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# Deuterium isotope effects on $^{15}\text{N}$ , $^{13}\text{C}$ and $^1\text{H}$ chemical shifts of proton sponges

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In memory of professor Stefaniak, who was instrumental in this study but who sadly has deceased

## Abstract

Deuterium isotope effects on  $^{15}\text{N}$ ,  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts have been measured in the protonated forms of DMAN, 4-bromo, 4-picryl, 4-nitro and 2- and 2,7-chloro derivatives. Structures have been geometry optimised using BPW91/6-31(d)G density functional theory (DFT) methods and show good correspondence to experimental X-ray data.  $^{15}\text{N}$ ,  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts are calculated using GIAO/DFT methods. Chemical shifts for the two tautomers are calculated. Equilibrium constants are determined from  $^1\text{J}(\text{N,H})$  coupling constants. A comparison of  $^1\text{J}(\text{N,H})$  and  $^1\text{J}(\text{N,D})$  couplings for the non-symmetrical derivatives show that upon deuteration the equilibrium is shifted towards the dominant form. The experimental deuterium isotope effect on chemical shifts of  $\text{DMANH}^+$  shows only small values despite the apparently strong intramolecular hydrogen bonds as judged from primary isotope effects. The counter ion has little effect on the one-bond isotope effect. Secondary isotope effects on  $^{15}\text{N}$  and  $^{13}\text{C}$  chemical shifts for the non-symmetrical derivatives are divided into intrinsic and equilibrium contributions. The one-bond deuterium intrinsic isotope effect on  $^{15}\text{N}$  chemical shifts is close to 0.3 ppm and is related to charge delocalisation and the close proximity of the positive charge. The equilibrium contributions to the isotope effects at the nitrogens and at carbons are seen to increase throughout the series in parallel with the increase of the equilibrium constant. For  $^1\text{H}$  resonances only equilibrium contributions are found at the aromatic hydrogens. An important feature in the analysis of the protonated DMANs is the multi-isotope effect approach. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Ab initio calculations; Equilibrium isotope effects; Geometry optimisation; Primary and secondary isotope effects on chemical shifts; Proton sponges

## 1. Introduction

Proton sponges have been studied intensely because of their interesting structure [1–18] and unusual acid–base properties [19,20] and strong

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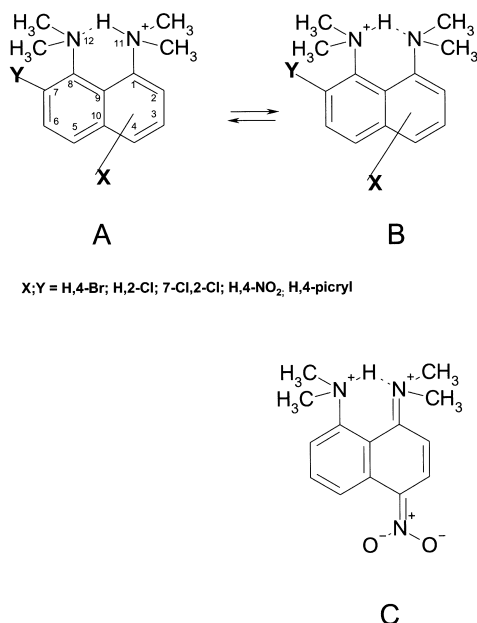


Fig. 1. Tautomeric structures (A and B). C shows a resonance form of the 4-nitro derivative. X and Y indicates substitution patterns.

intramolecular hydrogen bond judging from the <sup>1</sup>H chemical shift of the chelate proton [6,21–24]. In this relation the structure and the symmetry is of great interest. Likewise, the barrier for proton transfer [1, 24,25] and the hydrogen bond strength has been debated not the least as models for the alleged strong hydrogen bonds in enzyme catalysis [26–28]. Recently much interest has been given to the description of hydrogen bonded systems using isotope effects on chemical shift [29–42] both from a view of a static intermolecular hydrogen bond [40–43] and from a point of view of an equilibrium [33–39] as found in intramolecularly hydrogen bonded tautomeric systems. Deuterium isotope effects on chemical shifts have shown great promise in detection of otherwise invisible equilibria [34,39]. Many of the systems have been of the resonance assisted hydrogen bond (RAHB) type [32,44–46]. The DMANH<sup>+</sup> adds, being of non-RAHB type, another dimension to the use of deuterium isotope effect. The proton sponges are a very well suited system for the studies of deuterium isotope effects. First of all because the strong hydrogen bond allows easy deuteration at the chelate position, and because deuterium isotope effects can be studied at nuclei in the vicinity of the

hydrogen bridge. Furthermore, both on the average symmetrical and non-symmetrical compounds exist allowing a separation of intrinsic and equilibrium isotope effects. In addition, deuterium isotope effects on chemical shifts have proven valuable in studies of water and counter ions in the solvation sphere of ammonium ions [47–51].

Primary isotope effects are used to monitor the type of hydrogen potential well [52,53]. In DMANH<sup>+</sup> a value of 0.66 ppm was reported for the primary deuterium isotope effect [52], but smaller values for other proton sponges [53].

Theoretical calculations have shown great promise in calculations of structures of hydrogen bonded systems [16,54,55,60], in calculations of chemical shifts (nuclear shieldings) [54–60] and isotope effects on chemical shifts [54,55,60]. The secondary isotope effects are defined as

$${}^n\Delta X(D) = \delta X(H) - \delta X(D)$$

in which *n* is the number of bonds between the nuclei in question and the deuterium. The primary isotope effect is defined in a similar fashion, <sup>p</sup>ΔH(D) = δH – δD.

It is still a challenge to describe low barrier systems. Because of the large number of information both from the vicinity or deuteration and from remote positions, deuterium isotope effects on chemical shifts is a powerful tool in such studies, as seen in this and other studies [34,40–43,52,53].

The numbering is as shown in Fig. 1 irrespective of the position of the H<sup>+</sup>.

## 2. Results

### 2.1. Assignments

The assignments of <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N spectra are given in Refs. [6,20–24,61–64]. The <sup>15</sup>N chemical shifts of the DMANH<sup>+</sup> derivatives (Fig. 1) have been assigned based on heteronuclear multiple bond correlation (HMBC) spectra using the three-bond coupling to H-2 or H-7.

### 2.2. <sup>1</sup>Δ<sup>15</sup>N(D)

The one-bond deuterium isotope effects are given

Table 1

Coupling constants:  $^1J(^{15}\text{N},\text{H})$ ,  $^1J(^{15}\text{N},\text{D})$ ,  $^3J(\text{CH}_3,\text{NH})$  and one-bond deuterium isotope effects on  $^{15}\text{N}$  chemical shifts,  $^1\Delta\text{N}(\text{D})$ 

	Compound, solvent						
	Nitrogen	DMAN, TFA <sup>a</sup> /CD <sub>3</sub> CN	2,7-Dichloro, HBr <sup>a</sup> /CD <sub>3</sub> CN	4-Bromo, HClO <sub>4</sub> <sup>a</sup> /CD <sub>3</sub> CN	4-Picryl, HClO <sub>4</sub> <sup>a</sup> /CD <sub>3</sub> CN	4-Nitro, HClO <sub>4</sub> <sup>a</sup> /DMSO	2-Chloro, HBr <sup>a</sup> /DMF
$^1J(^{15}\text{N},\text{H})_{\text{obs}}$	11	30.9 ± 0.1 <sup>b</sup> 30.6 ± 0.1 <sup>d</sup>	33.0 ± 0.1	28.4 ± 0.5	27.0 ± 0.1 <sup>c</sup>	21.8 ± 0.1	9.1 ± 0.1
	12			33.6 ± 0.5	35.0 ± 0.1 <sup>c</sup>	40.4 ± 0.1	53.7 ± 0.1
$K(x_A)^c$	–	1(0.5)	1(0.5)	1.18(0.46 ± 0.02)	1.30(0.44 ± 0.02)	1.85(0.35 ± 0.02)	5.90(0.14 ± 0.02)
$^1J(^{15}\text{N},\text{D})^f$	11	4.85, 5.14 <sup>d</sup>	–	–	3.8 ± 0.1, 3.82 <sup>c</sup>	2.83	–
	12		–	–	5.8 ± 0.1, 6.0 <sup>d,g</sup>	6.67	8.65
$K^{\text{D}}(x_A)^{\text{De}}$		1(0.5)	1(0.5)	–	(0.40 ± 0.02)	(0.29 ± 0.01)	–
$^3J(\text{CH}_3,\text{NH})^h$	11	2.7 <sup>i</sup> , 2.63 (–20 °C)	2.60	2.44	2.41	1.87	1.24
	12		–	2.73	2.92	3.22	3.95
$K(x_A)^c$	–	–	–	1.12 (0.47 ± 0.01)	1.21 (0.45 ± 0.01)	1.72 (0.37 ± 0.01)	3.18 (0.24 ± 0.01)
$^1\Delta\text{N}(\text{D})^h$	11	0.18 <sup>b</sup> , 0.17 <sup>d</sup>	–	–	0.30, 0.29 <sup>c</sup>	0.32	1.13
	12		–	–	0.00, 0.00 <sup>c</sup>	–0.17	–0.40

<sup>a</sup> In some instances the salt was used in other cases the DMAN base was used and an equivalent of the indicated acid was added.<sup>b</sup> Varies very slightly with temperature, solvent and water content.<sup>c</sup> Solvent, CF<sub>3</sub>COOH, DMSO.<sup>d</sup> Solvent DMSO, counterion I<sup>–</sup>.<sup>e</sup> Value in bracket is mole fraction.  $K = [\text{B}]/[\text{A}]$ .<sup>f</sup> Taken from triplet. The given number is an average of the two measured couplings. Numbers ± 0.05 Hz.<sup>g</sup> Centre resonance is overlapped with N resonance belonging to the protio species.<sup>h</sup> Number ± 0.05 Hz.<sup>i</sup> Overlap.

Table 2  
Deuterium isotope effects on  $^{13}\text{C}$  chemical shifts of  $\text{DMANH}^+$ s

$^n\Delta\text{C(D)}$	DMAN, $\text{TFA}^{\text{a}}/\text{CD}_3\text{CN}$	2,7-Dichloro, $\text{HBr}^{\text{a}}/\text{CD}_3\text{CN}$	4-Bromo, $\text{HClO}_4^{\text{a}}/\text{CD}_3\text{CN}$	4-Picryl, $\text{HClO}_4^{\text{a}}/\text{CD}_3\text{CN}$	4-Nitro, $\text{HClO}_4^{\text{a}}/\text{DMSO}$	2-Chloro, $\text{HBr}^{\text{a}}/\text{DMF}$
Me-1(11)	−0.06	0.01	−0.05	−0.05	−0.05	−0.04
Me-8(12)			−0.06	−0.06	−0.08	−0.06
1	0.03	0.01	−0.04	−0.12	−0.26	−0.36
8			0.11	0.19	0.34	0.48
2	−0.02	−0.05	−0.03	−0.05	−0.03	−0.43
7			0.01	0.04	0.08 <sup>b</sup>	0.12
3	0.02	0	0.01	0	−0.03	−0.05
6			0.04	0.05	0.06	0.10
4	−0.03	−0.01	0.01	0.05	0.06	0.08/0.11 <sup>c</sup>
5			−0.04	−0.08	−0.10 <sup>b</sup>	−0.16/ −0.18 <sup>c</sup>
9	−0.07	−0.05	−0.07	−0.07	−0.04	−0.13
10	−0.07	−0.03	−0.04	−0.06	−0.07	−0.06

<sup>a</sup> Either the salt is used or the salt is produced by adding one equivalent of the indicated acid.

<sup>b</sup> The resonances are very close together, but the isotope effects could be assigned running samples with different content of  $\text{CD}_3\text{OD}$ .

<sup>c</sup> The resonances are too closely lying to allow an unambiguous assignment.

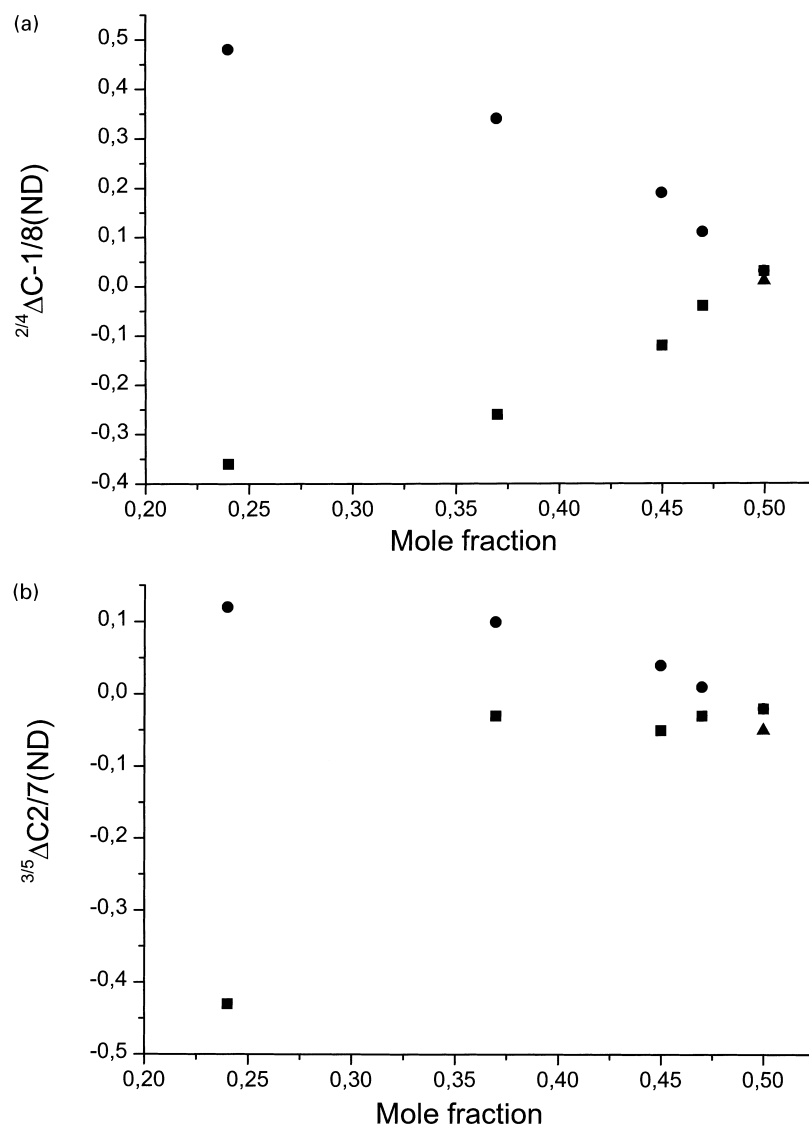


Fig. 2. Plots of deuterium isotope effects on chemical shifts vs. mole fractions,  $x_A$  (determined from  $^3J(\text{CH}_3, \text{NH})$ ) (the filled squares refer to C-1, C-2, C-3 and C-4 and the filled circles to the corresponding carbons C-7, C-6, C-5 and C-4) and the filled triangle to the 2,7-dichloroderivative. (a)  $^{2/4}\Delta_{C-1(ND)}$  or  $^{4/8}\Delta_{C-8(ND)}$  vs. mole fraction. (b)  $^{3/5}\Delta_{C-2(ND)}$  or  $^{5/7}\Delta_{C-7(ND)}$  vs. mole fraction.  $^{4/6}\Delta_{C-3(ND)}$  or  $^{6/6}\Delta_{C-6(ND)}$  vs. mole fraction. (d)  $^{5/5}\Delta_{C-4(ND)}$  or  $^{5/5}\Delta_{C-5(ND)}$  vs. mole fraction.

in Table 1. The averaged value for  $\text{DMANH}^+$  is seen to be small and of a magnitude similar to that observed in ammonium ions [47–51]. It is found to be independent of the counter ion. For 4-picryl- $\text{DMANH}^+$ , 4-nitro- and 2-chloro- $\text{DMANH}^+$  zero, positive or negative values are

observed. The general trend is an increase in the numerical values throughout the series. For the 4-picryl derivative, the average value of the effects at N-1 and N-8 is similar to that of  $\text{DMANH}^+$ . This is less so for the 4-nitro and 2-chloro derivative.

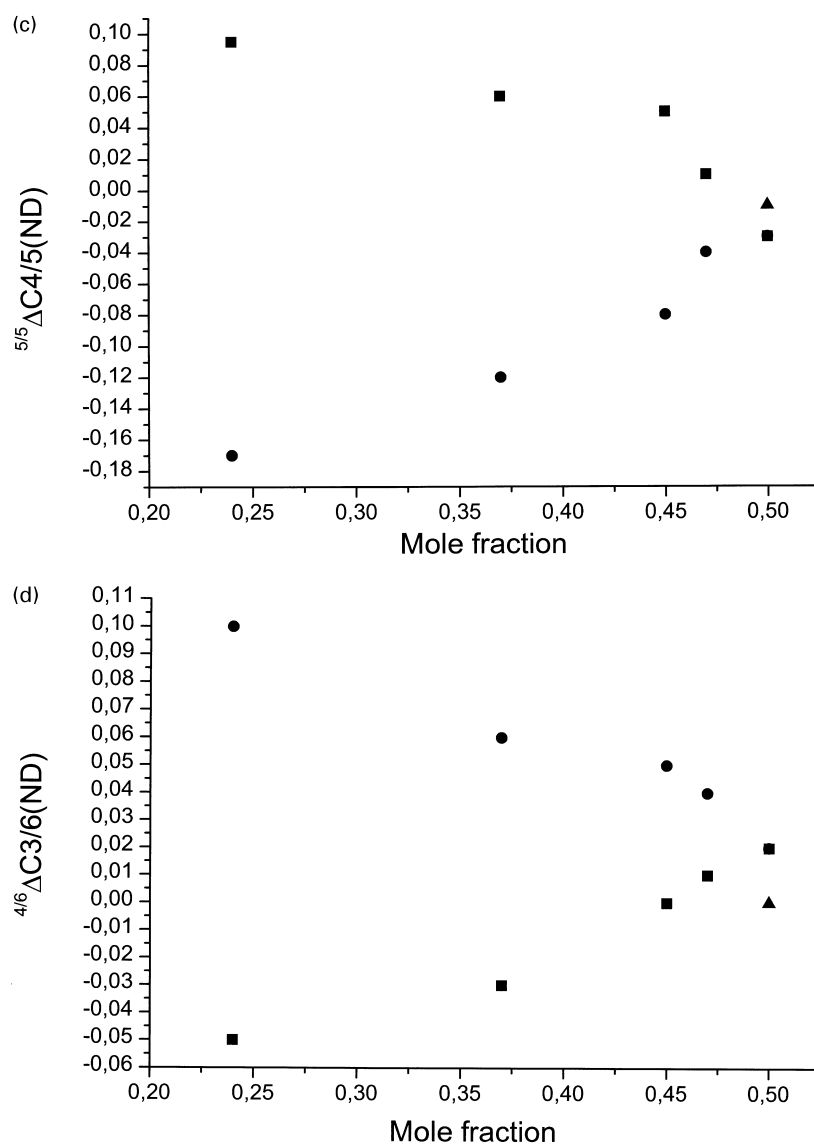


Fig. 2 (continued)

### 2.3. $^n\Delta C(D)$

Deuterium isotope effects on  $^{13}C$  chemical shifts are relatively small (Table 2) and again of both signs. It is noticeable that the numerical values found in  $DMANH^+$  are smaller than those observed for the derivatives. For 4-picryl- $DMANH^+$ , 4-nitro- $DMANH^+$  and 2-chloro- $DMANH^+$  the signs of the effects are opposite

for the carbons within the pairs C-1, C-8; C-2, C-7; C-3, C-6; and C-4, C-5. It is also interesting to notice that the average values of the isotope effects of these pairs (e.g.  $\Delta C-2(ND) + \Delta C-7(ND)$ ) are very similar to the isotope effects observed for  $DMANH^+$ . On the other hand for the carbons C-9 and C-10, which are on the symmetry axes of DMAN and therefore exposed to the same effect irrespective of the site of protonation,

Table 3

Secondary,  ${}^n\Delta\text{H}(\text{D})$  (in ppb) and primary deuterium isotope effects,  ${}^p\Delta({}^1\text{H}, {}^2\text{H})$  (in ppm) on  ${}^1\text{H}$  chemical shifts of  $\text{DMANH}^+$ s

	DMAN	2,7-Dichloro	4-Bromo	4-Picryl	4-Nitro <sup>a</sup>	2-Chloro <sup>b</sup>
${}^n\Delta\text{H-3}(\text{D})$	0	0	0	1.8	5.2	3.2
${}^n\Delta\text{H-5}(\text{D})$	0	0	−3.6	un. <sup>c</sup>	−3.8	−6.6
${}^n\Delta\text{H-7}(\text{D})$	0	0	0	1.4	−6.2	−18.2
${}^3\Delta\text{H}(\text{D})$ Me-1(11)	−0.0025	−0.001	0.003	0.006	0.016	0.028
${}^n\Delta\text{H}(\text{D})$ Me-8(12)			−0.005	−0.009	−0.019	−0.036
Difference	0	0	−0.008	−0.015	−0.035	−0.064
${}^p\Delta({}^1\text{H}, {}^2\text{H})$	0.728	–	–	0.756	0.757	0.662

<sup>a</sup>  ${}^n\Delta\text{H-2}(\text{D}) = 16.2$  ppb.<sup>b</sup>  ${}^n\Delta\text{H-4}(\text{D}) = 7.6$  ppb.<sup>c</sup> Assignment of isotope effect uncertain.

similar values are seen throughout the series. It can also be noticed that the average effects at C-1 and C-8 are positive contrary to the majority of isotope effects at the methyl carbons (Table 2) even though they have the same distance to the NH protons.

Plots of  ${}^n\Delta\text{C}(\text{ND})$  vs. the mole fractions derived from  ${}^3\text{J}(\text{CH}_3, \text{NH})$  are shown in Fig. 2a–d. The two pairs of isotope effects are defined by different symbols (see figure text). Similar mole fractions are obtained using one-bond  ${}^1\text{J}(\text{N}, \text{H})$  couplings (Table 1). A linear relationship is found for 4-Br-, 4-picryl-, 4-nitro- $\text{DMANH}^+$  and 2,7-dichloro. The data for 2-chloro- $\text{DMANH}^+$  fall outside the correlation lines.

#### 2.4. ${}^3\Delta\text{H}(\text{D})$

Deuterium isotope effects are very clearly seen on the methyl  ${}^1\text{H}$  resonances (Table 3). Both positive and negative values are observed. The value in  $\text{DMANH}^+$  itself is rather small,  $-0.0025$  ppm. The value is thus similar to that observed by Leyden and McCall for tertiary amines [65]. The difference in  ${}^3\Delta\text{H}(\text{D})$  between the two methyl groups of each compound,  $\Delta^3\Delta\text{H}(\text{D})$ , are plotted vs. mole fractions as seen in Fig. 3a. In Fig. 3b  $\Delta^3\Delta\text{H}(\text{D})$  is plotted vs. the difference in chemical shifts.

For the aromatic protons deuterium isotope effects are absent for the symmetrical compounds. The isotope effect observed at H-7 is seen to show a much more negative value for the 4-nitro and the 2-chloroderivatives (Table 3) in parallel to the isotope effects observed at the carbons (Table 2).

#### 2.5. Primary isotope effects

The primary isotope effect of  $\text{DMANH}^+$  is reported using  $\text{CD}_2\text{Cl}_2$  as reference. The literature value of 0.66 ppm [53] is hence slightly different from that reported in this paper in which  $\text{C}_6\text{D}_6$  is used as reference. The values found for  $\text{DMANH}^+$  (0.728 ppm), 4-picryl (0.756 ppm), 4-nitro (0.757 ppm) and 2-chloro (0.662 ppm) are similar except for the latter compound for which a slightly smaller value is observed.

#### 2.6. ${}^1\text{J}({}^{15}\text{N}, \text{H})$ and ${}^1\text{J}({}^{15}\text{N}, \text{D})$

One-bond nitrogen–proton couplings have been measured in solutions of the protio species as well as from solutions containing partially deuteriated species. Values are given in Table 1. Only a small variation in the sums of couplings of the two tautomers is found.

The magnitudes of  ${}^1\text{J}(\text{N}, \text{H})$  are comparable or smaller than values found in ammonium ions [47–49], methylammonium ions [66] and anilinium ions [67].

The  ${}^1\text{J}(\text{N}, \text{D})$  couplings can be measured from the partially deuteriated solutions. In the present compounds they always appear as well resolved 1:1:1 triplets with no signs of line broadening due to quadrupolar relaxation at room temperature.

The one-bond couplings can be used to estimate the ratio of the two tautomers. As the sums are always known, this is a very reliable method that does not rely on knowing the absolute value of the one-bond



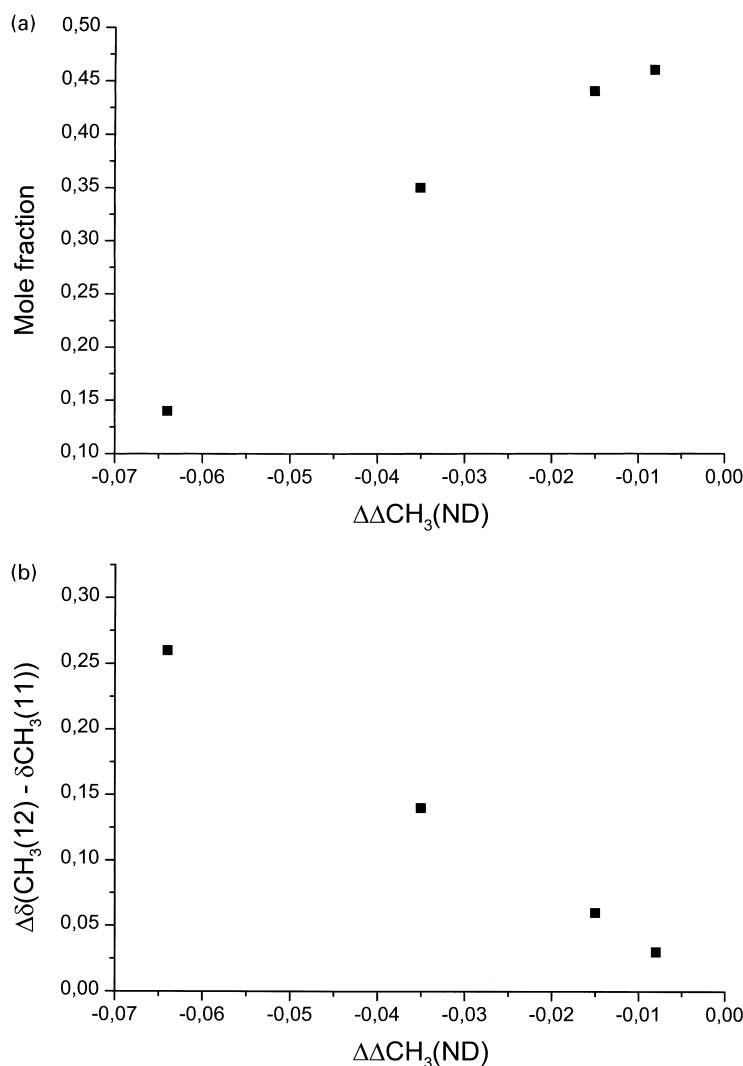


Fig. 3. Plots of differences in isotope effects of  $^1\text{H}$  chemical shifts of methyl groups,  $\Delta\Delta\text{CH}_3(\text{ND})$  vs. mole fraction,  $x_A$  or differences in chemical shifts. (a)  $\Delta\Delta\text{CH}_3(\text{ND})$  vs. mole fractions. (b)  $\Delta\Delta\text{CH}_3(\text{ND})$  vs. differences in  $^1\text{H}$  chemical shifts of methyl groups.

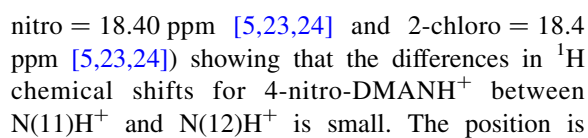
coupling constant,  $^1J(\text{N},\text{H})$ . The ratios and equilibrium constants are given in Table 1.

## 2.7. Chemical shifts

$^{13}\text{C}$  chemical shifts. The  $^{13}\text{C}$  chemical shifts corrected for substituent effects (Fig. 4) reflect the equilibrium constants. Extrapolating the data to  $x$  (the mole fraction) equal to 1 and zero we arrive at the chemical shift trends.  $\delta\text{C-7} > \delta\text{C-2}$  and  $\delta\text{C-3} > \delta\text{C-6}$ .

In the latter case based on  $\delta\text{C-3}$  being less than the average value found for  $\text{DMANH}^+$ . The fact that this cannot be done for all carbons just illustrates the small chemical shift differences between the carbons of the two tautomers.

$^1\text{H}$  chemical shifts. The difference in  $^1\text{H}$  chemical shifts of the  $\text{CH}_3$  group are good reporters of the position of the equilibrium. In both 4-nitro- $\text{DMANH}^+$  and 4-picryl- $\text{DMANH}^+$  the  $\Delta\delta^1\text{H}$  can be understood based on the position of the equilibrium.



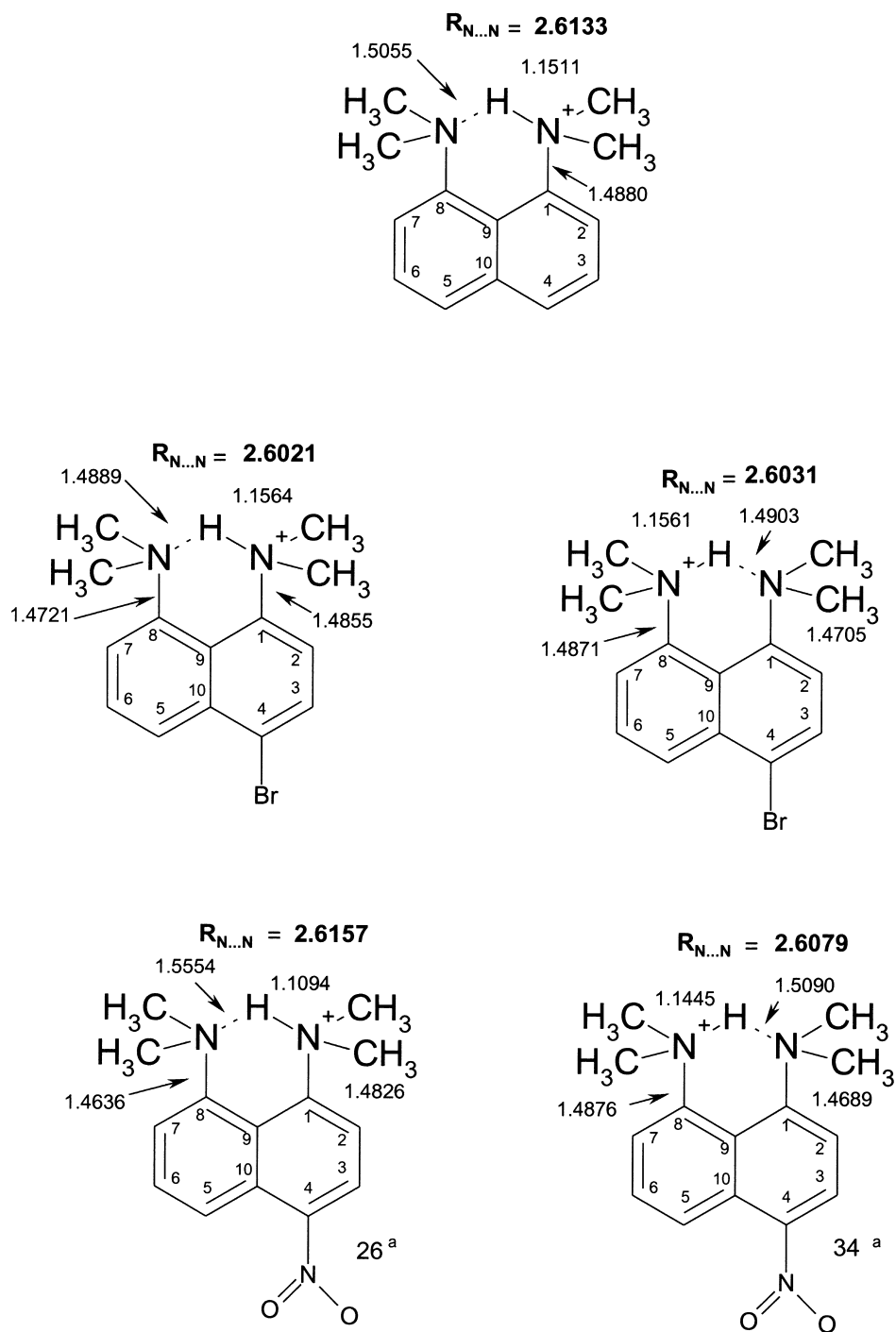
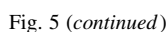


Fig. 5. Calculated structures using the BPW91/6-31G(d) approach (distances in Å).



### 2.8. Theoretical calculations

protonated species using BPW91/6-31(d) density functional theory (DFT) methods. The structures are shown in Fig. 5 and show numbers consistent with X-ray data [1–6,13]. The structures of the 4-picryl derivatives were not calculated because of the many atoms of this molecule. The X-ray structures show possible dependence on the type of counter ion [2]. For the X-ray structures, a mean  $R_{N...N}$  value of 2.590 Å [1,2] and a mean value of  $R_{N-H}$  of 1.08 Å were found. The general trend of the calculated structures is a  $R_{N...N}$  close to 2.60 Å but with a slight decreasing distance in the 2-chloro- and 2,7-dichloro derivatives presumably due to steric compression. This is followed by an increase in the NH bond lengths. This is also reflected in the NH chemical shift.

It is interesting to notice that for the calculations of 4-nitro-DMAN the nitro group is out of the plane by  $16^\circ$  in accord with the X-ray

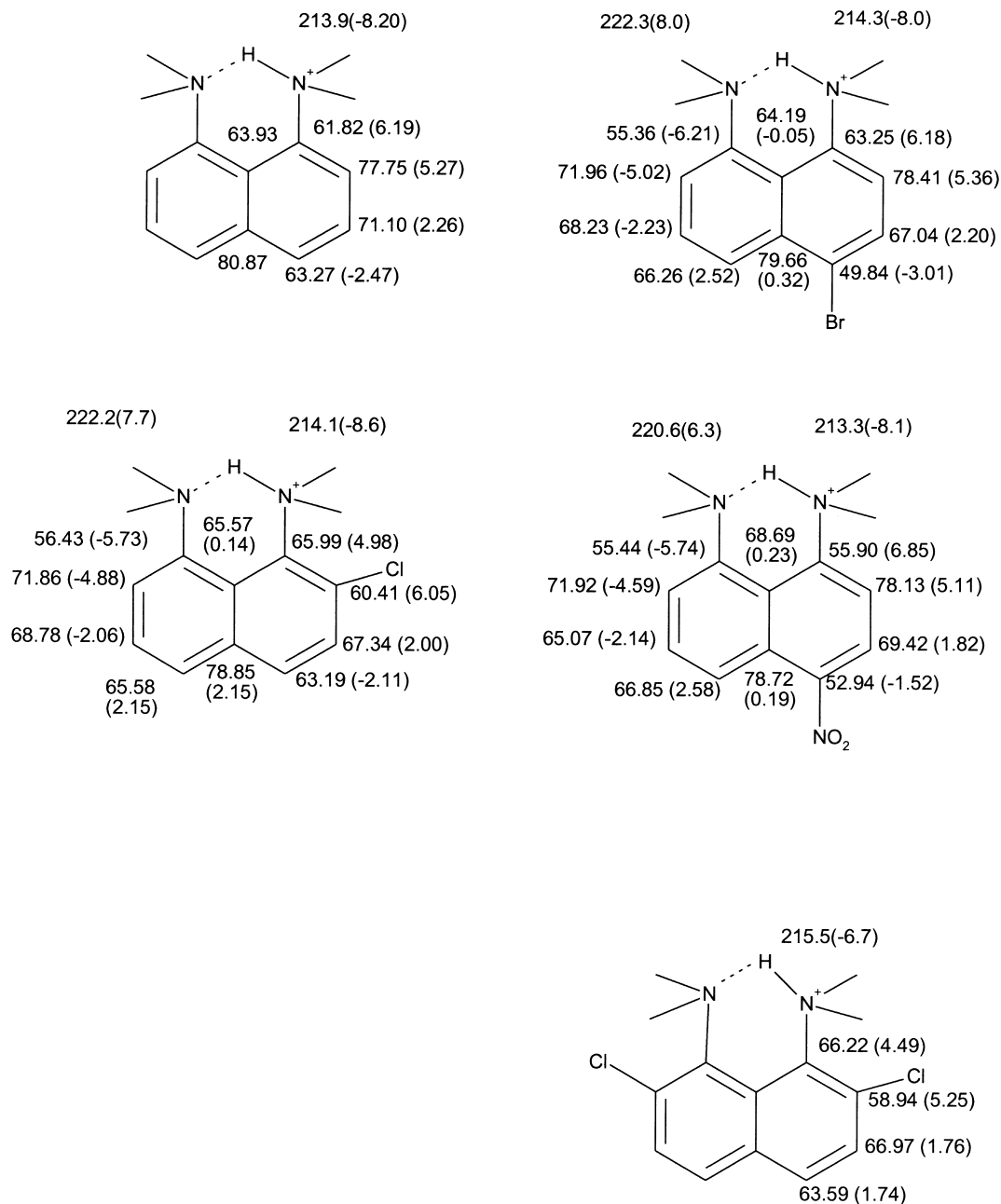


Fig. 6. Calculated nuclear shieldings (for a conversion from nuclear shieldings to chemical shifts see text) of aromatic carbons and the nitrogens of the shown tautomer and shielding differences between identical nuclei in tautomers A minus B.

structure (26°). For the 4-nitro-DMANH<sup>+</sup> the twist angle is 34° compared to the experimental X-ray finding of 26° [6].

It can be noticed that calculations of DMANH<sup>+</sup> at

the RHF level with 6-31G basis set gave a slightly shorter N–H bond of 1.05 Å and confirmed that the asymmetrical structure has the lowest energy [10]. Furthermore, the B3PW91 procedure leads to

oscillating structures with the nitro group being almost in the ring plane. This procedure was therefore replaced by the BPW91 one (see above).

**Chemical shifts.** The  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  nuclear shieldings are calculated for both DMAN, 4-bromo, 4-nitro-, 2-chloro- and 2,7-dichloro-DMAN and their protonated forms. A conversion from nuclear shieldings to chemical shifts is done plotting the calculated nuclear shielding vs. the observed chemical shifts leading to correlations for  $^{13}\text{C}$ :  $\delta\text{C}_{\text{obs}} = -1.062 \times \sigma\text{C}_{\text{calc}} + 202.49$ ,  $R^2 = 0.9914$ ; for  $^1\text{H}$ :  $\delta\text{H}_{\text{obs}} = -1.099 \times \sigma\text{H}_{\text{calc}} + 34.78$ ,  $R^2 = 0.9884$  and for  $^{15}\text{N}$ :  $\delta\text{N}_{\text{obs}} = -1.060 \times \sigma\text{N}_{\text{calc}} - 111.46$ ,  $R^2 = 0.9949$  (the latter fit included also the  $^{15}\text{N}$  data for nitro groups). Two outliers are found for the  $^{13}\text{C}$  data, that of C-4 of 4-bromo-DMAN and 4-bromo-DMANH $^+$ . These data are not included in the correlations.

Of particular interest is the calculation of chemical shift differences between nuclei in the two tautomers shown in Fig. 6. It should of course be considered that no effects of solvent and counter ions are included in the calculations. The differences in chemical shifts are important in understanding the equilibrium isotope effects (see later). It is also interesting to notice that these differences cannot be obtained from the solid state NMR measurements at ambient temperature because of fast averaging in the solid on the NMR time scale [9]. The differences in chemical shifts calculated for N-1 in the two tautomers have the opposite sign to that of C-1 (for N-8 and C-8 opposite sign are also calculated). This is very interesting as the isotope effects on chemical shifts depend strongly on these differences and show a behaviour in accord with these observations (see later).

The calculated change in shielding as a function of the N–H bond length,  $d\sigma(x)/dR_{\text{NH}}$ , values in which  $x$  is either  $^{15}\text{N}$ ,  $^{13}\text{C}$  or  $^1\text{H}$  show an interesting feature. The  $d\sigma(x)/dR_{\text{NH}}$  values for N-1 and N-8 are almost the same irrespective of the site of protonation  $\sim 30$  and  $\sim 33$  ppm/Å for protonation of N-1. Assuming a change in the bond length upon deuteration of 0.01 Å, a value of 0.30 ppm is predicted, very close to the experimental value. A change of 0.01 Å seems very plausible although probably on the low side (see below) comparing the length of the hydrogen bond with those of *o*-hydroxy acetophenones [54]. The calculated  $d\sigma\text{C-i}/dR_{\text{NH}}$  values for the carbons reflect the number of bonds between the nuclei in question

and the site of deuteration and the conjugation of the system, but are in general not very accurate.

The slopes of the  $^1\text{H}$  nuclear shieldings are calculated as 25–30 ppm/Å, leading to a too small primary isotope effect for DMANH + itself if using the change in the N–H bond length upon deuteration as 0.01 Å as done for ammonium ions [51]. However, the change in the bond length upon deuteration is probably larger judging from the rather long N–H bond.

### 3. Discussion

The protonated DMAN systems are supposed to be tautomeric [1,3]. The H $^+$  proton is bound rather strongly and do not exchange fast with non-protonated DMAN, as both resonances from DMAN and the protonated species can be observed in mixtures with less than one equivalent of acid added. Furthermore, neither addition of methanol or water broadens the NH resonance. As pointed out earlier [23]  $^1\text{J}(\text{N},\text{H})$  and  $^3\text{J}(\text{CH}_3,\text{NH})$  [24] are potentially useful parameters to determine the equilibrium constant. In the present study we are very much interested in establishing the position of the equilibrium in both the protio and the deuterio species in order to determine the change in the position of the equilibrium upon deuteration.

Measurement of  $^1\text{J}(\text{N},\text{H})$  and  $^1\text{J}(\text{N},\text{D})$  in DMANH $^+$  revealed that the ratio of the two couplings is close to 6.5 showing that no isotope effects on the coupling constants is found in line with previous findings in ammonia [68] and ammonium ions [47–49] and in line with the general finding that isotope effects on coupling constants are very small [69]. Furthermore, the sum of the two  $^1\text{J}(\text{N},\text{H})$  couplings is rather constant ( $61.9 \pm 1.1$  Hz, excluding 2,7-dichloro at 66.0 Hz) and do not change very much with solvent or temperature [21,63]. The large value of the 2,7-dichloro derivative is probably due to steric compression. As the ratio between the two  $^1\text{J}(\text{N},\text{H})$  couplings of a compound is insensitive to concentration and temperature it is even possible to compare data from different recordings as long as the solvent is the same.

The finding that the sums of the two one-bond couplings are very similar in all compounds supports

the idea of a simple two state tautomeric system as shown in Fig. 1.

Based on one-bond couplings, the equilibrium constant has been determined as seen in Table 1. A comparison of  $^1J(\text{N,H})$  and  $6.51 \times ^1J(\text{N,D})$  for 4-nitro-DMANH<sup>+</sup> (Table 1) shows clearly that the B/A ratio is increased upon deuteration. In other words the amount of the most abundant tautomer is increased upon deuteration. This is similar to findings in  $\beta$ -diketones [37],  $\beta$ -thioxoketones [35] and piroxicams [38].

### 3.1. Structural features

The N–H and the N $\cdots$ N bond lengths are of prime importance in understanding the intrinsic deuterium isotope effects, as the N–H bond length is proportional to the change in the N–H(D) bond length which is proportional to the isotope effect [54]. The N–H bond length is shown to vary very little upon deuteration from a solid state study [42]. The intrinsic isotope effect is hence expected to be small.

Variation in the heavy atom positions have been implied as an important factor in intermolecularly hydrogen bonded systems [40–43]. For the present system it is seen that  $R_{\text{N}\cdots\text{N}}$  varies as little as  $\pm 0.05$  Å for a large series of DMANH<sup>+</sup> derivatives [1–3] including the values for 4-nitro-DMANH<sup>+</sup> [6]. Based on this invariability deuteration most likely will have a negligible effect on the heavy atom positions and in this case the  $R_{\text{N}\cdots\text{N}}$  distance.

### 3.2. $^1\Delta^{15}\text{N(D)}$

One-bond deuterium isotope effects on  $^{15}\text{N}$  chemical shifts have been studied in some detail in partially deuterated ammonium ions [47–52] and inclusion complexes thereof [50]. Theoretical calculations showed that  $^1\Delta\text{N(D)}$  in ammonium ions depend on the orientation and the distance to the ligands ( $\text{H}_2\text{O}$  or  $\text{NH}_3$ ). Directional hydrogen bonds gave the smallest  $^1\Delta\text{N(D)}$ s, but also non-directional ligands have an effect [51]. These results may be applied to the proton sponges in which the N–H(D) bond is fixed in a non-directional manner and very close to the other nitrogen. The N $\cdots$ N distances are:  $R_{\text{N}\cdots\text{N}} \sim 2.58$  Å and  $R_{\text{N}\cdots\text{H}} \sim 1.50$  Å according to theoretical calculations. Therefore, the smallness of the intrinsic isotope

effects observed in DMANH<sup>+</sup> may be understood as an effect of the lone-pair on the protonated (deuteriated) nitrogen as just described for ammonium ions.

The magnitudes of  $^1\Delta\text{N(D)}$  isotope effects of ammonium ions show a dependence on counter ions [49,50]. The largest variation with concentration was found for the soft ion,  $\text{I}^-$ , and the smallest for hard ions like  $\text{ClO}_4^-$ ,  $\text{NO}_3^-$  and  $\text{CF}_3\text{COO}^-$ . For ammonium ions complexed inside cryptands no counter ion effects were seen [50]. In the present case no effect of changing from the hard ion,  $\text{CF}_3\text{COO}^-$  to the soft,  $\text{I}^-$ , was found indicating either that the counter ion is not getting very close to the positively charged nitrogen or that also for counter ions a directional dependence is found. The latter possibility is under investigation.

In principle three different scenarios can be envisaged to explain the observed deuterium isotope effects at chemical shifts. (i) Only intrinsic effects are present and these depend on the hydrogen bond strengths and on the mole fractions of the particular tautomers. (ii) The effects are also caused by changes in the heavy atom distance by deuteration as suggested by Limbach et al. [40–43]. (iii) The observed isotope effects are a combination of (i) and equilibrium isotope effects as suggested for a series of tautomeric systems [30,33,35,37–39]. The first solution is highly unlikely as data from ammonium ions show that the intrinsic one-bond deuterium isotope effect on  $^{15}\text{N}$  is positive [32,47–51], and from the theoretical calculations we know that the long range effect,  $^5\Delta\text{N(D)}$ , is also positive. This will not likely lead to negative values. Another possibility is that the  $^5\Delta\text{N(D)}$  (for technical reason this is labelled like this although the effect may be transmitted via the hydrogen bond) is negative as found in strongly hydrogen bonded systems, acid/pyridine complexes [41] and in Schiff bases [73]. Assuming only intrinsic effects these would be a weighted average of  $^5\Delta\text{N(D)}$  and that of  $^1\Delta\text{N(D)}$ . However, this is not the case as seen for the 2-chloro derivative. N-11 is having a larger effect than N-12 which is opposite to what can be obtained from averaging as N-11 is the least protonated nitrogen and therefore having an effect with most weight of the negative five bond effect.

The negative values therefore could better come from equilibrium contributions to the isotope effects,

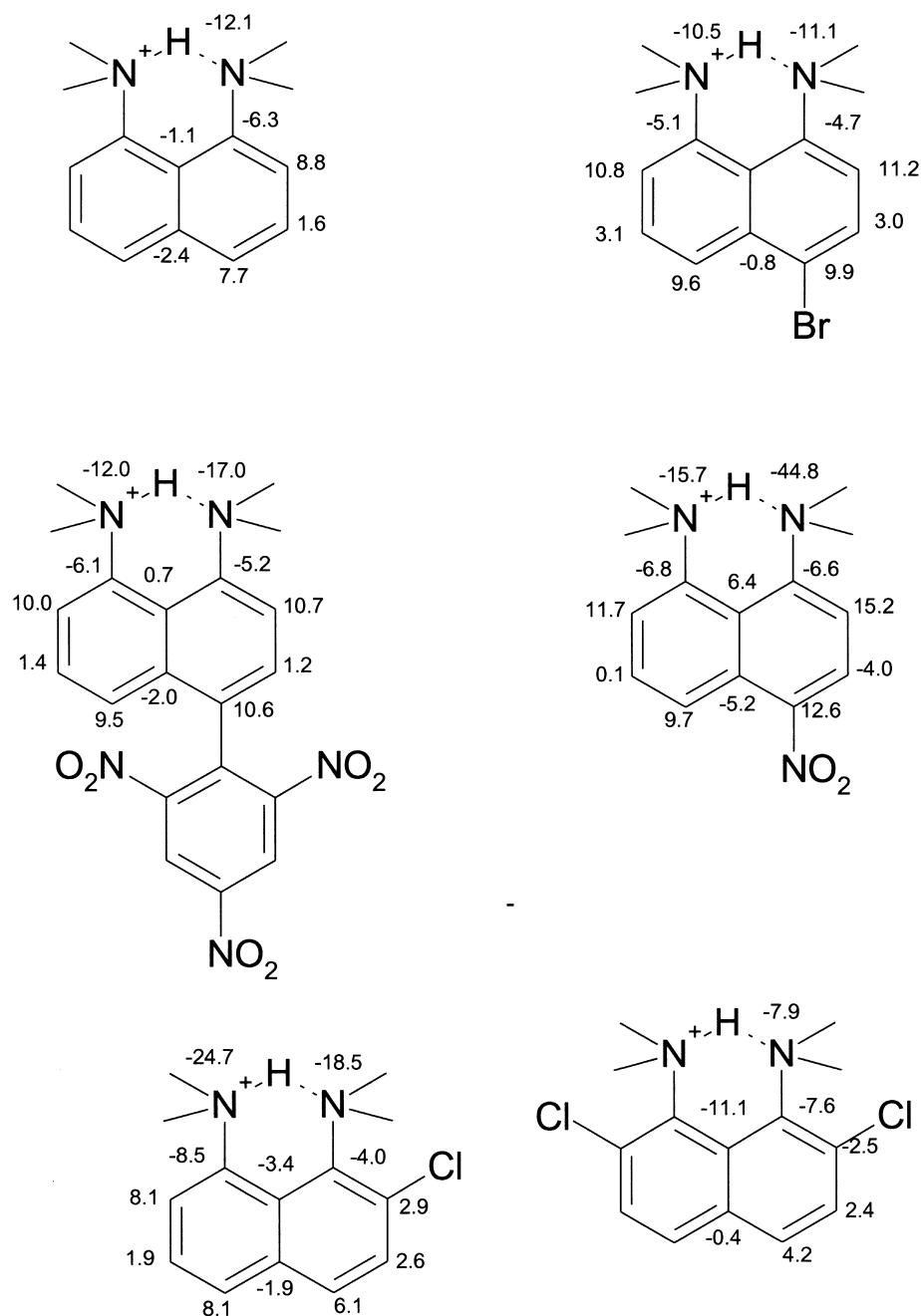


Fig. 7. Experimental titration shifts (defined as the difference between the charged and the non-charged species).

see below. In relation to (ii) the geometric effect on  $R_{N...N}$  upon deuteration is likely to be very small, because not even introduction of two chlorine substituents at positions 2 and 7 change the geometry

and the heavy atom distance very much (Fig. 5). If this contrary to expectation was not so, we would expect increasing effects in the series  $DMANH^+$ , 2-chloro- $DMANH^+$  and 2,7-dichloro- $DMANH^+$  as the  $R_{N...N}$



distance is decreased slightly and the potential barrier therefore is reduced. This clearly is not the case when comparing  $^3\Delta\text{H}(\text{ND})$  or  $^n\Delta\text{C}(\text{ND})$  deuterium isotope effects of the 2-chloro and the 2,7-dichloro- $\text{DMANH}^+$ . The best explanation is therefore (iii). In the averaged but not symmetrical systems like 4-bromo, 4-picryl-, 4-nitro- and 2-chloro- $\text{DMANH}^+$ , the isotope effects can be discussed in the framework of equilibrium isotope effects [35–37]. The large difference in the two one-bond coupling constants for the 4-nitro and similarly for the 2-chloro derivatives (Table 1) shows how easy it is to perturb the system. The equilibrium isotope effect depends on the change in the equilibrium constant upon deuteration (this has been demonstrated by the measurement of the one-bond  $^1\text{J}(\text{N},\text{H})$  and  $^1\text{J}(\text{N},\text{D})$  couplings and on the difference in the chemical shifts of the  $^{15}\text{N}$  nuclei in the two tautomers [37]. For 4-nitro- $\text{DMANH}^+$  the B-form is dominant. The calculated chemical shift for the  $\text{NH}^+$  nitrogen is at lower frequency than that of the non-charged nitrogens. By deuteration a shift towards the B-form will cause a high frequency contribution to the  $\text{N}_{12}$  chemical shift and therefore give rise to a negative total isotope effect in accordance with observation.

This can be seen from the following expressions, in which the total observed isotope effects can be written as a sum of the intrinsic and the equilibrium parts:

$$^1\Delta\text{N-11}(\text{D})_{\text{obs}} = x\Delta_{\text{int}} + \Delta x_{\text{D}}(\delta\text{N-11}_{\text{A}} - \delta\text{N-11}_{\text{B}}) \quad (1)$$

$$^1\Delta\text{N-12}(\text{D})_{\text{obs}} = (1 - x)\Delta_{\text{int}} + \Delta x_{\text{D}}(\delta\text{N-12}_{\text{B}} - \delta\text{N-12}_{\text{A}}) \quad (2)$$

$x$  is the mole fraction and  $\Delta x_{\text{D}}$  is the change in the mole fraction upon deuteration.

As indicated in the theoretical calculations, the chemical shift difference for N-11 between the A- and the B-forms are very similar to that of N-12 (Fig. 6). The sums of  $^1\Delta\text{N-11}(\text{D})_{\text{obs}} + ^1\Delta\text{N-12}(\text{D})_{\text{obs}}$  will give the intrinsic effects, as the equilibrium parts cancel each other as they have opposite signs [37]. This is to some extent found as  $\text{DMANH}^+$  itself gives a sum of 0.36 ppm (twice the measure number as this is an average), the 4-picryl-derivative gives 0.30 ppm, the 4-nitro derivative, 0.15 ppm and the 2-chloro-derivative gives 0.73 ppm. The increase in the latter case can to some extent be explained as the NH bond is longer

(Fig. 5) and hence is expected to give a larger intrinsic isotope effect [54].

It is also interesting to notice that the difference in  $^1\Delta\text{N}(\text{D})$  for the two nitrogens (which according to the equations above to a large extent depends on the equilibrium isotope effect contributions) increase (Table 1) with an increase in the equilibrium constant. Such a behaviour has previously been observed in  $\beta$ -diketones [37] and  $\beta$ -thioxoketones [35] and possibly in Mannich bases [70,71]. That equilibrium isotope effects are important in this system is also shown recently by the elegant use of isotopic perturbation of equilibrium using  $\text{DMANH}^+$ s deuteriated at the methyl groups [34].

### 3.3. $^n\Delta\text{C}(\text{ND})$

The deuterium isotope effects on  $^{13}\text{C}$  chemical shifts of  $\text{DMANH}^+$  are unusually small for a strongly hydrogen bonded system. As pointed out in the Section 2, the average values for substituted compounds are similar to those of  $\text{DMANH}^+$ . On the other hand, especially  $^2\Delta\text{C-1}(\text{ND})$  increases numerically in compounds with larger equilibrium constants. This is similar to observations for  $^1\text{N}(\text{D})$  and  $^3\Delta\text{H}(\text{D})$ . The equilibrium isotope effects found in the isotopic perturbation of equilibrium study [34] are smaller than those observed in this study in line with a smaller effect from a  $\text{CD}_3$  than an XD [36]. For the pairs of carbons, C-2, C-7, etc. (see previously) the signs of the isotope effects are opposite for C-2 and C-7 and the average value of the isotope effects are identical with those found in  $\text{DMANH}^+$  (and therefore small) again supporting the finding that we are dealing with isotope effects with an equilibrium isotope effects component and that the latter cancel each other when forming the sum for each pair [37] (see Equations 1 and 2). The finding of small and identical isotope effects at C-9 and C-10 for all compounds can be understood as follows. These two carbons are symmetrically oriented with respect to N-11 and N-12 and are expected to show very small chemical shift differences between the two tautomers (see Fig. 7) and hence to show no equilibrium isotope effect contributions.

From the plots of Fig. 2a–d it may also be seen that for mole fractions smaller than 0.25 the isotope effects levels off as demonstrated in a number of cases [35, 37,38].

From the ab initio calculations, both the intrinsic

isotope effects and the differences in chemical shifts of carbons of tautomers A and B are calculated for  $\text{DMANH}^+$ , 4-nitro- and 2-chloro- $\text{DMANH}^+$ . The intrinsic isotope effects are seen to be small and possibly because of this not calculated particularly well.

### 3.4. $^3\Delta H(D)$

The findings that these isotope effects differences show linear correlation with the mole fraction (Fig. 3a) and also with the chemical shift difference between the methyl groups (Fig. 3b) strongly support that these isotope effects are of equilibrium type.

### 3.5. Primary isotope effects

The almost uniform size of the primary isotope effect can be ascribed to the small difference in chemical shifts between  $\text{H-11}^+$  and  $\text{H-12}^+$  as judged from the theoretical calculations, but also from the invariance of the  $\text{H}^+$  chemical shifts for different compounds (see Section 2) in spite of the variation in the equilibrium constant for the various compounds (see Table 1). The primary isotope effects are therefore primarily determined by the intrinsic contribution and are indicative of a rather strong hydrogen bond of the two-bond potential well type [52,53].

### 3.6. $^1J(^{15}\text{N},\text{H})$

The smallness of these couplings in  $\text{DMANH}^+$  is clearly interesting. The one-bond coupling for ammonium ions is close to 73 Hz [47–49], whereas that of ammonia is only 61.8 Hz [68]. If we compare  $^1J(^{15}\text{N},\text{H})$  of the latter with those of methylammonium ion [66] and the anilinium ion [67] we find an increase of 3.2 and 1.7 Hz, respectively. Naively, considering  $\text{DMANH}^+$  as a dimethylnaphthylammonium ion we would predict an increase of  $2 \times 3.2 + 1.7 = 8.1$  Hz, resulting in a  $^1J(\text{N},\text{H})$  of 81.4 Hz, which is much larger than the  $\sim 62$  Hz found.

As  $^1J(^{15}\text{N},\text{H})$  is rather insensitive to counter ions and to the presence of water we assume that the small value can be attributed to five factors, (i) the rather long N–H bond, (ii) the presence of the lone-pair at the other nitrogen ( $^1J(\text{N},\text{H})$  coupling constants of

ammonium ions were found to be slightly smaller in strongly complexed cases [50]), (iii) according to Wasylishen and Schaefer [72]  $^1J(\text{N},\text{H})$  decreases with decreasing C–N–H angle, (iv) a negative through bond coupling, and (v) strong delocalisation of the positive charge.

Some of these factors may be estimated by a comparison of data of  $\text{DMANH}^+$  and the corresponding 2,7-dichloro derivative.  $^1J(^{15}\text{N},\text{H})$  is larger in the latter and so is the  $R_{\text{N}\cdots\text{N}}$  distance. However, in similar systems  $^1J(^{15}\text{N},\text{H})$  is supposed to decrease with increasing N–H distance [41]. (iii) Regarding the C–N–H angle we can estimate this angle to  $\sim 100^\circ$ . Again the angles of  $\text{DMANH}^+$  and the dichloro derivatives are very similar, but coupling constants are different so this is probably not the cause (ii) could clearly contribute but (iv) couplings across hydrogen bonds have been reported for Schiff bases [75]. In that case the coupling is rather small, 1.65 Hz and the sign not determined. The sign can be assumed to be negative in parallel to observations in  $\text{HF-F}^-$  systems [74, 76]. The magnitude is likely to depend on the  $R_{\text{N}\cdots\text{N}}$  distance and hence being larger in  $\text{DMANH}^+$ , but not large enough to explain the large difference between observed and predicted coupling constants and (v) seems to be the controlling factor making the nitrogen more ammonia like and therefore leading to a smaller coupling constant.

### 3.7. $^{13}\text{C}$ chemical shifts

A comparison of substituent corrected chemical shifts as given in Fig. 4 reveals that the chemical shift differences within each pair are very similar except for possibly C-1, C-8. This confirms the finding that the equilibrium contributions to  $^n\Delta\text{C}(\text{ND})$  are very small. The set of chemical shift differences between pairs of carbons arrived at for C-2, C-7 and C-3, C-6 are similar to those calculated.

## 4. Conclusions

The proton sponges represent an ideal equilibrium system for investigation of primary and secondary isotope effects on chemical shifts in a non-resonance assisted system. This system can be considered similar to an intermolecular hydrogen bonded system,

but with a fixed distance between donor and acceptor. The isotope effects of this low barrier system can be described accurately by a simple two-stage equilibrium model. In support of an equilibrium model is the finding that the isotope effects observed at C-2, C-7, C-3, C-6, C-4 and C-5 are proportional to the mole fractions (Fig. 2a–d), that the three-bond isotope effects,  $^3\Delta\text{CH}_3(\text{ND})$  show the same trend (Fig. 3a) and that  $^1\Delta\text{N}(\text{D})$  isotope effects despite the intrinsic contribution to the isotope effect also show such a trend. Additionally, in favour of an equilibrium is the finding that the isotope effects for large mole fractions start levelling off as demonstrated in a number of cases [35,37,38].

The height of the barrier is still a matter of debate. Llamas-Saiz et al. [1] suggest a very low barrier based on model calculations and recently Grech et al. [14] have suggested something similar based on an X-ray structure. An interesting challenge is to see if the reported trends will also hold for systems with even lower barriers. Equilibrium positions can be determined. Deuteration is shown to shift the equilibrium in the direction of the most abundant tautomer. The isotope effects are also used to gauge the influence of counter ions on the charged centre.

## 5. Experimental

### 5.1. Compounds

The DMAN-derivatives were prepared according to previously published procedures [6,62,77,78].

### 5.2. NMR

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  NMR spectra were recorded on a Varian Inova 600 MHz instrument or a Bruker DRX 500 Avance instrument. Concentrations typically 0.1–0.5 M (saturated solutions) at ambient temperature.  $^{13}\text{C}$  NMR spectra were recorded with a digital resolution of 0.55 Hz/point and  $^{15}\text{N}$  NMR spectra with a digital resolution of 0.25 Hz/point. One-bond NH couplings were measured using the INEPT technique as described previously [23].

Isotope effects were measured in one-tube experiments. Several samples of different degrees of

deuteration were used in case of doubt about signs of isotope effects.

Deuteration was achieved by addition of  $\text{CD}_3\text{OD}$ . Solutions were prepared using either the salts or by addition of an equivalent amount of the acid. Addition of water was tested as well variation of the temperature.

### 5.3. Calculations

The molecular geometries were optimised using the GAUSSIAN96 suite of programs [79] and BPW91 DFT (Beckes exchange [80] and Perdew–Wang correlation term [81]), and a mix of the built in Gaussian type basis sets. The 6-31G(d) (5D) basis set was used. No symmetry constraints were used in the geometry optimisations except for 4-nitro-DMANH<sup>+</sup>. During many iterations, the structure oscillated around an almost flat structure without reaching convergence. A symmetry plane through aromatic rings and the three nitrogens were imposed to reach convergence. The resulting geometries with some relevant bond lengths and angles are shown in Fig. 5. Nuclear shieldings are calculated using the GIAO approach [82].

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