroaromatic system. Deviations from electron interactions in alternating systems have been observed earlier in 1-methyl-4-phenyl-2-quinazolinone compounds substituted in position 6 where the correlation analysis between the half neutralization potential gives satisfactory results when *Hammett* σ_p constants are used [11]. However, it should be noticed that the typical aromatic structure is destroyed in the pyrimidine ring in this case. An analogy between the cited example and the considered system could be found in a bulky group interaction (N,N-dimethylamino group) in position 4 by steric and electron effects. The primary steric effect which is connected with the interaction of the substituent in position 2



1-14

	R^1	R^2		R^1	R^2
1:	C_6H_5	H	**8**:	$N(C_2H_5)_2$	H
2:	C_6H_5	6-OCH_3	**9**:	$N(C_2H_5)_2$	6-OCH_3
3:	C_6H_5	6-CH_3	**10**:	$N(C_2H_5)_2$	6-Cl
4:	C_6H_5	6-Br	**11**:	$N(C_2H_5)_2$	6-NO_2
5:	C_6H_5	7-OCH_3	**12**:	$N(C_2H_5)_2$	7-OCH_3
6:	C_6H_5	7-CH_3	**13**:	$N(C_2H_5)_2$	7-Cl
7:	C_6H_5	7-NO_2	**14**:	$N(C_2H_5)_2$	7-NO_2

Scheme 1

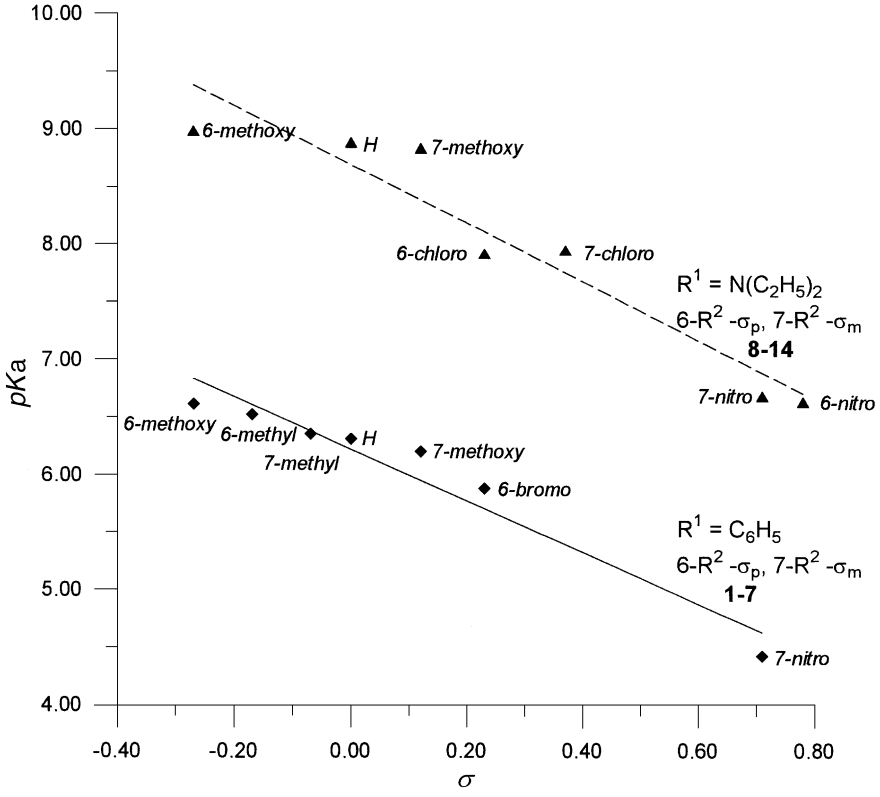


Fig. 1. Correlation of *Hammet's* constants with pK_a

Table 1. Results of pK_a *vs* σ correlation for two (6,7)-R^2-4-N,N-dimethylamino-2-R^1-quinazoline series (**1–7**, **8–14**)

Entry	R^1	Correlation type	Equation	S^a	r^b	n^c
1	C_6H_5	6-R^2-σ_p, 7-R^2-σ_m	$pK\text{a} = 6.218–2.245 \cdot \sigma$	0.1979	0.9417	7
2.	C_6H_5	6-R^2-σ_m, 7-R^2-σ_p	$pK_a = 6.236–1.746 \cdot \sigma$	0.9748	0.7132	7
3.	$N(C_2H_5)_2$	6-R^2-σ_p, 7-R^2-σ_m	$pK_a = 8.685–2.549 \cdot \sigma$	0.5133	0.9151	7
4.	$N(C_2H_5)_2$	6-R^2-σ_m, 7-R^2-σ_p	$pK_a = 8.666–2.481 \cdot \sigma$	0.8042	0.8671	7

[a] Residual sum of squares; [b]correlation coefficient; [c]number of data points used

or 4 with the free electron pairs of the ring nitrogen atoms should not be of great importance. The secondary steric effect [12], interpreted as the interaction between a large substituent in position 4 of the quinazoline with a hydrogen atom in position 5, becomes important here. Single crystal X-ray diffraction analysis of **12** showed that the C4-C4a bond measures 1.455 Å (Table 2) and is thus considerably longer than that in the corresponding quinazoline (1.410 Å) [13]. The data from the X-ray diffraction analysis have been corroborated by MNDO calculations for **1** and **8** where the calculated bond lengths are 1.461 Å and 1.445 Å (Table 2).

It might be assumed that the secondary steric effect resulting from the interaction of the large N,N-dimethylamino group with the hydrogen atom at position 5 and its strong induction effect cause a decrease of the electron density of the C4-C4a bond.

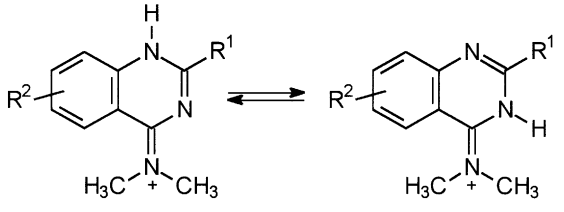
Table 2. Selected bond lengths (Å) for quinazoline [13] and its derivatives taken from MNDO calculations and X-ray structure analysis

	Quinazoline	Quinazoline	**1**	**8**	**12**
N1–C2	1.310	1.331	1.339	1.349	1.348
C2–N3	1.351	1.383	1.330	1.388	1.328
N3–C4	1.307	1.327	1.347	1.333	1.338
C4–N$(CH_3)_2$	–	–	1.403	1.437	1.342
C2–R^1	–	–	1.488	1.395	1.346
C4–C4a	1.410	1.441	1.461	1.445	1.455
C8a–N1	1.372	1.381	1.373	1.372	1.393
Method	X-ray	MNDO	MNDO	MNDO	X-ray

In that case, the electron effects of the substituents in the benzene ring of the 4-N,N-dimethylamino-2-R^1-quinazoline derivatives are mostly transferred *via* C8a-N1 bond. Its length is similar to that in unsubstituted quinazoline and indicates delocalization features. Thus, the electron transfer in these systems occurs in the same way as in substituted aniline, where the substituents in position 4 correspond to those in position 6 of the quinazoline system and are well correlated with the *Hammett* σ_p constants. The substituents in position 3 of aniline correspond to quinazoline substituents in position 7 and are correlated with the *Hammett* σ_m constants. Unsufficient correlation coefficients ($r_1 = 0.9417$, $r_3 = 0.9151$) in these cases could suggest that there is not only one explicity defined protonation site. Single crystal X-ray diffraction analysis of 2-(4-methoxyphenyl)-4-N,N-dimethylamino-quinazoline hydrochloride shows that protonation occurs on the endocyclic nitrogen atom in position 1 [2]. However, ^{15}N NMR measurements of $\mathbf{1} \cdot CF_3COOH$ indicate that there is a fast hydrogen exchange between the two endocyclic nitrogen atoms and that a positive charge is concentrated on the exocyclic nitrogen atom of the dimethylamino group (Scheme 2) [14].

In the ^{1}H NMR spectrum of $\mathbf{1} \cdot CF_3COOH$, an NH signal has been observed at 11.3 ppm. The coupling constant between the exocyclic nitrogen atom and the proton in the ^{15}N NMR spectrum (5 Hz) also testifies to the occurrance of only a weak interaction of the proton and the exocyclic nitrogen atom [14].

In conclusion, electron effects of large substituents in position 4 of the quinazoline strongly disturb the aromacity of the heterocyclic system of the title compounds and lead to a weakening of the C4-C4a bond. In consequence, the effect of the electron transfer through this bond is considerably limited, and an untypical correlation between pK_a values and σ parameters is obtained.



Scheme 2

Experimental

UV spectra were recorded with a Shimadzu UV-2102 spectrophotometer; basic medium: 0.05 *M* NaOH in 50% aqueous methanol solution, acidic medium: 0.05 *M* HCl in 50% aqueous methanol solution. Absorption maxima of the quinazoline ions (E_2 and B band) were selected as analytical wavelengths. Elementary analysis were carried out by means of a Perkin Elmer 240 c analyser and were in satisfactory agreement with the calculated values. ^{1}H NMR spectra were recorded on a Varian Inova 300 NMR spectrometer, mass spectra on a Shimadzu QP-200 mass spectrometer. Single crystal X-ray analysis was carried out on Siemens R3m/V apparatus.

4-N,N-Dimethylamino-2-phenylquinazoline (**1**; $C_{16}H_{15}N_3$)

Ref. [3]; $pK_a = 6.31 \pm 0.07$.

6-Methoxy-4-N,N-dimethylamino-2-phenylquinazoline (**2**; $C_{17}H_{17}N_3O \cdot 0.5H_2O \cdot HCl$)

Yield: 85%; m.p.: 215–216°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.50$ (6H, s, $N(CH_3)_2$), 3.90 (3H, s, OCH_3), 6.90–8.45 (8H, m) ppm; UV: λ_{max} ($\varepsilon \times 10^{-3}$): acidic: 277.2 (25.36), 215.7 (21.02), basic: 327.6 (12.42), 251.1 (26.34), 216.6 (27.90) nm; MS: *m/z* (%) 279 (M^+, 45); $pK_a = 6.61 \pm 0.16$.

6-Methyl-4-N,N-dimethylamino-2-phenylquinazoline (**3**; $C_{17}H_{17}N_3 \cdot 0.5H_2O \cdot HCl$)

Ref. [3]; $pK_a = 6.52 \pm 0.13$.

6-Bromo-4-N,N-dimethylamino-2-phenylquinazoline (**4**; $C_{16}H_{17}N_3Br \cdot 0.5H_2O \cdot HCl$)

Ref. [3]; $pK_a = 5.88 \pm 0.15$.

7-Methoxy-4-N,N-dimethylamino-2-phenylquinazoline (**5**; $C_{17}H_{17}N_3O \cdot 0.5H_2O \cdot HCl$)

Ref. [3]; $pK_a = 6.20 \pm 0.04$.

7-Methyl-4-N,N-dimethylamino-2-phenylquinazoline (**6**; $C_{17}H_{17}N_3 \cdot 0.5H_2O \cdot HCl$)

Ref. [3]; $pK_a = 6.35 \pm 0.20$.

7-Nitro-4-N,N-dimethylamino-2-phenylquinazoline (**7**; $C_{16}H_{14}N_4O_2 \cdot H_2O$)

Yield: 45%; m.p.: 103–105°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.50$ (6H, s, $N(CH_3)_2$), 7.20–9.15 (8H, m) ppm; UV:λ_{max} ($\varepsilon \times 10^{-3}$): acidic: 234.8 (24.03), 200.5 (30.06), basic: 269.3 (21.24), 235.3 (19.50), 203.0 (33.28) nm; MS: *m/z* (%) = 294 (M^+, 51); $pK_a = 4.42 \pm 0.25$.

2-N,N-Diethylamino-4-N,N-dimethylamino-quinazoline (**8**; $C_{14}H_{20}N_4 \cdot H_2O \cdot HCl$)

Ref. [4]; $pK_a = 8.88 \pm 0.09$.

6-Methoxy-2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline (**9**; $C_{15}H_{22}N_4O \cdot H_2O \cdot HCl$)

Ref. [4]; $pK_a = 8.98 \pm 0.05$.

6-Chloro-2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline (**10**; $C_{14}H_{19}N_4 \cdot H_2O \cdot HCl$)

Ref. [4]; $pK_a = 7.91 \pm 0.05$.

6-Nitro-2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline (**11**; $C_{14}H_{19}N_5O_2$)

Ref. [4]; $pK_a = 6.63 \pm 0.06$.

7-Methoxy-2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline (**12**; $C_{15}H_{22}N_4O \cdot H_2O \cdot HCl$)

$pK_a = 8.83 \pm 0.08$; X-ray analysis: MW 328.8, monoclinic space group, $P2_1/n$, $a = 8.927(3)$, $b = 9.844(2)$, $c = 19.902(4)$ Å, $\beta = 95.10(2)^\circ$, $V = 1741.5(5)$ Å^3, $D_{calc} = 1.254\,mg/m^3$, $\mu(MoK_\alpha) = 0.232\,mm^{-1}$.

7-Chloro-2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline (**13**; $C_{14}H_{19}N_4 \cdot H_2O \cdot HCl$)

Ref. [4]; $pK_a = 7.94 \pm 0.13$.

7-Nitro-2-N,N-diethylamino-4-N,N-dimethylamino-quinazoline (**14**; $C_{14}H_{19}N_5O_2$)

Ref. [4]; $pK_a = 6.68 \pm 0.24$.

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