

Acid-base interactions in some isoquinoline and quinazoline amino derivatives

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Dedicated to Professor Lubor Fisera on the occasion of his 60th birthday
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Abstract

Few groups of substituted 1-aminoisoquinoline, 4-amino- and 2,4-diaminoquinazoline derivatives have been examined in order to find general relationships between the basicity and a kind of substituent. pK_a Values have been determined for these compounds and correlated with the original Hammett σ_m and σ_p constants. They clearly showed that the steric effects of the bulky substituents neighbouring the protonated ring nitrogen atom influence the electron transfer in such arrangements. Different tendencies in the electron transfer caused by the same groups in the position 1 of isoquinoline and position 4 of quinazoline have been also discussed. The ρ value, single crystal X-ray analysis, ^{15}N -NMR spectra and MNDO calculations give evidence about the electronic effects and the preferential site of protonation in such arrangements.

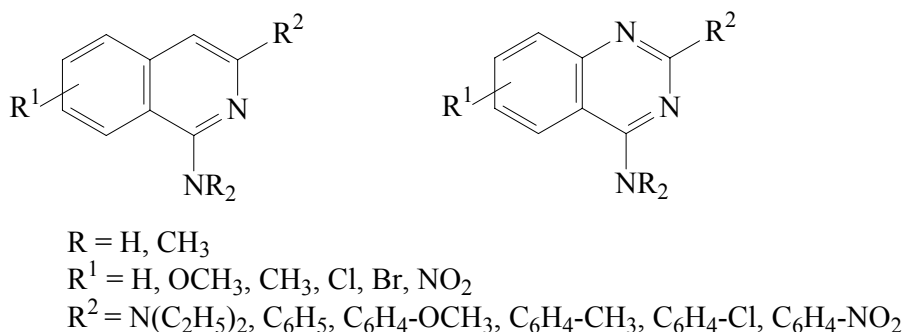
Keywords: 1-Aminoisoquinolines, 4-aminoquinazolines, 2,4-diaminoquinazolines, pK_a dissociation constants, pK_a vs σ correlation, basicity, steric effect

Introduction

Compounds containing a fused quinazoline or isoquinoline ring belong to a broad class of compounds which has received a considerable attention over the past years due to their wide range of biological activities.^{1,2} Some of aminoquinazoline derivatives were found to be inhibitors of the tyrosine kinase^{3,4} or dihydrofolate reductase enzymes^{5,6} so they work as potent anticancer agents. They are also used to work out medicines against hypertension, malaria and to fight infections involving AIDS.⁷ Some isoquinoline derivatives are known due to the central-nervous-system activity which they show.⁸

A biological activity of the compound strongly depends on acid-base interactions which is an addition to behaviour associated with its permeability through cell membranes and its spatial structure.¹ That is why an analysis of acid-base equilibrium and factors influencing these equilibrium are very important questions. The matter of this study is the analysis of acid-base interactions of the three groups of compounds: 1-aminoisoquinolines, 4-aminoquinazolines and 2,4-diaminoquinazolines. Such different compounds are characterized by the common amidine function built in the aromatic ring and a presence of two basic centers at least connecting with free electron pairs of endocyclic and exocyclic nitrogen atoms. If the basicity of 1-aminoisoquinolines is well defined in so far⁹⁻¹³ it is still controversial question in the case of 4-amino- or 2,4-diaminoquinazolines. It is proved that the first protonation of the nitrogen heterocycles with the amino substituent takes place unexpectedly at the ring nitrogen atom. In contrast to the first proton addition which occurs in dilute acid solutions, the second protonation needs strong acids because the basicity of the monoprotonated form is relatively small. An introduction of the second electronwithdrawing nitrogen atom to the ring decreases the basicity of the compound in respect to isoquinoline moiety. Generally, aminoquinazolines^{1,4,15} are weaker bases in comparison to their isoquinoline counterparts.¹⁶ An interpretation of pK_a dissociation constants of some quinazolines determined in water solutions is complicated in many cases by the covalent hydration of water molecule across a 3,4-double quinazoline bond.^{15,17} The observed values are lower even about 2 units in pK_a scale in respect to the values of the anhydrous species.¹⁴ The 4 position of quinazoline is directly involved in the reversible water addition so it was proved that the steric and inductive effects of the substituents in this position have a marked effect on the covalent hydration.¹⁸ The introduction of the amino group in the 2 or 4 position of quinazoline decreases hydration in cation considerably. The covalent hydration is almost prevented if hydrogen atoms of the amino group in the mentioned positions are replaced by the electron donating substituents such as CH_3 .¹⁵

Few groups of aminoisoquinolines and mono- and diaminoquinazolines (Scheme 1) were analyzed to find general relationships between the basicity and a kind of substituent.



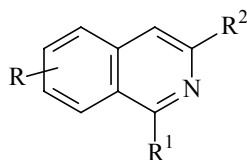
Scheme 1

There were 3-methyl-1-(*N,N*-dimethylamino)isoquinoline and 3-(*N,N*-diethylamino)-1-(*N,N*-dimethylamino)isoquinoline derivatives substituted in the position 6 or 7 with electron-donating and withdrawing groups, 1-amino-3-(*N,N*-diethylamino)isoquinoline and 1-amino-3-methylisoquinoline in the first studied group. Four series of quinazoline derivatives such as: 4-(*N,N*-dimethylamino)-2-phenylquinazoline, 4-amino-2-phenylquinazoline, 2-(*N,N*-diethylamino)-4-(*N,N*-dimethylamino)quinazoline, 4-amino-2-(*N,N*-diethylamino)quinazoline substituted in the position 6 or 7 with electron-donating and withdrawing groups and a series of 2-aryl-4-(*N,N*-dimethylamino)quinazolines were examined in the second group. We have determined the influence of the substituents attached both to benzene and pyridine or pyrimidine fragments on the basicity of the parent system. We have also discussed the electronic effects of the bulky substituents at the 1-position of isoquinoline and at 4-position of quinazoline which in our opinion lead to untypical correlations between pK_a values and *Hammett* σ constants.

Results and Discussion

Preparation and pK_a determination of 1-aminoisoquinoline, 4-amino- and 2,4-diaminoquinazoline derivatives

3-Methylisoquinolines were prepared by a known method from the substituted at the benzene ring benzyl-methyl ketones in the reaction with *N,N*-dimethylcyanamide or cyanamide with the use of $TiCl_4$ as the *Lewis* acid catalyst.¹⁹⁻²³ The rest of 3-(*N,N*-diethylamino)isoquinolines were synthesized in the reaction of the appropriate *N,N*-diethylarylacetamides with $POCl_3$ and then with *N,N*-dimethylcyanamide or cyanamide.²⁴ Aminoquinazolines were prepared from *N*-arylbenzamides or *N*-phenyl-*N',N'*-diethylureas in the reaction with PCl_5 and then with *N,N*-dimethylcyanamide or cyanamide in the presence of $TiCl_4$.²⁵⁻³⁰ The determination of the pK_a dissociation constants was performed according to the spectrophotometric method³¹ of *Albert* and *Serjeant* in 50% aqueous methanol solution (10^{-5} M, room temperature) due to the low solubility of the compounds in water and characteristic UV spectrum (Table 1, 3, 4). Absorption maxima of the isoquinoline and quinazoline ions were selected as analytical wavelengths, bearing in mind their considerable shifts relative to the maxima of the non-protonated forms. The pK_a values determined in aqueous-methanolic solution are lower about 0.6 pK_a units comparing with those determined in aqueous solution which is the result of different ionic products of these solvents.

Table 1. Dissociation constants pK_a of isoquinoline bases

Product	R:	R ¹ :	R ² :	λ_{ANAL} [nm]	pK_a^*
1	H	H	H	261.0	4.79 ± 0.06
2	H	NH ₂	CH ₃	275.0	7.27 ± 0.03
3	H	C ₆ H ₅	CH ₃	353.0	4.99 ± 0.08
4	H	CH ₃	CH ₃	353.0	6.30 ± 0.12
5	H	NH ₂	N(C ₂ H ₅) ₂	246.0	7.24 ± 0.18
6a	H	N(CH ₃) ₂	CH ₃	308.0	6.29 ± 0.07
6b	6-OCH ₃	N(CH ₃) ₂	CH ₃	344.0	6.75 ± 0.04
6c	7-OCH ₃	N(CH ₃) ₂	CH ₃	284.0	6.23 ± 0.10
6d	6-CH ₃	N(CH ₃) ₂	CH ₃	309.0	6.74 ± 0.05
6e	7-CH ₃	N(CH ₃) ₂	CH ₃	293.0	6.28 ± 0.02
6f	6-Cl	N(CH ₃) ₂	CH ₃	315.0	5.69 ± 0.07
6g	7-Cl	N(CH ₃) ₂	CH ₃	299.0	5.40 ± 0.12
6h	7-Br	N(CH ₃) ₂	CH ₃	323.0	5.60 ± 0.09
7a	H	N(CH ₃) ₂	N(C ₂ H ₅) ₂	284.0	6.70 ± 0.12
7b	6-OCH ₃	N(CH ₃) ₂	N(C ₂ H ₅) ₂	289.0	7.15 ± 0.12
7c	7-OCH ₃	N(CH ₃) ₂	N(C ₂ H ₅) ₂	210.0	6.61 ± 0.12
7d	6-Cl	N(CH ₃) ₂	N(C ₂ H ₅) ₂	253.0	6.45 ± 0.12
7e	7-Cl	N(CH ₃) ₂	N(C ₂ H ₅) ₂	296.0	6.14 ± 0.12

* The measurements were made in 50% methanol-water solution at room temperature.

Basicity of 1-aminoisoquinoline derivatives

The results show that electron-donating groups in positions 6 or 7 of the isoquinoline ring cause an increase compared with the pK_a of the parent compound (R=H); the opposite holds for electron-withdrawing groups. The difference between the basicity of 6-R and 7-R isomers was caused mainly by the possibility of the substituent–reaction centre coupling but also by steric and electronic effects of the substituents in the 1-isoquinoline or – which will be shown later - 4-quinazoline positions.

Generally, 1-aminoisoquinolines are stronger bases than the corresponding isoquinolines (Table 1). This is the result of the introduction in the position 1 of isoquinoline the strongly electron-donating amino or dimethylamino group whose free electron pair participates in the coupling with the ring π electrons. This leads to the increasing of the electron density of the ring nitrogen atom. 6-R-Isoquinolines substituted with the electron-donating groups are stronger bases than their 7-R isomers which is caused mainly by the possibility of the substituent–ring nitrogen

atom coupling. The determined pK_a values were correlated with appropriate *Hammett* σ constants.³² According to *Charton's* suggestions who has examined the application of different substituent constants in aromatic systems³³ we have used the original *Hammett* σ_m and σ_p constants. The least squares method was applied and each correlation was characterized by a correlation coefficient r . The results of pK_a versus σ correlation for two isoquinoline series (**6a-h**, **7a-e**) are presented in the Table 2 and the best correlations are visualized at the Figure 1.

Analyzing these data it was found that much better correlations for 6-R substituted isoquinoline derivatives were obtained when σ_p *Hammett* constants were used whereas for 7-R substituted derivatives the correlations are better for σ_m *Hammett* constants (Table 2, Figure 1). The correlation of pK_a for 7-R substituted isoquinoline derivatives with σ_m constants and 6-R substituted derivatives with σ_p constants is consistent with *Charton's* suggestions³³ and investigations on electron interactions in monosubstituted alternateng systems.³⁴

Table 2. Results of pK_a vs σ correlations for two 1-(*N,N*-dimethylamino)isoquinoline (**6a-h**, **7a-e**) series

Entry	Product	Correlation type	Equation $pK_a = \rho\sigma + pK_0$	S ^{a)}	r ^{b)}	n ^{c)}
1 ^{d)}	6a-h	6-R- σ_p , 7-R- σ_m	$pK_a = -2.017\sigma + 6.274$	0.142	0.966	8
2	6a-h	6-R- σ_m , 7-R- σ_p	$pK_a = -1.384\sigma + 6.199$	0.442	0.597	8
3 ^{d)}	7a-e	6-R- σ_p , 7-R- σ_m	$pK_a = -1.506\sigma + 6.745$	0.009	0.991	5
4	7a-e	6-R- σ_m , 7-R- σ_p	$pK_a = -0.433\sigma + 6.649$	0.501	0.285	5

^a S – residual sum of squares; ^b r – correlation coefficient; ^c n – number of data points used.

^d best correlations presented at the Figure 1.

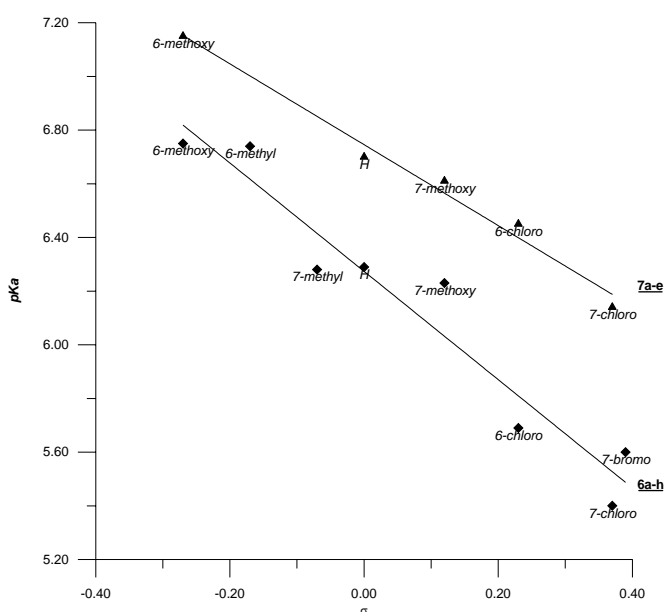
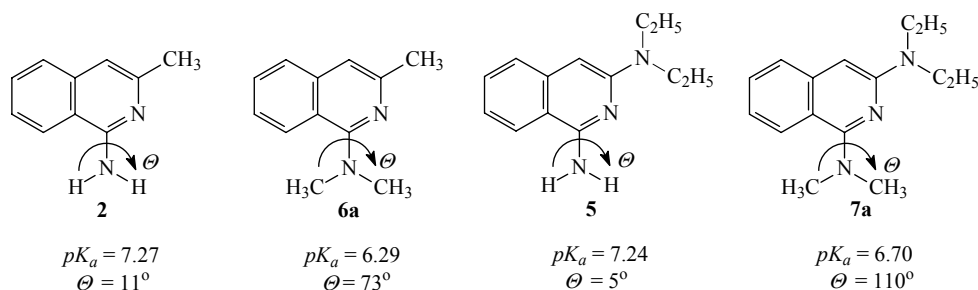


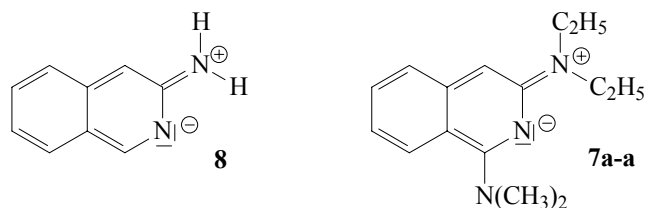
Figure 1. Correlation of Hammett's constants with pK_a for isoquinolines (**6a-h**, **7a-e**).

A special attention should be paid to the influence of the substituents in the position 1 of 3-methylisoquinoline on the basicity of the arrangement. It is quite complicated to interpret the interaction of substituents in *ortho* position since the equilibrium achieved between field, induction, resonance and steric effects is complex.³² The primary steric effect which is connected with the interaction of the substituent in 1 position with free electron pair of the ring nitrogen atom should not be of a great importance.³⁵ Therefore, the effect of substituents on a reaction centre can be mainly explained by the induction and resonance effects. It can be supposed that in case of small groups like CH₃ (**4**) and NH₂ (**2**) in the 1-isoquinoline position the resonance effect dominates and a higher basicity is observed. In contrast, the derivatives with phenyl (**3**) or dimethylamino (**6a**) groups behave quite unexpectedly. For such compounds a considerable secondary steric effect³⁵ related to the interaction of bulky substituents in position 1 of isoquinoline with hydrogen in position 8 can not be neglected. This interaction leads to a twist of the bulky group (C₆H₅, N(CH₃)₂) in 1-position from the ring plane and finally to the electron coupling limitations (Scheme 2). It is not observed for small substituents (CH₃, NH₂) which are left untwisted in the ring plane.



Scheme 2

As the result the resonance effect is reduced in comparison with the inductive one. It is estimated that the interaction between a substituent in the *ortho* position and the ring nitrogen atom is in 70% of the induction nature.³⁵ That is why 3-methyl-1-(*N,N*-dimethylamino)isoquinoline (**6a**) and 3-(*N,N*-diethylamino)-1-(*N,N*-dimethylamino)-isoquinoline (**7a**) are weaker bases than 1-amino-3-methylisoquinoline (**2**) in spite of the fact that the N(CH₃)₂ and N(C₂H₅)₂ groups are more electron donating than NH₂. Similarly to **6a** and **7a** isoquinolines behaves 1-phenyl-3-methylisoquinoline (**3**). The replacement of the methyl group in the position 3 of the isoquinoline with strongly electron donating diethylamino group leads to unexpected changes in the basicity. It is known that two *ortho* isomers of aminoisoquinoline behave quite different.¹⁶ 3-Aminoisoquinoline is considerably weaker base than 1-aminoisoquinoline (Table 1). This decrease in the base strength is attributed to the lower contribution of the **8** structure in the resonance hybrid (Scheme 3).



Scheme 3

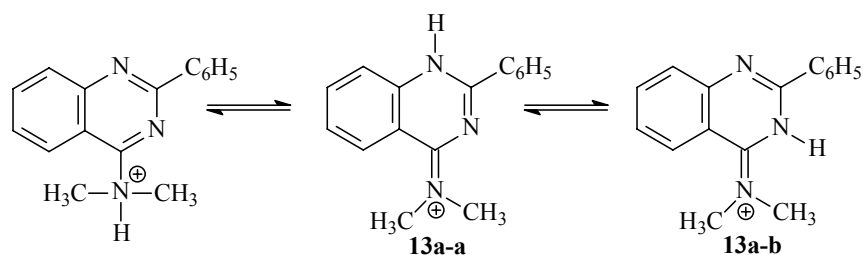
If such foundation is right the induction effect of the substituent in position 3 should be mainly responsible for the basicity. According to this isoquinoline **7a** should be less basic than isoquinoline **6a** because $N(C_2H_5)_2$ and CH_3 groups have got the opposite induction effects. Meanwhile, we could observe different effects according to the character of the substituent in the position 3. It is not of the great importance in the case of 1-aminoisoquinolines unsubstituted at the amino group (**2**, **5**) where its free electron pair couples with ring π electrons. A replacement of the methyl group in the considered position by diethylamino group increases the basicity of the arrangement in these isoquinolines which have the bulky and twisted from the ring plane dimethylamino group at position 1. The mesomeric effect ($+M$) of diethylamino group leads probably to the higher contribution of the structure **7a-a** in the resonance hybrid (Scheme 3) and 3-(*N,N*-diethylamino)-1-(*N,N*-dimethylamino)isoquinoline (**7a**) is considerably stronger base as expected.

Basicity of 4-amino- and 2,4-diaminoquinazoline derivatives

4-Aminoquinazolines have three potential protonation sites and it is not established which one is the most susceptible to the proton attack till now. In order to identify it we have proceeded in two ways. Correlation analysis of pK_a dissociation constants with the *Hammett* σ constants constitutes an indirect approach whereas single crystal X-ray analysis of the protonated compounds and ^{15}N -NMR analysis represent direct solid state and solution approaches. Single crystal X-ray analysis of 4-(*N,N*-dimethylamino)-2-(*p*-methoxyphenyl)quinazoline hydrochloride (**13b**·HCl) proves that the protonation occurs on the nitrogen atom at the 1 position in the solid state.²⁵ The material crystallizes with two organic molecules, two ionic HCl and one water molecule per asymmetric unit in a cell. Details of bonding are substantially the same for two independent molecules. There is no hydrogen bonding interaction involving the second endocyclic nitrogen atom N3 or the exocyclic nitrogen atom of the dimethylamino group $C4-N(CH_3)_2$. It proves besides that the covalent hydration of the water molecule across a 3,4-double quinazoline bond does not exist here.

However, ^{15}N -NMR measurements of 4-(*N,N*-dimethylamino)-2-phenyl-quinazoline trifluoroacetate (**13a**· CF_3COOH) indicate that the protonation process in the solution is more dynamic.²⁵ There are three signals observed in the spectrum of the free quinazoline **13a** registered in chloroform. Two of them come from the ring nitrogen atoms: N1 at $\delta = -137.675$ and N3 at $\delta = -144.551$ ppm and the third one from the amino nitrogen atom at the 4-quinazoline

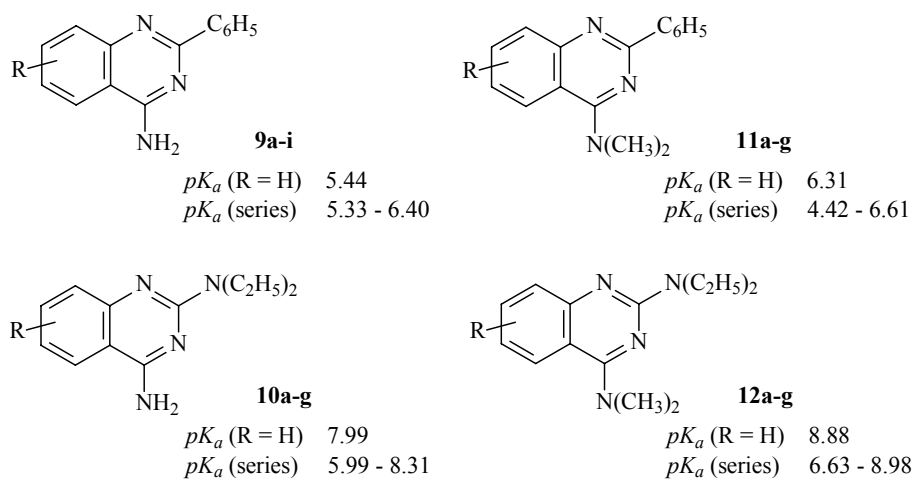
position: N-C4 at $\delta=306.062$ ppm. The protonation of the arrangement causes great changes of chemical shifts. There are only two signals observed in the spectrum of the salt **13a**·CF₃COOH: the intermediary one for the atoms N1 and N3 at $\delta=154.374$ ppm and the second one of N-C4 shifted about 35ppm in respect to the free quinazoline. Spectral analysis indicates 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 4). Thus structures **13a-a** and **13a-b** dominate.



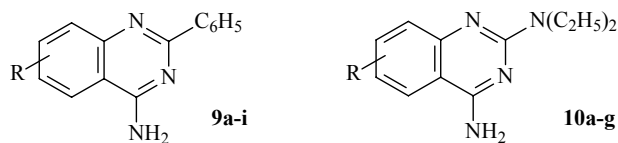
Scheme 4

In the ¹H-NMR spectrum of **13a**·CF₃COOH, an N-H signal has been observed at 11.3 ppm. The coupling constant ($J^{15}\text{N}-^1\text{H} = 5\text{Hz}$) between the exocyclic nitrogen atom and the proton in the ¹⁵N-NMR also testifies to the occurrence of only a weak interaction of the proton and the exocyclic nitrogen atom.³⁶ This observation is in contrast to the protonation preference observed in 4-aminopyrimidine salts.³⁷

Within two groups of 4-amino- and 2,4-diaminoquinazoline derivatives substituted in the position 6 or 7 with electron-donating and withdrawing groups (Table 3, 4, Scheme 5) the strongest bases are quinazolines with the diethylamino substituent at the position 2 (**12a-g**).



Scheme 5

Table 3. Dissociation constants pK_a of two 4-aminoquinazoline series (**9a-i**, **10a-g**)

Product	R:	λ_{ANAL} [nm]	pK_a^*
9a	H	262.0	5.44 ± 0.13
9b	6-CH ₃	303.5	5.16 ± 0.18
9c	7-CH ₃	325.0	5.53 ± 0.07
9d	6-OCH ₃	308.5	5.33 ± 0.08
9e	7-OCH ₃	324.5	5.62 ± 0.07
9f	6-NO ₂	322.0	4.54 ± 0.27
9g	7-NO ₂	259.0	4.27 ± 0.18
9h	6-Br	248.0	4.78 ± 0.08
9i	6-Cl	277.7	4.98 ± 0.06
10a	H	236.4	7.79 ± 0.15
10b	6-OCH ₃	251.2	7.82 ± 0.09
10c	7-OCH ₃	254.8	8.31 ± 0.05
10d	6-Cl	270.6	6.98 ± 0.17
10e	7-Cl	261.0	7.09 ± 0.12
10f	6-NO ₂	270.0	6.05 ± 0.08
10g	7-NO ₂	268.4	5.99 ± 0.21

* The measurements were made in 50% methanol-water solution in room temperature.

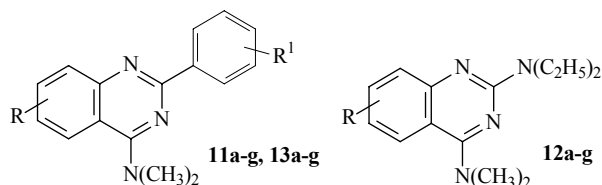
The introduction of the strongly electron donating dimethylamino group in the position 4 changes the basicity considerably.

The values of pK_a dissociation constants of 4-(*N,N*-dimethylamino)quinazolines differ from their 4-aminoquinazoline counterparts at about 1 pK_a unit. This is opposite to the behaviour of isoquinolines (**1-7e**, Table 1) where the derivatives with bulky substituents in 1-isoquinoline position ($R^1 = N(CH_3)_2, C_6H_5$) were considerably weaker bases than those with small substituents ($R^1 = NH_2, CH_3$). But this is clear bearing in mind the presence of the second nitrogen atom N1 in the position *para* towards strongly electron donating amino group in the position 4. Such protonated arrangements are stabilized by the resonance and a *para-quinoid* form (Scheme 6) dominates in the resonance hybride.^{38,39}

Generally, 4-aminoquinazoline derivatives (**9a-i**, **10a-g**) substituted in the position 7 with electron donating groups are stronger bases than their 6-R isomers. In contrast, 4-(*N,N*-dimethylamino)quinazolines (**11a-g**, **12a-g**) substituted in the position 7 are weaker bases than

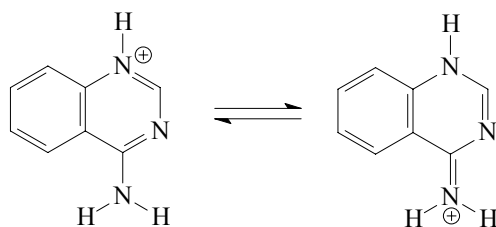
their 6-R isomers. Such situation testifies to the different electron transfer in quinazolines with the bulky group in the position 4.

Table 4. Dissociation constants pK_a of three 4-(*N,N*-dimethylamino)quinazoline series (**11a-f**, **12a-g**, **13a-h**)



Product	<i>R</i> :	<i>R</i> ¹ :	λ_{ANAL} [nm]	pK_a^*
11a	H	H	262.5	6.31 ± 0.07
11b	6-OCH ₃	H	280.0	6.61 ± 0.16
11c	7-OCH ₃	H	298.6	6.20 ± 0.04
11d	6-CH ₃	H	272.3	6.52 ± 0.12
11e	7-CH ₃	H	232.5	6.35 ± 0.02
11f	6-Br	H	320.0	5.88 ± 0.16
11g	7-NO ₂	H	236.6	4.42 ± 0.25
12a	H	H	279.0	8.88 ± 0.09
12b	7-Cl	H	277.8	7.94 ± 0.13
12c	6-Cl	H	255.7	7.91 ± 0.05
12d	7-OCH ₃	H	252.8	8.83 ± 0.08
12e	6-OCH ₃	H	252.0	8.98 ± 0.05
12f	7-NO ₂	H	257.8	6.68 ± 0.14
12g	6-NO ₂	H	294.0	6.63 ± 0.06
13a	H	4-OCH ₃	322.0	6.62 ± 0.05
13b	H	4-CH ₃	287.0	6.40 ± 0.08
13c	H	3-CH ₃	283.0	6.28 ± 0.06
13d	H	4-Cl	287.0	5.88 ± 0.09
13e	H	3-Cl	279.0	5.54 ± 0.05
13f	H	4-NO ₂	285.0	4.52 ± 0.01
13g	H	3-NO ₂	309.0	4.94 ± 0.02

* The measurements were made in 50% methanol-water solution in room temperature.



Scheme 6

The pK_a values of the considered quinazolines were correlated with appropriate *Hammett* σ constants. In the case of 4-aminoquinazoline derivatives (**9a-i**, **10a-g**) the best correlations were obtained applying σ_m *Hammett* constants for 6-R substituted derivatives and σ_p *Hammett* constants for 7-R substituted derivatives (Table 5, Figure 3). The application of this correlation type is consistent with *Charton's* suggestions,³³ the investigations on electron interactions in monosubstituted alternating systems³⁴ and our earlier studies connected with isoquinolines.^{19,20} A typical correlation was obtained in the case of 2-phenyl-4-(*N,N*-dimethylamino)quinazoline derivatives substituted in the position *meta* and *para* of the phenyl group (**11a**, **13a-g**).

Table 5. Results of pK_a vs σ correlations for two 4-aminoquinazoline (**9a-i**, **10a-g**) series

Entry	Product	Correlation type	Equation $pK_a = \rho\sigma + pK_0$	S^a	r^b	n^c
1 ^d	9a-i	6-R- σ_m , 7-R- σ_p	$pK_a = -1.188\sigma + 5.317$	0.132	0.962	9
2	9a-i	6-R- σ_p , 7-R- σ_m	$pK_a = -1.231\sigma + 5.352$	0.273	0.871	9
3 ^d	10a-g	6-R- σ_m , 7-R- σ_p	$pK_a = -2.335\sigma + 7.794$	0.170	0.985	7
4	10a-g	6-R- σ_p , 7-R- σ_m	$pK_a = -2.088\sigma + 7.730$	0.464	0.880	7

^a S – residual sum of squares. ^b r – correlation coefficient. ^c n – number of data points used.

^d best correlations presented in Figure 2.

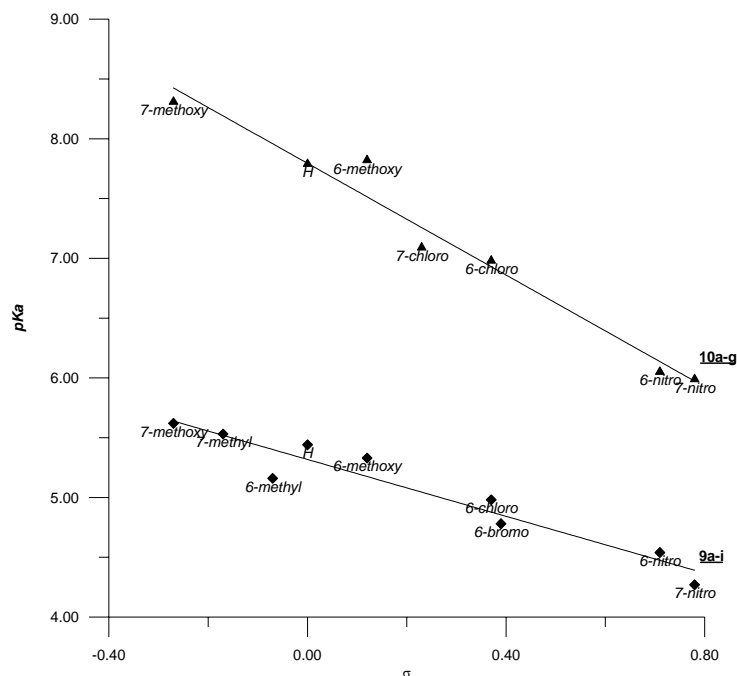


Figure 2. Correlation of σ Hammett's constants with pK_a for 4-aminoquinazolines (**9a-i**, **10a-g**).

Table 6. Results of pK_a vs σ correlations for three 4-*N,N*-dimethylaminoquinazoline (**11a-g**, **12a-g**, **13a-g**) series

Entry	Product	Correlation type	Equation $pK_a = \rho\sigma + pK_0$	S^a	r^b	n^c
1 ^d	11a,13a-g	4-R- σ_p , 3-R- σ_m	$pK_a = -1.895\sigma + 6.173$	0.127	0.988	8
2	11a,13a-g	4-R- σ_m , 3-R- σ_p	$pK_a = -1.913\sigma + 6.270$	0.381	0.886	8
3 ^d	11a-g	6-R- σ_p , 7-R- σ_m	$pK_a = -2.246\sigma + 6.218$	0.199	0.970	7
4	11a-g	6-R- σ_m , 7-R- σ_p	$pK_a = -1.747\sigma + 6.236$	0.441	0.844	7
5 ^d	12a-g	6-R- σ_p , 7-R- σ_m	$pK_a = -2.550\sigma + 8.685$	0.320	0.957	7
6	12a-g	6-R- σ_m , 7-R- σ_p	$pK_a = -2.482\sigma + 8.666$	0.401	0.931	7

^a S – residual sum of squares. ^b r – correlation coefficient. ^c n – number of data points used.

^d best correlations presented at the Figure 3.

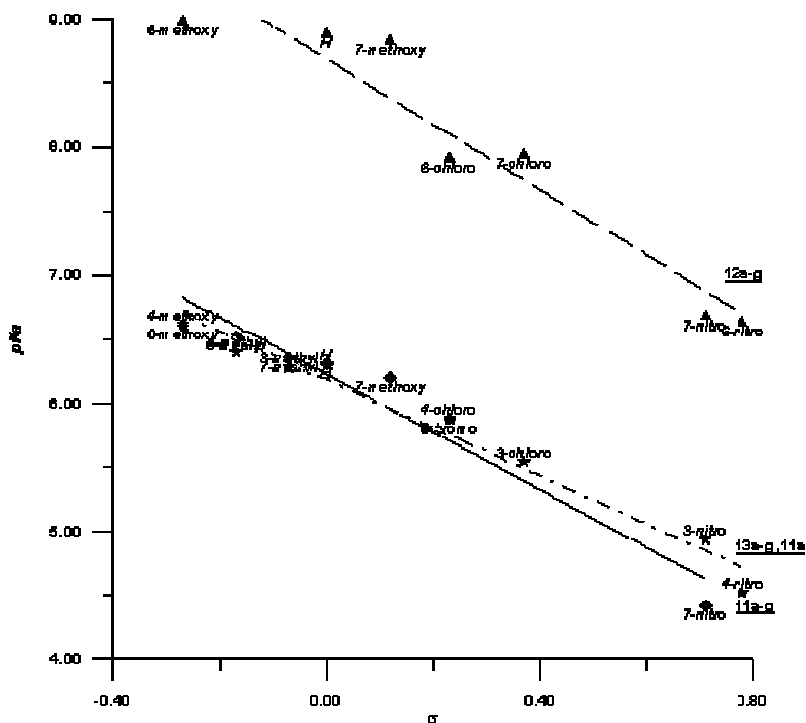
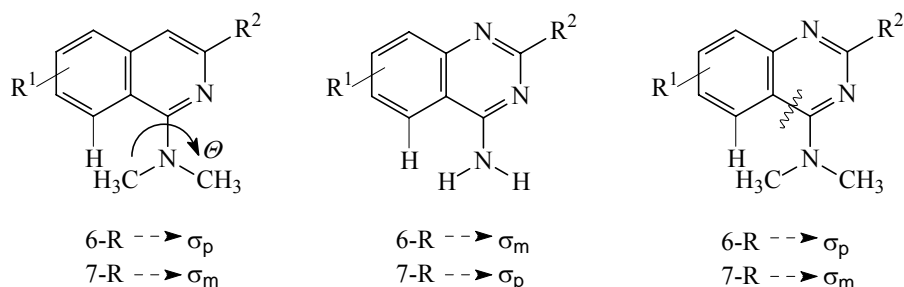


Figure 3. Correlation of σ Hammett's constants with pK_a for 4-*N,N*-dimethylaminoquinazolines (**11a-g**, **12a-g**, **13a-g**).

This group of compounds is closely related to the *Hammett* type – electrons are transferred from the substituents to the protonation site through the benzene ring and it is free from the steric interactions. The application of σ_p constants for 2-(*para*- R^1 -phenyl) substituted derivatives and σ_m constants 2-(*meta*- R^1 -phenyl) substituted derivatives gives satisfactory results (correlation coefficient $r=0.988$; Table 6, Figure 3). The untypical correlation was obtained in the case of 6 and 7 substituted 4-(*N,N*-dimethylamino)quinazolines (**11a-g**, **12a-g**). The application of σ_p constants for 6-*R* substituted derivatives and σ_m constants for 7-*R* substituted compounds gives satisfactory results (Figure 3; Table 6) though it is not consistent with the previously presented ideas (Table 5, Figure 2). This is the first stated case where the reversed electron effect transfer takes place in a bicyclic benzo-fused heteroaromatic system, opposite to alternating systems. It is true that deviations from electron interactions in alternating systems were observed earlier in series of the 1-methyl-4-phenyl-2-quinazolinone compound substituted in the 6 position where the correlation analysis between the half neutralization potential gives satisfactory results when *Hammett* σ_p constants are used.⁴⁰

In our opinion such situation is the result of the steric hindrance of the bulky group in the 4-quinazoline position. The primary steric effect which is connected with the interaction of the substituent in 2 or 4 position with free electron pairs of the ring nitrogen atoms should not be of the great importance. The secondary steric effect interpreted as the interaction between a large substituent in the 4 quinazoline position with a hydrogen atom in the 5 position becomes important here. Contrary to 1-(*N,N*-dimethylamino)isoquinolines where the secondary steric

effect causes twisting of the big group from the ring plane and finally decreases the basicity, the opposite effect is noticed in the case of 4-(*N,N*-dimethylamino)quinazolines (**11a-g**, **12a-g**, Scheme 7). A strong resonance stabilization of the protonated 4-(*N,N*-dimethylamino)quinazolines which involves N1 ring nitrogen atom to form a very stable *para*-quinoid structure prevent the twisting of the dimethylamino group from the ring plane. 4-(*N,N*-Dimethylamino)quinazolines are indeed stronger bases than their counterparts unsubstituted at the amino group (Scheme 5).



Scheme 7

Single crystal X-ray diffraction analysis of 7-methoxy-2-(*N,N*-dimethylamino)-4-(*N,N*-dimethylamino)quinazoline hydrochloride²⁶ (**12d·HCl**, Table 7) testifies that the tendency of the arrangement to the steric hindrance minimalization is expressed by the C4-C4a lengthening. This bond measures 1.455 Å and is thus considerably longer than that in the corresponding quinazoline¹⁴ (1.410 Å).

Table 7. Selected bond lengths (Å) for quinazoline and its derivatives taken from MNDO calculations and X-ray structure analysis

Selected bond	Quinazoline	Quinazoline	13a	12a	12d
<i>method</i>	<i>X-ray</i>	<i>MNDO</i>	<i>MNDO</i>	<i>MNDO</i>	<i>X-ray</i>
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

Moreover, these data concerning the analysis of single crystal X-ray diffraction have been corroborated by MNDO calculations for 4-(*N,N*-dimethylamino)-2-phenylquinazoline (**11a**) and its hydrochloride²⁷ where the calculated bond lengths are 1.461 Å and 1.445 Å. The shortening of the C4-N(CH₃)₂ bond (1.342 Å, Table 7) could also testify to the presence of a strong

coupling of the free electron pair of the dimethylamino group with N1 ring nitrogen atom. Moreover, diethylamino group in the position 2 is also involved to the coupling but less stable *ortho-quinoid* form has a lower contribution in the resonance hybrid. In the result C2-R bond (1.346 Å) is a little longer than C4- N(CH₃)₂ bond.

In that case the electron effects of the substituents in the benzene ring of the 4-(*N,N*-dimethylamino)-2-R¹-quinazoline derivatives are mostly transferred by the C8a-N1 bond. The length of the C8a-N1 is similar to that in the unsubstituted quinazoline and indicates delocalized bond feature. Thus the electron transfer in these systems (**11a-g**, **12a-g**) occurs in the same way as in substituted aniline, where the substituents in the 4 position correspond to those in the 6 position of the quinazoline system and are well correlated with the *Hammitt* σ_p constants. The substituents in position 3 of aniline correspond to quinazoline substituents in the 7 position and are correlated with the *Hammitt* σ_m constants.

The values of correlation coefficients r (Table 4, 5, 6) obtained for 4-(*N,N*-dimethylamino)-2-R¹-quinazoline derivatives which are not very high (R¹=C₆H₅, **11a-g**, $r=0.970$; R¹=N(C₂H₅)₂, **12a-g**, $r=0.957$) could be caused in our opinion by two reasons. One of them is that part of electronic effects of the substituents presented in the benzene ring could be also transferred to pyrimidine ring through C4-C4a bond. It could also mean that there is not one specifically defined protonation site in such arrangements.

Conclusions

Correlation analyses of pK_a dissociation constants with *Hammitt* σ constants clearly show that the steric effects of the bulky substituents neighbouring the protonated ring nitrogen atom influence the electron transfer in the arrangement. The bulky substituents in the position 1 of isoquinoline derivatives are twisted from the ring plane and the contribution of the resonance effect in the entire electronic effect interacted by these substituents decreases. That is why the arrangements with the big and strongly electron donating groups are weaker bases in comparison with those with small groups. In contrast to isoquinolines the aromaticity disturbance of the heterocyclic system is observed in quinazoline derivatives with the bulky substituents in the position 4. The strong resonance stabilization of the protonated 4-(*N,N*-dimethylamino)quinazolines which involves N1 ring nitrogen atom to form very stable *para-quinoid* structure prevent the twisting of the dimethylamino group from the ring plane. Therefore the tendency of the arrangement to the steric hindrance minimalization is expressed by the C4-C4a weakening. In consequence the effect of the electron transfer through this bond is considerably limited and the untypical correlations between pK_a values and σ parameters are obtained.

Experimental Section

General procedures. UV spectra were recorded on 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. Elemental analysis was carried out with a Perkin Elmer 240C analyser. The $^1\text{H-NMR}$ spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as internal standard. MS spectra were obtained with a Shimadzu QP-200 mass spectrometer. Thin layer chromatography was carried out on silica gel 60 F₂₅₄ (Merck) thin layer chromatography plates using a benzene-ethyl acetate mixture (3:1 v/v) as the mobile phase. MNDO calculations have been carried out by means of the WinMopac V2.0 program.

1-amino-3-(*N,N*-diethylamino)isoquinoline (5; C₁₃H₁₇N₃). was synthesized according to the procedure given in ²⁰. Yield: 75%; b.p.: 144-146°C/Torr; R_f = 0.64; $^1\text{H-NMR}$: δ = 1.17 (6H, t, CH₂CH₃), 3.43 (4H, q, CH₂CH₃), 4.36 (2H, s, NH₂), 7.17 (1H, s, H-4), 7.24-7.31 (2H, m, H-6, H-7), 7.81 (1H, d, J=7.8 Hz, H-5), 7.92 (1H, d, J=7.8 Hz, H-8) ppm; UV: λ_{max} ($\epsilon \cdot 10^{-3}$) = acidic: 209.0 (14.44), 247.2 (9.53), 306.8 (3.97), basic: 209.8 (14.70), 244.0 (10.56), 308.2 (5.16) nm; MS: m/z (%) = 215 (M⁺, 85); Anal. Calcd. for C₁₃H₁₇N₃: C, 72.52; H, 7.97; N, 19.51. Found: C, 72.46; H, 8.04; N, 19.50. pK_a 7.24±0.18 ($\lambda_{\text{ANAL}}=246$ nm).

pK_a Measurements. The determination of the pK_a dissociation constants was performed according to the spectrophotometric method of Albert and Serjeant³¹ in 50% aqueous methanol solution (10⁻⁵ M, room temperature) (Table 1, 3, 4).

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