Spectrophotometric Determination of the
Second Dissociation Constants of the Aminoquinolines

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The second dissociation constants representing the transition from monocation to dication for all of the isomeric aminoquinolines have been determined as pK_a' values. The analogous values for 2- and 4-aminopyridine have been recalculated using a revised H_0 scale. The accurate determination of the second pK_a values follows from measurement, for the first time, of the ultraviolet spectra of all the mono- and dications of the aminoquinolines.

It has been shown that the first protonation of nitrogen heterocycles containing amino substituents on the ring occurs at the ring nitrogen and not at the substituent amino group (1-4). A large number of ionization constants corresponding to this first protonation have been determined by various workers and compiled by Albert (5). However, relatively little information is available in the literature concerning the determination of the second pK_a' of nitrogen heterocycles with primary amino substituents. This primary amino function is a very weak base, so the second protonation occurs only in strongly acidic solutions which require the use of the H_0 acidity scale (14). The only compounds for which this has been demonstrated are the isomeric aminopyridines (6,7) some aminoacridines (8) and approximately for 5- and 6-amino-quinoline (9).

In the past we have been concerned with the chemistry of the aminoquinolines, (10,11) primarily with the function and reactivity of the primary amino group. It was thus of interest to investigate the relative basicity of this amino group for the isomeric aminoquinolines (in pK_a' terms) by ultraviolet spectroscopy and by use of the sulfuric acid-water H_0 scale (12,13).

Hearn, Morton and Simpson have previously found the second pK_a' values for 5- and 6-aminoquinoline "to be about 0.97 and 1.63, respectively" (9). However, the spread of ±0.49 and ±0.46 obtained for these two values far exceeds the acceptable limits of ±0.06 for pH above 0 and ±0.1 for negative pH or H_0 measurements (14).

There is neither mention of the temperature at which their measurements were obtained nor that temperature was, in fact, controlled, despite the fact that pK_a' values of organic bases may change considerably with temperature (5,15). The refined pK_a' values we have established are 0.66 ± 0.03 for 5-aminoquinoline and 1.19 ± 0.05 for 6-aminoquinoline. It can be seen that the variation of the previous values lies well outside the acceptable range of

±0.06 pK units, whereas the ones we have established fall within it. The temperature at which our measurements have been made are recorded in Table 1.

The method selected for these pK_a' determinations is that used by Albert for the determination of the second dissociation constant of 3-aminopyridine (6,14,16). Briefly, it consists of isolating the ultraviolet spectra of the mono- and dications and selecting an analytical wavelength at which there is a definite relationship between the degree of protonation and the extinction coefficient and a considerable difference in the absorbance of the isolated mono- and dications. The absorbance is then measured at that wavelength for 7 different degrees of protonation and the pK_a' calculated from one of the following equations, where A_d is the absorbance of the dication, A_m is the absorbance of the monocation

$$pK_a' = H_0 + \log \frac{A - A_m}{A_d - A} \qquad (1)$$

$$pK_a' = H_0 + \log \frac{A_m - A}{A - A_d} \qquad (2)$$

and A is the absorbance of the mixture of the two ions (14). Equation (1) is used when $A_d > A_m$ and equation (2) when $A_m > A_d$. These seven pK_a' values are then averaged. This method not only gave good results when applied to the 5- and 6-isomers, but to all the remaining isomers as well. The results are in Table I.

A discussion of electron density and structures which contribute to the free base and monocations can be found elsewhere in the literature (15,17,18).

Bender and Chow have determined the second pK_a' values for 2- and 4-aminopyridine (7) according to the H_0 scale of Paul and Long (19). However, this scale has since been revised by Jorgenson and Hartter with a conversion table for differences between the two scales (13). We have applied these corrections to Bender and Chow's values and

TABLE I

Compound	First (a) pK$_a'$	Second pK$_a'$	Spread	Concentration M	Temp. °C ±1°	Analytical Wavelength mμ
Quinoline	4.94 (b)	---	---	---	---	----
2-Aminoquinoline	7.34 (b)	-9.08	0.08	2×10^{-5}	24.0	244
3-Aminoquinoline	4.95 (b)	-0.40	0.08	1×10^{-4}	24.0	371
4-Aminoquinoline	9.17 (b)	-5.99 (g)	0.07	2×10^{-5}	24.5	239
5-Aminoquinoline	5.46 (b)	0.66	0.03	2×10^{-5}	24.0	264
6-Aminoquinoline	5.63 (b)	1.19	0.05	2×10^{-5}	23.5	258
7-Aminoquinoline	6.65 (b)	-0.03	0.05	2×10^{-5}	24.0	234
8-Aminoquinoline	3.99 (b)	-0.13	0.06	2×10^{-5}	24.5	234
Pyridine	5.23 (b)	---	---	---	----	----
2-Aminopyridine	6.86 (b)	-8.1 (f)	---	---	---	----
3-Aminopyridine	6.07 (d)	-1.5 (d)	---	---	---	----
4-Aminopyridine	9.25 (e)	-6.7 (f,c)	---	---	---	----

(a) All determined at 20°C. (b) Reference 8. (c) Reference 20 estimates value at -6.55. (d) Reference 6. (e) Reference 15. (f) Corrected values. Bender and Chow reported -7.6 for the 2-isomer and -6.3 for the 4-isomer, in Reference 7. (g) Reference 20 estimates value at -7.11 at 10°.

have entered them in Table I. It can be seen that the second pK$_a'$ values for 2- and 4-aminopyridine lie in the same general area as those of the 2- and 4-aminoquinolines. Note that, in both cases, the value for the 2-isomer is the more negative. This is probably due to the close proximity of the two positive charges on the molecule.

Ewing and Steck have recorded the ultraviolet spectra for the aminoquinolines in 0.01 N hydrochloric acid (3). It seems, however, that they were not concerned with pure electronic species, for in the 3-, 5-, and 6-isomers, they had mixtures of the mono- and dications. Hearn, Morton and Simpson (9) have shown that for 5- and 6-aminoquinolines, the monocations are isolated at a pH of 2.965. They also state both exist solely as dications in concentrated hydrochloric acid, but give spectral data for only the 5-isomer. We have determined the ultraviolet spectra of all of the pure mono- and dicationic species of the aminoquinolines in sulfuric acid of accurately determined pH and H$_0$ values. The results, along with those of the above workers, are in Table II.

The absorption spectra of the 3-, 5-, 6-, 7-, and 8-aminoquinoline isomers show a bathochromic shift when they are mono-protonated but the 2- and 4-isomers do not behave this way (3). It has been shown for the 5-isomer that, after the second protonation, the spectrum strongly resembles that of the quinolinium ion (9). The data in Table II for all of the isomers of the aminoquinolines show that the spectra of all of their dications resembles that of the quinolinium ion.

EXPERIMENTAL

A stock solution of each amine (1 x 10^{-3} M) was made by accurately weighing out 0.0721 g. (0.0005 mole) of the amine and dissolving it in 500 ml. of distilled water which had been boiled vigorously for 30 minutes and cooled to room temperature. From Baker Analyzed sulfuric acid, checked for optical clarity, solutions of 10N, 1N, and 0.1N sulfuric acid were made by dilution with distilled water prepared as above. These solutions or aliquots of them were standardized against primary standard sodium carbonate by the method of Brumblay (23). The spectra of the mono- and dications were isolated at their respective pH or H$_0$ values. From the approximate pK$_a'$, seven solutions of equal concentration, but varying ±0.6 units in 0.2 pH or H$_0$ increments from the approximate pK$_a'$, were prepared along with solutions of the mono- and dications. A solvent blank of the exact composition as that containing the compound was used for each measurement. Measurements of absorbance were made on a Cary 15 recording spectrophotometer with 10 mm. Beckman silica cells and pH measurements were made with a Beckman Zeromatic pH meter. In solutions where the H$_0$ and pH overlapped the H$_0$ scales were found to coincide within the error of the pH meter (±.015). The pH meter was used to pH 3. From H$_0$ = 3 to -4.2 the scale of Bascomb and Bell (12) was used. Beyond H$_0$ = -4.2 the scale of Jorgenson and Hartter (13) was used.

Preparation and Purification of the Aminoquinolines.

2-Aminoquinoline.

2-Acetamidoquinoline (0.5 g.) was refluxed in 50 ml. of 10% sodium hydroxide for one hour. The solution was cooled, the solid collected and recrystallized twice from a 1:1 toluene-Skelly C mixture, m.p. 128-129° as white plates.

3-Aminoquinoline.

A commercial sample was recrystallized twice from benzene to give a white powder, m.p. 93-95°.

TABLE II

Ultraviolet Spectra of Aminoquinolines

Compound	Solvent	pH or H_0	Species(a)	λ max mμ	Log ε max
2-Aminoquinoline	95% ethanol (b)	---	N	237, 334	4.39, 3.53
	0.01 N NaOH (b)	~12	N	235, 330	4.36, 3.48
	H_2SO_4-H_2O	3.00	M	231, 245, 249	4.30, 4.16, 4.20,
				280, 326	3.83, 3.95
	H_2SO_4	-10.35	D (c)	244, 320, 334	4.49, 3.88, 3.71
3-Aminoquinoline	95% ethanol (b)	---	N	243, 353	4.32, 3.45
	0.01 N NaOH (b)	~12	N	241, 339	4.24, 3.36
	H_2SO_4-H_2O	3.00	M	237, 371	4.48, 3.56
	H_2SO_4-H_2O	-4.00	D	238, 316	4.62, 3.78
4-Aminoquinoline	95% ethanol (b)	---	N	240, 318	4.19, 3.93
	0.01 N NaOH (b)	~12	N	312	3.58
	H_2SO_4-H_2O	-3.00	M	229, 321, 334	4.40, 4.19, 4.13
	H_2SO_4-H_2O	-8.03	D	239, 321	4.57, 3.92
5-Aminoquinoline	95% ethanol (b)	---	N	250, 345	4.16, 3.29
	0.01 N NaOH (b)	~12	N	244, 338	4.19, 3.31
	HCl-H_2O (d)	2.965	M	264, 313	4.47, 3.01
	H_2SO_4-H_2O	3.00	M	264	4.35
	Conc. HCl (d)	---	D	240, 315	4.56, 3.86
	H_2SO_4-H_2O	-4.00	D	233, 313	4.56, 3.82
6-Aminoquinoline	95% ethanol (b)	---	N	246, 352	4.40, 3.45
	0.01 N NaOH (b)	~12	N	240, 337	4.35, 3.37
	HCl-H_2O (d)	2.965	M	258, 305, 382	4.48, 3.40, 3.55
	H_2SO_4-H_2O	3.60	M	258, 383	4.50, 3.53
	H_2SO_4-H_2O	-4.00	D	232, 301, 312	4.59, 3.84, 3.88
7-Aminoquinoline	95% ethanol (b)	---	N	247, 354	4.37, 3.48
	0.01 N NaOH (b)	~12	N	241, 345	4.38, 3.46
	H_2SO_4-H_2O	3.00	M	257, 392	4.46, 3.92
	H_2SO_4-H_2O	-4.00	D	232, 302, 309	4.56, 3.84, 3.89
8-Aminoquinoline	95% ethanol (b)	---	N	250, 338	4.27, 3.18
	0.01 N NaOH (b)	~12	N	246, 331	4.28, 3.18
	H_2SO_4-H_2O	2.00	M	222, 228, 258	4.14, 4.14, 4.34
	H_2SO_4-H_2O	-4.00	D	234, 304, 309	4.53, 3.84, 3.87
Quinoline	H_2O (e)	6.3	N	226, 275, 299,	4.36, 3.51, 3.46,
				312	3.52
	HCl-H_2O	1.1	M	233, 313	4.50, 3.80

(a) N = neutral molecule, M = monocation, D = dication. (b) Reference 3. (c) The dication may not be 100% isolated at this H_0 value. Albert states that a species is considered isolated when the spectrum changes 1% or less in one pH unit. From 10.00 to 10.35 the maximum change in the spectrum is 0.4% or about 1.2% per H_0 unit. (d) Reference 9. (e) Reference 21.

4-Aminoquinoline.

This compound was prepared from 4-nitroquinoline N-oxide (22) and recrystallized from benzene, m.p. 153-154° as white plates.

5-Aminoquinoline.

This compound was obtained by low pressure reduction of 5-nitroquinoline, sublimed under vacuum at 100°, and recrystallized from Skelly C to give white needles, m.p. 108.5-110°.

6-Aminoquinoline.

This compound was purified by recrystallization twice from Skelly C, sublimation under vacuum at 100°, and recrystallization once more from Skelly C as light yellow plates, m.p. 113.5-115°.

7-Aminoquinoline.

This compound was purified by subliming twice under vacuum at 85-90°, m.p. 94.5-96°, a yellow powder.

8-Aminoquinoline.

This compound was purified by recrystallization four times from Skelly C and sublimed twice at 50-55° under vacuum to give a yellow powder, m.p. 63-64°.

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