Carbon-13 N.m.r. Investigation on the Nitrogen Methylation of the Mono- and Diazanaphthalenes

Peter van de Weijer,* (the late) Chandra Mohan and Dirk M. W. van den Ham
Chemical Physics Laboratory, Twente University of Technology, P.O. Box 217, Enschede, The Netherlands

The ^{13}C n.m.r. spectra of the *N*-methylated mono- and diazanaphthalenes have been recorded and analysed. It has been shown that *N*-methylation as well as *N*-protonation in cinnoline occur predominantly at the β-nitrogen atom. *N*-methylation and *N*-protonation show a similar effect on the ^{13}C chemical shifts.

INTRODUCTION

Pugmire and Grant[1] have investigated the *N*-protonation behaviour of the azabenzenes by means of ^{13}C n.m.r. These authors have shown that the changes in ^{13}C chemical shifts under the influence of *N*-protonation ($\Delta\delta_P$) in the diazabenzenes could be predicted by using the $\Delta\delta_P$ values of pyridine as protonation parameters. (Additivity rules).

In a previous contribution[2] we have shown that a similar relationship exists between the $\Delta\delta_P$ values of the diazanaphthalenes and those of quinoline and of isoquinoline. The high reliability of this relationship permitted us to establish the site of protonation in some asymmetric diazanaphthalenes.

The analysis of the ^{13}C n.m.r. spectra of protonated aza-aromatics is facilitated by the fact that the proton is in rapid exchange between the aza-aromatic molecule and the solvent (water). Once the assignment of the ^{13}C n.m.r. spectrum of the neutral molecule is known, the spectrum of the protonated species can be analysed by recording a titration curve of the n.m.r. resonance line of each individual carbon atom.

In contrast to the behaviour of protonated aza-aromatics, their *N*-methylated counterparts are stable ions; hence analysis of spectra that belong to the latter type of ion must be carried out in a different way.

Recently we reported a ^{13}C n.m.r. investigation on the *N*-methylation of some azabenzenes.[3] The analysis of the spectra was based on selective proton-decoupled ^{13}C experiments. From these experimental data it has been shown that, by analogy with *N*-protonation, the changes in ^{13}C chemical shifts under the influence of *N*-methylation ($\Delta\delta_M$) in the diazabenzenes could be predicted well by the $\Delta\delta_M$ values in pyridine. Moreover it appeared that, despite their different thermodynamic behaviour, *N*-methylation and *N*-protonation have a very similar effect on the ^{13}C chemical shifts.

The observations mentioned above suggest that the ^{13}C n.m.r. spectra of the *N*-methylated azanaphthalenes can be analysed in two ways. First the assignment of the spectra can be performed by a direct comparison with the ^{13}C n.m.r. spectra of the corresponding *N*-protonated species. Secondly, once the spectra of *N*-methylated quinoline and isoquinoline have been analysed by the first procedure, the spectra of the *N*-methylated diazanaphthalenes can be assigned using the $\Delta\delta_M$ values in quinoline and isoquinoline as the α- and β-methylation parameter sets respectively.

Because of the rapid tautomeric proton exchange between equivalent nitrogen atoms, monoprotonation, as opposed to monomethylation, does not alter the symmetry of a symmetric diazacompound. Therefore the spectra of the *N*-methylated products of symmetric diazanaphthalenes can only be analysed on the basis of the methylation parameters. The compounds that have been studied are the mono-*N*-methyl derivatives of 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**), 2,7-naphthyridine (2,7-diazanaphthalene, **10**), quinoline (1-azanaphthalene, **11**) and isoquinoline (2-azanaphthalene, **12**), all counter ions being FSO_3^-.

RESULTS AND DISCUSSION

Analysis of the spectra

The spectral data of quinoline and isoquinoline have been collected in Table 1. Assignments of the resonance lines to the respective carbon atoms have been made by comparison with the data derived for the corresponding *N*-protonated product. From Table 1 it can be seen that the correspondence between the $\Delta\delta_P$ and $\Delta\delta_M$ values is good. The correlation coefficient $c = 0.949$. The largest differences between methylation

* Author to whom correspondence should be addressed.

Table 1. Carbon-13 chemical shifts in quinoline and isoquinoline

C[a]	δ_R[b]	δ_{RH^+}[c]	$\delta_{RCH_3^+}$[d]	$\Delta\delta_P$[e]	$\Delta\delta_M$[f]
11–2	150.79	145.49	150.47	−5.30	−0.32
11–3	122.28	122.99	122.88	+0.71	+0.60
11–4	137.91	148.46	148.60	+10.55	+10.69
11–5	128.87	130.17	131.29	+1.30	+2.42
11–6	127.69	131.26	131.44	+3.57	+3.75
11–7	130.87	136.35	137.05	+5.48	+6.18
11–8	128.59	121.14	119.28	−7.45	−9.31
11–9	147.49	137.90	139.45	−9.59	−8.04
11–10	128.87	129.50	130.50	+0.63	+1.63
12–1	152.41	147.42	150.66	−4.99	−1.75
12–3	142.03	131.98	136.10	−10.05	−5.93
12–4	122.03	126.57	127.26	+4.54	+5.23
12–5	127.15	128.33	128.19	+1.18	+1.04
12–6	131.96	138.11	138.05	+6.15	+6.09
12–7	128.57	132.25	132.46	+3.68	+3.89
12–8	128.57	131.22	130.97	+2.65	+2.40
12–9	129.16	127.62	131.66	−1.54	+2.50
12–10	136.42	139.29	139.39	+2.87	+2.97

[a] Compound and carbon atom number.
[b] Chemical shifts of the neutral molecule R, (Ref. 4).
[c] Chemical shifts of the protonated molecule RH^+ (Ref. 4).
[d] Chemical shifts of the methylated molecule RCH_3^+.
[e] Protonation shifts.
[f] Methylation shifts.

and protonation shifts are found for carbon atoms in *ortho* position with respect to the methylated nitrogen atom.

The $\Delta\delta_M$ value of quinoline and isoquinoline have been subsequently used to analyse the spectra of compounds **1–10**. With the exception of **2**, the analysis of these spectra was straightforward. The results have been collected in Table 2.

The failure to analyse the spectrum of the *N*-methylquinazolinium ion must be attributed to its rapid pseudo-base formation.[5]

In the spectrum of *N*-methylated 2,6-naphthyridine only one resonance line was found for the bridge atoms. The analytical procedure allows two explanations. Either both bridge atoms have the same chemical shift or one resonance line coincides with that of C-4. In the spectrum of *N*-methylated 2,7-naphthyridine, the signals of C-9 and C-4 probably coincide. From Table 2 it can be concluded that there is a satisfactory correspondence between the observed and expected methylation shifts (correlation coefficient $c = 0.951$).

The spectra of *N*-methylated 1,6- and 1,7-naphthyridine yield additional support for the reliability of the analytical procedure used. Paudler and Kress[6] have proven that *N*-methylation in these two compounds occurs on the β-nitrogen only. If we use the α-methylation parameter set to predict the shifts, there is no correlation at all between expected and observed data ($c = 0.439$ and 0.015 respectively), whereas the β-parameter set works very well for both compounds ($c = 0.979$ and 0.955).

The interpretaton of the spectrum of *N*-methylated cinnoline needs further comment. Conflicting results are reported on the site of protonation and methylation.[7,8] Theoretical studies (e.g. Ref. 9) indicate that there is hardly any difference in the electron-densities on the two nitrogen atoms. Molecular potential calculations[10] show a slight preference for α-nitrogen protonation (0.69 kcal mole^{-1})[11] whereas our previous experiments led to the conclusion that α- and β-nitrogen protonation occur in a 2:3 ratio. Palmer and McIntyre[12] suggested that the preferential β-nitrogen protonation is simply the result of steric hindrance exerted by the *peri*-8-proton. They substantiated this suggestion by *N*-methylation experiments on substituted 4-methylcinnolines. *N*-methylation of 4-methylcinnoline yielded two isomeric products in a 9:1 ratio. *N*-methylation of 3,4-dimethylcinnoline, however, yielded two isomers in a 1:1 ratio. Substitution in the 3 position clearly balances the steric hindrance exerted by the *peri*-8-proton.

The ^{1}H n.m.r. spectrum of mono-*N*-methylated cinnoline revealed the existence of two methylated products. If we take the resonance signals of the *N*-methyl protons as a gauge, a ratio of 10:1 is found. In a similar experiment Zoltewicz and Deady[13] found a 9:1 ratio. The ^{13}C spectrum of the more abundant compound could be accounted for only with the β-methylation parameter set. Of the other, less concentrated, compound only four lines were found. The absence of the other lines must be attributed to the lack of a nuclear Overhauser effect for the bridge atoms and to the accidental coincidence with the resonance lines of the more abundant isomer. The four observed lines, however, could be well correlated with the α-methylation parameter set ($c = 0.998$).

Two resonance lines show considerable line-broadening in the spectra of all the compounds. From the analytical procedure followed, it appeared that these are the resonance lines of the *ortho* carbon atoms except in *N*-methylated quinoline and 1,5-naphthyridine. Assuming this phenomenon to be general the assignments of C-2 and C-4 in *N*-methylated quinoline and 1,5-naphthyridine are reversed with respect to the analytical procedure followed.

Comparison of *N*-methylation and *N*-protonation

In solutions of monoprotonated symmetric diaza compounds a rapid tautomeric exchange exists between the two equivalent nitrogen atoms. Mono-*N*-methylated aza-compounds form stable ions in solution. The spectrum of a monoprotonated symmetric diazanaphthalene, therefore, shows only four resonance lines, whereas the spectrum of the corresponding monomethylated species shows eight lines. Thus, in comparing the methylation with the protonation shifts, the methylation shifts of those carbon atoms that remain equivalent in the monoprotonated symmetric diazanaphthalenes must be averaged. For the asymmetric diazanaphthalenes, a direct comparison is possible. The results (Table 3) show that the methylation shifts are similar to the protonation shifts ($c = 0.943$). Figure 1 is a pictorial representation of these results. It can be seen that the absolute values of the negative $\Delta\delta$ values for the *ortho* carbons are smaller

Table 2. Influence of *N*-methylation on ^{13}C chemical shifts in the diazanaphthalenes

C[d]	δ_R	$\delta_{RCH_3}^+$	$\Delta\delta_{obs}$[a]	$\Delta\delta_{exp}$[b]	C[d]	δ_R	$\delta_{RCH_3}^+$	$\Delta\delta_{obs}$[a]	$\Delta\delta_{exp}$[b]
1–3	144.93	141.89	−3.04	−5.93	6–6	142.63	138.23	−4.40	−5.93
1–4	125.87	135.85	+9.98	+5.23	6–8	151.35	151.27	−0.08	−1.75
1–5	127.36	128.46	+1.10	+1.04	6–9	141.03	142.91	+1.88	+2.50
1–6	132.75	139.51	+6.76	+6.09	6–10	131.37	136.48	+5.11	+2.97
1–7	132.68	137.51	+4.83	+3.89	7–2	153.85	152.58	−1.27	−0.32
1–8	127.75	130.41	+2.66	+2.40	7–3	123.54	124.13	+0.59	+0.60
1–9	149.33	150.47	+1.14	+2.50	7–4	139.27	150.20	+10.93	+10.69
1–10	126.86	131.37	+4.51	+2.97	7–5	139.27	141.31	+2.04	+2.42
3–2	145.19	141.93	−3.26	−0.32	7–6	123.54	127.52	+3.98	+3.75
3–3	145.19	148.16	+2.97	+0.60	7–7	153.85	158.58	+4.73	+6.18
3–5	128.42	132.10	+3.68	+2.42	7–9	153.37	145.44	−7.93	−8.04
3–6	131.58	135.58	+4.00	+3.75	7–10	123.15	124.13	+0.98	+1.63
3–7	131.58	138.04	+6.46	+6.18	8–1	152.01	152.43	+0.42	−1.75
3–8	128.42	119.98	−8.44	−9.31	8–4	152.01	156.06	+4.05	+5.23
3–9	141.17	132.78	−8.39	−8.04	8–5	127.23	129.48	+2.25	+1.04
3–10	141.17	146.74	+5.57	+1.63	8–6	134.67	140.62	+5.95	+6.09
4–2	151.31	151.60	+0.29	−0.30	8–7	134.67	137.74	+3.07	+3.89
4–3	125.72	126.88	+1.16	+0.60	8–8	127.23	131.26	+4.03	+2.40
4–4	136.99	148.48	+11.49	+10.69	8–9	126.73	128.82	+2.09	+2.50
4–6	151.31	155.72	+4.41	+3.75	8–10	126.73	129.11	+2.38	+2.97
4–7	125.72	130.76	+5.04	+6.18	9–1	151.53	152.12	+0.59	−1.75
4–8	136.99	129.48	−7.51	−9.31	9–3	143.87	139.12	−4.75	−5.93
4–9	141.78	137.94	−3.84	−8.04	9–4	120.73	127.75	+7.02	+5.23
4–10	141.78	144.20	+2.42	+1.63	9–5	151.53	153.27	+1.74	+1.04
5–2	155.66	161.71	+6.05	+6.09	9–7	143.87	147.70	+3.83	+3.89
5–3	124.16	127.64	+3.48	+3.89	9–8	120.73	122.68	+1.95	+2.40
5–4	137.80	140.47	+2.67	+2.40	9–9	129.82	131.63[c]	+1.81	+2.50
5–5	152.95	153.04	+0.09	−1.75	9–10	129.82	131.63[c]	+1.81	+2.97
5–7	145.91	141.09	−4.82	−5.93	10–1	152.61	153.17	+0.56	−1.75
5–8	121.64	127.64	+6.00	+5.23	10–3	146.24	140.95	−5.29	−5.93
5–9	148.67	151.11	+2.44	+2.97	10–4	120.58	126.84	+6.26	+5.23
5-10	123.48	125.34	+1.86	+2.50	10–5	120.58	121.45	+0.87	+1.04
6–2	152.53	157.70	+5.17	+3.89	10–6	146.24	151.94	+5.70	+6.09
6–3	126.74	131.70	+4.96	+6.09	10–8	152.61	155.79	+3.18	+2.40
6–4	136.50	137.49	+0.99	+1.04	10–9	123.27	126.84[c]	+3.57	+2.50
6–5	121.70	128.02	+6.32	+5.23	10–10	138.57	141.71	+3.14	+2.97

[a] Observed methylation shift.
[b] Expected methylation shift.
[c] Uncertain assignment (see text).
[d] Compound and carbon atom number.

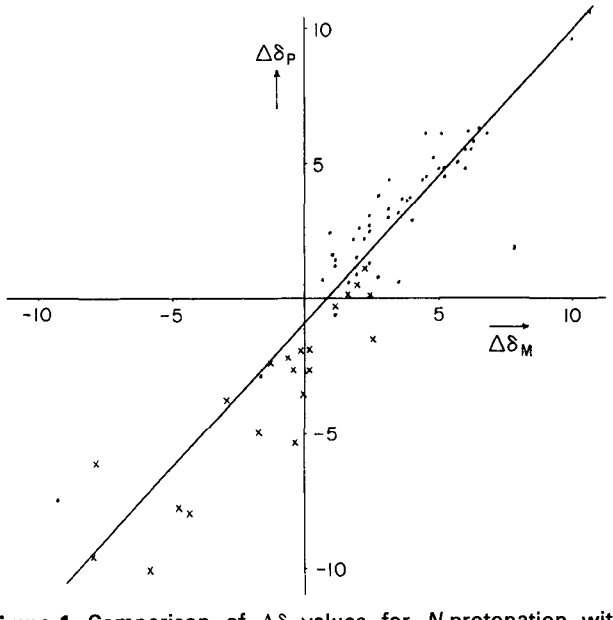

Figure 1. Comparison of $\Delta\delta$ values for *N*-protonation with those for *N*-methylation. x = *ortho* carbon atoms.

for methylation than for protonation. This was noticed before in the series of the aza-benzenes.[3]

For β-*N*-methylated cinnoline the correlation between expected and observed shifts was considerably lower ($c = 0.883$) than that for *N*-methylated 1,6- and 1,7-naphthyridine ($c = 0.979$ and 0.955 respectively). The same was observed for the protonation shifts.[2] As, in contrast to *N*-methylation, a dynamic protonation equilibrium between both nitrogen atoms is possible, a linear combination of the α- and β-protonation parameter set was chosen in order to obtain a better correlation between experimental and expected protonation shifts. The optimal combination corresponded to a 2:3 ratio of α- and β-protonation. Since no dynamic equilibrium exists in the methylated compound the low correlation must simply be attributed to the lack of additivity when two nitrogen atoms are adjacent to each other.

The present work shows that the methylation shifts in cinnoline are in excellent agreement with the protonation shifts (Table 3).

In view of this observation we may conclude that in

Table 3. Comparison of protonation shifts with methylation shifts

C[a]	$\Delta\delta_P$	$\Delta\delta_M$	C[a]	$\Delta\delta_P$	$\Delta\delta_M$
1–3	−3.78	−3.04	**6**–3	+4.77	+4.96
1–4	+9.59	+9.98	**6**–4	+1.55	+0.99
1–5	+1.42	+1.10	**6**–5	+5.80	+6.32
1–6	+6.08	+6.76	**6**–6	−7.96	−4.40
1–7	+5.17	+4.83	**6**–8	−3.58	−0.08
1–8	+0.75	+2.66	**6**–9	+0.89	+1.88
1–9	−0.60	+1.14	**6**–10	+6.14	+5.11
1–10	+6.10	+4.51	**7**–2/7	+0.15	+1.73
3–2/3	−1.97	−0.15	**7**–3/6	+2.52	+2.29
3–5/8	−1.74	−2.88	**7**–4/5	+6.23	+6.49
3–6/7	+5.04	+5.73	**7**–9	−6.12	−7.93
3–9/10	−2.44	−1.41	**7**–10	+2.45	+0.98
4–2/6	+0.08	+2.35	**8**–1/4	+1.22	+2.24
4–3/7	+2.96	+3.10	**8**–5/8	+3.29	+3.14
4–4/8	+2.61	+1.99	**8**–6/7	+4.49	+4.51
4–9/10	−2.18	−0.71	**8**–9/10	+2.26	+2.24
5–2	+5.48	+6.05	**9**–1/5	−0.29	+1.17
5–3	+3.14	+3.48	**9**–3/7	−2.67	−0.46
5–4	+3.80	+2.67	**9**–4/8	+4.50	+4.49
5–5	−2.71	+0.09	**9**–9/10	+2.25	+1.81
5–7	−7.81	−4.82	**10**–1/8	+0.53	+1.87
5–8	+4.75	+6.00	**10**–3/6	−1.95	+0.20
5–9	+3.05	+2.44	**10**–4/5	+3.66	+3.57
5–10	+1.53	+1.86	**10**–9	+0.59	+3.75
6–2	+4.80	+5.17	**10**–10	+4.44	+3.14

[a] Compound and carbon atom number.

the previous study the effect of the tautomeric exchange was overrated and that the protonation equilibrium is shifted much more to the β-protonated product.

EXPERIMENTAL

Compounds **1–12** were prepared by the addition of a 10% solution of methylfluorosulphate[14] in dichloromethane to solutions of the parent compound in a dichloromethane/ether (1:1) mixture. The amount of methylating agent used was always smaller than that calculated for complete *N*-methylation. This procedure was necessary to prevent formation of dimethylated products.

The parent compounds of **1–4**, **8** and **11–12** were commercial products (Aldrich). The other parent compounds were synthesized according to Refs. 15–19.

The 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 decays (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 instrument (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 1.0 M concentrations, 500 transients were required to obtain an acceptable signal to noise ratio. The probe temperature was 20 °C. A capillary was centred with the aid of three Teflon® rings in the tube (outer diameter 10 mm) containing the aqueous solution. This capillary contained deuterated acetone to provide a signal for the deuterium field-frequency lock and TMS as an internal standard.

Acknowledgements

The investigations were supported in part by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

REFERENCES

1. R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.* **90**, 697 (1968).
2. P. van de Weijer, H. Thijsse and D. van der Meer, *Org. Magn. Reson.* **8**, 187 (1976).
3. P. van de Weijer and C. Mohan, *Org. Magn. Reson.* **9**, 53 (1977).
4. P. van de Weijer, D. M. W. van den Ham and D. van der Meer, *Org. Magn. Reson.* **9**, 281 (1977).
5. A. R. Osborn and K. Schofield, *J. Chem. Soc.* 4191 (1956).
6. W. W. Paudler and T. J. Kress, *J. Heterocycl. Chem.* **5**, 561 (1968).
7. D. E. Ames, G. V. Boyd, A. W. Ellis and A. C. Lovesey, *Chem. Ind.* 458 (1966).
8. M. H. Palmer and B. Semple, *Chem. Ind.* 1766 (1965).
9. M. H. Palmer, A. J. Gaskell, P. S. McIntyre and D. W. W. Anderson, *Tetrahedron* **27**, 2921 (1971).
10. R. Bonaccorsi, E. Scrocco and J. Tomasi, *J. Chem. Phys.* **52**, 5270 (1970).
11. P. van de Weijer, D. van der Meer and J. L. Koster, *Theor. Chim. Acta* **38**, 223 (1975).
12. M. H. Palmer and P. S. McIntyre, *Tetrahedron* **27**, 2913 (1971).
13. J. A. Zoltewicz and L. W. Deady, *J. Am. Chem. Soc.* **94**, 2765 (1972).
14. R. W. Alder, *Chem. Ind.* 983 (1973).
15. T. J. Kress and W. W. Paudler, *Chem. Commun.* 3 (1967); 1,6-naphthyridine.
16. H. Rapoport and A. Batcho, *J. Org. Chem.* **28**, 1753 (1963); 1,7-naphthyridine.
17. T. J. Kress and W. W. Paudler, *J. Org. Chem.* **32**, 832 (1967); 1,8-naphthyridine.
18. A. Taurins and R. Tanli, *Can. J. Chem.* **52**, 843 (1974); 2,6-naphthyridine.
19. W. W. Paudler and S. J. Cornich, *J. Heterocycl. Chem.* **7**, 419 (1970); 2,7-naphthyridine.

Received 16 April 1977; accepted 3 June 1977