^{13}C N.m.r. Investigation on the First and Second Nitrogen Protonation in the Diazanaphthalenes

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The ^{13}C chemical shifts of the diazanaphthalenes have been recorded as a function of the pH value, providing classical titration curves. From these curves the pK_1 and pK_2 values have been determined taking into account the activity coefficients. The changes in ^{13}C chemical shift under the influence of nitrogen protonation ($\Delta\delta$) can be described by two protonation parameter sets.

INTRODUCTION

Recently we have reported a ^{13}C n.m.r. investigation on the site of protonation in the diazanaphthalenes.[1] This group of *N*-heterocycles consists of ten compounds: cinnoline (1,2-diazanaphthalene, **1**), quinazoline (1,3-diazanaphthalene, **2**), quinoxaline (1,4-diazanaphthalene, **3**), 1,5-naphthyridine (1,5-diazanaphthalene, **4**), 1,6-naphthyridine (1,6-diazanaphthalene, **5**), 1,7-naphthyridine (1,7-diazanaphthalene, **6**), 1,8-naphthyridine (1,8-diazanaphthalene, **7**), phthalazine (2,3-diazanaphthalene, **8**), 2,6-naphthyridine (2,6-diazanaphthalene, **9**) and 2,7-naphthyridine (2,7-diazanaphthalene, **10**).

In order to establish the site of protonation we recorded the pH dependence of the chemical shift of each separate carbon atom in all isomers.

From the titration curves thus obtained we simultaneously derived the p*K* values of the first nitrogen protonation (pK_1) by application of the Henderson–Hasselbach equation.[2] These pK_1 values correlated very well with those values from the literature that were derived by conventional titration methods. However, the pK_1 values determined with the n.m.r. technique proved to be systematically smaller than the literature values. The same has been noticed for other aza-aromatics by Breitmaier and Spohn.[3]

The most obvious explanation of this systematic deviation is that in the ^{13}C n.m.r. experiment the concentration of the titrant is much higher than in a normal titration procedure. As a consequence, the activity coefficients of the participating species will deviate seriously from unity. In ^{13}C n.m.r. determinations of the second nitrogen protonation constants (pK_2) this factor gains even more importance because of the still higher ionic strength of the solutions involved.

In this contribution we apply a procedure that takes into account these activity coefficients. Since this method proved to be successful for the pK_1 values a similar approach was used for the determination of the pK_2 values.

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While determining the p*K* values the changes in the ^{13}C chemical shifts could be followed. These changes upon first and second nitrogen protonation ($\Delta\delta_1$ and $\Delta\delta_2$, respectively) can be described by two protonation parameter sets.[1]

pK DETERMINATION

Method

In a previous study[1] we made the assumption that the ratio of activity coefficients f_{RH^+}/f_R is equal to unity. This holds for dilute solutions. However, for the ^{13}C n.m.r. experiment relatively high concentrations are desirable, causing f_{RH^+}/f_R to deviate from unity. By taking into account this deviation we intend to establish better agreement between our pK_1 values and the ones described in the literature.

The pK_1 value of the equilibrium

$$R + H^+ \leftrightarrows RH^+$$

may be described by the Henderson-Hasselbach equation:[2]

$$pK_1 = pH + \log[(f_{RH^+} \cdot c_{RH^+})/(f_R \cdot c_R)]$$

where *c* is the concentration.

The ratio $I = c_{RH^+}/c_R$ has been determined by the ^{13}C n.m.r. technique as $(\delta_1 - \delta)/(\delta - \delta_2)$ where δ_1 is the chemical shift of R, δ_2 is the chemical shift of RH^+ and δ is the chemical shift of a mixture of R and RH^+ at a certain pH value. Although the δ_1 and δ_2 values are slightly solvent and counter ion dependent we assumed them to be constant. It has been demonstrated[1] that this is a reasonable assumption since the correlation between log *I* and pH is excellent (correlation coefficient > 0.999).

Hammett has demonstrated[4] that for structurally similar compounds the ratio f_{RH^+}/f_R is a constant at a certain fixed pH value. The diazanaphthalenes seem to satisfy this condition very well. Consequently the difference between the pK_1 values of two structurally similar compounds at the same pH value may be

determined by

$$\Delta pK_1 = \Delta \log (c_{RH^+}/c_R = \Delta \log I$$

This equation provided us with the relative pK_1 values of the diazanaphthalenes. The absolute pK_1 value of one compound of the series was determined by recording the pH dependence of the ^{13}C chemical shifts in a dilute solution where the ratio f_{RH^+}/f_R could be assumed to be unity. The reference value thus obtained enabled us to determine the absolute pK_1 values of the other compounds.

Although the Hammett concept has been the object of criticism (see for example Ref. 5) this procedure for determination of pK values has often been applied with good results (e.g. for primary anilines[6] and indoles[7]). Experimental evidence is available that this concept holds at least for water/sulphuric acid mixtures.[8] Since sulphuric acid is a very strong acid it has the additional advantage that it hardly dilutes the solution when added to set the pH at the desired value.

Results

In order to determine the relative pK_1 values of the diazanaphthalenes a plot was made of pH vs log I (Fig. 1) for all compounds except quinazoline which is not stable in aqueous acid solution.[9] The log I value of a compound at a certain pH value was taken as the average of the log I values of the separate carbon atoms. Since carbon atoms with a higher $\Delta\delta$ value provide more accurate log I values, only the four carbon atoms with the highest $\Delta\delta$ values were taken into account.

From Fig. 1 it is seen that the slope of the lines representing the relationship between log I and pH is not the same for all compounds. In particular the values for quinoxaline and 1,8-naphthyridine are quite different from the others (0.75 and 1.16, respectively). The slope of the lines for the other compounds is between 0.96 and 1.08.

The difference in pK_1 value between two compounds was determined as the average difference between the log I values—at constant pH value—in the region where the log I values of both compounds were between -1 and $+1$. The pK_1 value of 1,5-naphthyridine has been determined in dilute solution as a reference value.

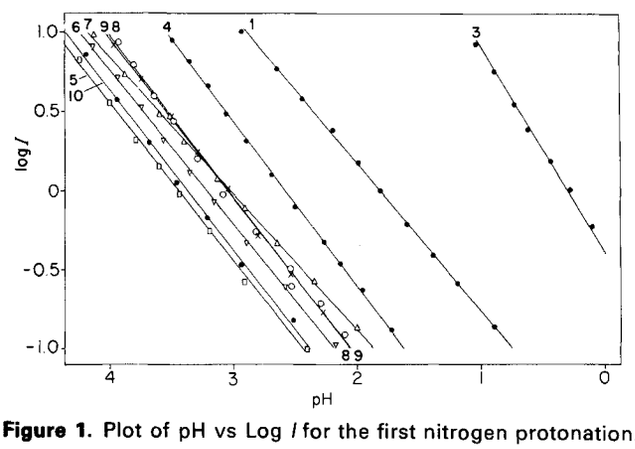

Figure 1. Plot of pH vs Log I for the first nitrogen protonation.

Table 1. Comparison of pK values measured by the ^{13}C n.m.r. technique with literature values

Compound	pK_1 (n.m.r.)	pK_1 (lit).	Ref.	pK_2 (n.m.r.)	pK_2 (lit.)	Ref.
1	2.20	2.29	11	—	—	—
3	0.58	0.56	11	—	—	—
4	2.93	2.91	11	−1.13	−1.10	13
5	3.81	3.78	10	−0.18	−0.30	13
6	3.57	3.63	10	−1.12	—	—
7	3.40	3.39	10	−3.10	−2.95	13
8	3.42	3.47	12	—	—	—
9	3.41	3.48	[a]	0.37	—	—
10	3.74	3.73	[a]	0.46	—	—

[a] Measured in the same way as in Ref. 10–12

Since the pK_1 values determined with the ^{13}C n.m.r. technique are in good agreement with the literature values (see Table 1; correlation coefficient $c = 0.9990$) it seems justified to determine the pK_2 values also with this technique.

For determination of the pK_2 values it is necessary to measure the ^{13}C chemical shifts of the diprotonated species (δ_3). Since these values may be achieved at very low pH values, dilution effects become important. Therefore the pK_2 value of 1,8-naphthyridine is inaccurate and compounds with lower pK_2 values—i.e. compounds with two nitrogen atoms in one ring—were omitted in this part of our investigation.

The relative pK_2 values were determined from Fig. 2 in the same way as mentioned above for the pK_1 values. The slope of the lines is between 0.53 and 0.80. This indicates that for the latter pH region the proton activity coefficient is smaller than the corresponding coefficient in the pH region of the pK_1 values. The pH dependence of the ^{13}C chemical shifts of 2,7-naphthyridine was also measured in dilute solution, providing the reference pK_2 value.

All pK values are listed in Table 1. From the agreement with the literature values ($c = 0.9996$) we conclude that the ^{13}C n.m.r. technique is a good, though time-consuming method for pK measurement.

It is noteworthy that as the separation between the nitrogen atoms increases from 1 carbon atom (1,8-naphthyridine) up to 4 carbon atoms (2,6-naphthyridine) the pK_2 value becomes higher. This may suggest that the pK_2 value is largely determined

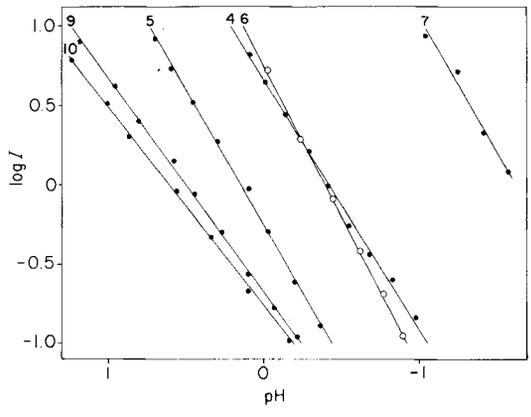

Figure 2. Plot of pH vs log I for the second nitrogen protonation.

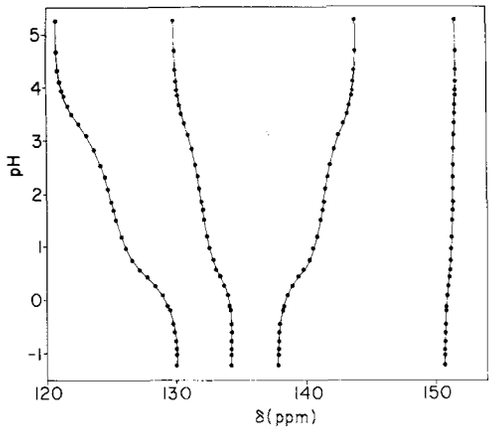

Figure 3. pH dependence of the ^{13}C chemical shifts of 2,6-naphthyridine.

by the repulsion between the protons. We believe that calculations on the second nitrogen protonation are not significant at the moment, since the experimental structure is not yet known for all molecules (compare pK_1 calculations in Ref. 14). However, we hope to substantiate this suggestion with detailed calculations as soon as the experimental structures of all compounds are known. Single crystal X-ray diffraction measurements are in progress in our laboratory.

pH DEPENDENCE OF THE ^{13}C CHEMICAL SHIFTS

Measurement

In determining the pK values of the diazanaphthalenes we recorded the pH dependence of the ^{13}C chemical shifts for all isomers except quinazoline. As a consequence of the dynamic nature of the protonation equilibrium, protonation does not affect the symmetry of the diazanaphthalenes.[1] Therefore the first and second protonation of the symmetric diazanaphthalenes involve the same, equivalent nitrogen atoms. Thus the change in ^{13}C chemical shifts under the influence of the first nitrogen protonation ($\Delta\delta_1$) is similar to that of the second nitrogen protonation ($\Delta\delta_2$); see for example, 2,6-naphthyridine (Fig. 3). In the asymmetric diazanaphthalenes the first and second protonation involve different nitrogen atoms, resulting in different effects on the ^{13}C chemical shifts; see for example 1,7-naphthyridine (Fig. 4) where the first protonation only affects the β-nitrogen atom and the second protonation the α-nitrogen atom.

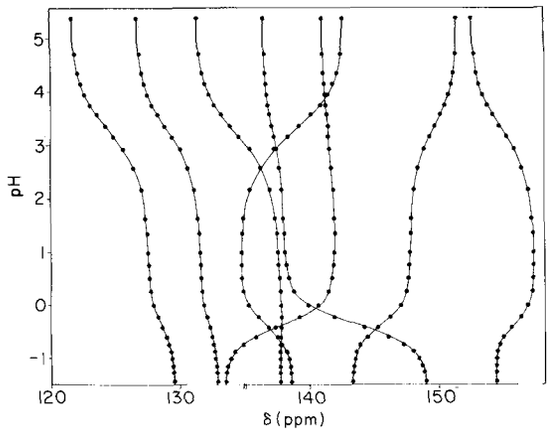

Figure 4. pH dependence of the ^{13}C chemical shifts of 1,7 naphthyridine.

Table 2. Protonation parameter sets for α- and β-nitrogen protonation

C[a]	$\Delta\delta_\alpha$	$\Delta\delta_\beta$
1	—[b]	−2.84
2	−4.67	—[b]
3	+0.58	−9.61
4	+10.58	+5.08
5	+1.86	+2.36
6	+4.71	+5.71
7	+5.14	+4.27
8	−5.36	+4.02
9	−6.30	+0.33
10	+2.27	+4.18

[a] Atom number.
[b] Nitrogen atom.

The ^{13}C chemical shifts of the neutral molecules (δ_1), monoprotonated molecules (δ_2), diprotonated molecules (δ_3) and the changes in ^{13}C chemical shifts ($\Delta\delta_1$ and $\Delta\delta_2$) are listed in Tables 3 and 4. For the molecules which have both nitrogen atoms in one ring (**1**, **3** and **8**) the pK_2 value is so low that the δ_3 values could not be measured by our method due to excessive dilution.

Table 3. pH dependence of the ^{13}C chemical shifts in the symmetric diazanaphthalenes

C[a]	δ_1[b]	δ_2[b]	δ_3	$\Delta\delta_1$[b]	$\Delta\delta_2$	$\Delta\delta$(exp)[c]
3-2/3	145.19	143.22	—	−1.97	—	−2.04
3-5/8	128.42	126.68	—	−1.74	—	−1.74
3-6/7	131.58	136.62	—	+5.04	—	+4.93
3-9/10	141.17	138.73	—	−2.44	—	−2.02
4-2/6	151.31	151.39	151.55	+0.08	+0.16	+0.02
4-3/7	125.72	128.68	131.64	+2.96	+2.96	+2.86
4-4/8	136.99	139.60	142.16	+2.61	+2.56	+2.61
4-9/10	141.78	139.60	135.30	−2.18	−4.30	−2.02
7-2/7	153.85	154.00	153.60	+0.15	−0.40	+0.23
7-3/6	123.54	126.06	128.83	+2.52	+2.77	+2.64
7-4/5	139.27	145.50	153.40	+6.23	+7.90	+6.23
7-9	153.37	147.25	139.10	−6.12	−8.15	−6.30
7-10	123.15	125.60	127.22	+2.45	+1.62	+2.27
8-1/4	152.01	153.23	—	+1.22	—	+1.12
8-5/8	127.23	130.52	—	+3.29	—	+3.19
8-6/7	134.67	139.16	—	+4.49	—	+4.49
8-9/10	126.73	128.99	—	+2.26	—	+2.26
9-1/5	151.53	151.24	150.68	−0.29	−0.56	−0.24
9-3/7	143.87	141.20	137.90	−2.67	−3.30	−2.67
9-4/8	120.73	125.23	130.07	+4.50	+4.84	+4.55
9-9/10	129.82	132.07	134.24	+2.25	+2.17	+2.26
10-1/8	152.61	153.14	153.49	+0.53	+0.35	+0.59
10-3/6	146.24	144.29	141.50	−1.95	−2.79	−1.95
10-4/5	120.58	124.24	127.83	+3.66	+3.59	+3.72
10-9	123.27	123.86	123.99	+0.59	+0.13	+0.33
10-10	138.57	143.01	146.49	+4.44	+3.48	+4.18

[a] Compound and carbon atom number.
[b] Results concerning the first protonation are slightly different from the values given in Ref. 1 because of different experimental conditions (see Experimental).
[c] Expected values from protonation parameters.

Table 4. pH dependence of the ^{13}C chemical shifts in the asymmetric diazanaphthalenes

C[a]	δ_1[b]	δ_2[b]	δ_3	$\Delta\delta_1$[b]	$\Delta\delta_1$[c](exp)	$\Delta\delta_2$	$\Delta\delta_2$[c](exp)
1-3	144.93	141.14	—	−3.78	−5.16[e]	—	—
1-4	125.87	135.46	—	+9.59	+7.50	—	—
1-5	127.36	128.78	—	+1.42	+2.14	—	—
1-6	132.75	138.83	—	+6.08	+5.27	—	—
1-7	132.68	137.85	—	+5.17	+4.65	—	—
1-8	127.75	128.40	—	+0.75	−0.07	—	—
1-9	149.33	148.73	—	−0.60	−2.56	—	—
1-10	126.86	132.96	—	+6.10	+3.35	—	—
5-2	155.66	161.14	156.70	+5.48	+5.71	−4.44	−4.67
5-3[d]	124.16	127.30	129.10	+3.14	+4.27	+1.80	+0.58
5-4	137.80	141.60	152.60	+3.80	+4.02	+11.00	+10.58
5-5	152.95	150.24	152.25	−2.71	−2.84	+2.01	+1.86
5-7	145.91	138.10	141.65	−7.81	−9.61	+3.55	+5.14
5-8[d]	121.64	126.39	121.70	+4.75	+5.08	−4.69	−5.36
5-9	148.67	151.72	144.55	+3.05	+4.18	−7.17	−6.31
5-10	123.48	125.01	125.78	+1.53	+0.33	+0.77	+2.27
6-2	152.53	157.33	154.43	+4.80	+4.02	−2.90	−4.67
6-3	126.74	131.51	132.95	+4.77	+5.71	+1.44	+0.58
6-4	136.50	138.05	149.15	+1.55	+2.36	+11.10	+10.58
6-5	121.70	127.50	129.60	+5.80	+5.08	+2.10	+1.86
6-6	142.63	134.67	138.70	−7.96	−9.61	+4.03	+4.71
6-8	151.35	147.77	143.27	−3.58	−2.84	−4.50	−5.36
6-9	141.03	141.92	133.38	+0.89	−0.33	−8.54	−6.30
6-10	131.37	137.51	137.78	+6.14	+4.18	+0.27	+2.28

[a–c] See Table 3.
[d] Because of their $\Delta\delta_2$-values the assignment of C-3 and C-8 has been reversed compared with Ref. 1.
[e] $\Delta\delta_1$(exp) for cinnoline: 0.44 $\Delta\delta_\alpha$ + 0.56$\Delta\delta_\beta$ (see Ref. 1).

The first nitrogen protonation of the symmetric diazanaphthalenes provides us with two protonation parameter sets,[1] one for α- and one for β-nitrogen protonation (Table 2.).

These protonation parameters give a very good description of the $\Delta\delta_1$ values (Tables 3 and 4; $c = 0.986$). The $\Delta\delta_2$ values could also be described quite well by these protonation parameters (Table 3 and 4; $c = 0.978$). This is in contrast with the results which Pugmire and Grant[15] have reported for the diazabenzenes. However, we have to realize that the diazabenzenes contain two nitrogen atoms in one ring, whereas we have not been able to measure the second protonation of the corresponding diazanaphthalenes.

EXPERIMENTAL

The proton noise-decoupled ^{13}C n.m.r. spectra were recorded on a Varian XL-100 spectrometer (25.2 MHz for ^{13}C and 15.4 MHz for ^{2}H lock). The data acquisition of the free induction delays (pulse width 22 μs; acquisition time 0.8 s; pulse delay 0.5 s) and Fourier transformation were performed with a Varian 620/L data machine (16 K). With a spectral width of 5120 Hz and 4096 memory points the resolution is 0.05 ppm. Using water as a solvent and concentration of (150 ± 1) mg ml^{-1}, 500 transients were required to obtain an acceptable signal to noise ratio. The measurements for the reference pK values were performed on solutions with concentrations of (15 ± 0.5) mg ml^{-1}. In this case 30 000 transients were required for each ^{13}C n.m.r. spectrum.

In the tube (o.d. 10 mm) containing the aqueous solution, a capillary was centred with the aid of three Teflon rings. The capillary contained deuterated acetone to provide a signal for the deuterium field-frequency lock and TMS as an internal standard.

The pH was decreased progressively with sulphuric acid (98%, Merck) and measured with a Knick pH-meter at 20 °C (probe temperature 20 ± 2 °C) with an Ingold combined electrode (type 405M5). This electrode was calibrated with Elektrofact buffer powder at pH = 4 and pH = 7. Compounds **1**, **3** and **8** are commercial products (Aldrich). The other compounds were synthesized according to Refs. 16–20.

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