Symmetry of N−H−N Hydrogen Bonds in 1,8-Bis(dimethylamino)naphthalene·H^+ and 2,7-Dimethoxy-1,8-bis(dimethylamino)naphthalene·H^+

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Abstract: In solution, are the hydrogen bonds in monoprotonated *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamines single- or double-well? To answer this question, isotopic perturbation of equilibrium is applied to a mixture of -d_0, -d_3, -d_6, -d_9, and -d_{12} isotopologs. The *N*-methyls of the 2,7-dimethoxy analogue show intrinsic isotope shifts from the geminal CD_3 and from only one distant CD_3, an unusual stereochemical effect transmitted across the hydrogen bond. The ^{13}C NMR splittings and intensities at the various ring carbons of both ions are consistent with perturbation isotope shifts, intrinsic shifts, or a combination of both. The perturbation shifts mean that the protons reside in a double-minimum potential and that each ion is a pair of rapidly interconverting tautomers. The significance of this result for the role of low-barrier hydrogen bonds in enzyme-catalyzed reactions is discussed.

Introduction

Hydrogen bonds are a key feature of molecular structure and the subject of a vast number of theoretical and experimental studies.[1] Hydrogen bonding is thought to arise largely from electrostatic attractions. In the usual hydrogen bonds the hydrogen resides in a double-well potential, but in a symmetric one it resides in a single-well potential (Figure 1). These latter hydrogen bonds seem to have extra stabilization, perhaps arising from covalent character or from a maximum resonance energy when the two contributing forms are of equal or nearly equal energy.[2] Indeed, symmetric O−H−O hydrogen bonds seem to be stronger than asymmetric ones, and they require an unusually short O−O distance of ≤2.5 Å.[3] These have been referred to as short, strong hydrogen bonds or as low-barrier hydrogen bonds (LBHBs) or as centered or symmetric hydrogen bonds, depending on the observational criterion. An excellent review is available.[4]

Actually there is a continuum of hydrogen-bond strengths, from weaker ones to stronger ones that have a low barrier to very strong ones, where the barrier has disappeared. In this study we do not address the strength, but only the symmetry, as a yes-or-no question. The question is whether some unusually strong hydrogen bonds might derive their strength from their symmetry. Also, it should be recognized that, according to one classification,[3] the intermediate hydrogen bonds, where the zero-point energy of H is above the barrier but that of D is below, will appear symmetric by our criterion.

Recently LBHBs have been proposed to play a stabilizing role in enzymatic catalysis.[5] An extra hydrogen-bond strength of as much as 10−20 kcal/mol can lower the activation barrier for the formation of high-energy intermediates and transition states. Yet various estimates of hydrogen-bond strengths in solution are considerably lower.[6] Consequently, this proposal has generated controversy.[7] Even though there are some enzymic reactions where LBHBs are not required,[8] they may be involved in others. An impartial review is available.[9]

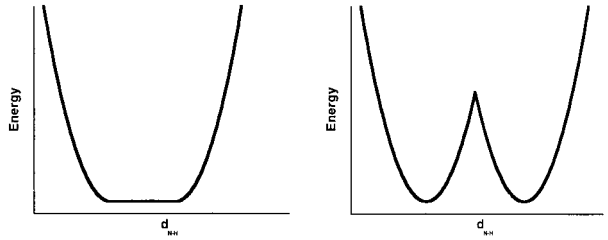

Figure 1. Single-well and double-well potentials for H motion in an NHN hydrogen bond.

The N−H−N hydrogen bonds of protonated 1,8-bis(dimethylamino)naphthalene (**1**) and 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene (**2**) are paradigmatic. These molecules belong to a class of compounds known as Proton-Sponge

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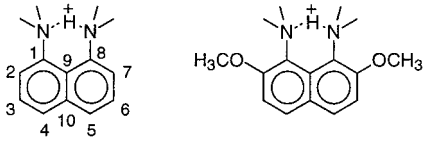

1·H⁺ **2·H⁺**

because of their strong basicity.[10] Relative to *N*,*N*-dimethylaniline their basicities are enhanced by 7.5 and 11.5 p*K* units, respectively, an enhancement that has been attributed to a strengthening of the hydrogen bond by 10−16 kcal/mol.

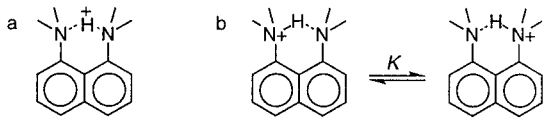

Figure 2. Symmetric (a) and asymmetric (b) hydrogen bonds of protonated bis(dimethylamino)naphthalene.

Why are these hydrogen bonds so strong? Is it because they are LBHBs where the barrier is so low that the hydrogen bonds have become symmetric? Do they exist as a single structure (Figure 2a) or as a pair of interconverting tautomers (Figure 2b)? These are certainly good candidates for symmetric hydrogen bonds, according to a variety of criteria: The NH chemical shift is far downfield, at δ 18.46,[11] a feature that is considered the most unambiguous for characterizing LBHBs,[12] and comparable to the δ 18 seen in chymotrypsin and trypsin.[13] Identical amino groups guarantee equal basicity, a necessary condition for equal sharing of the proton.[3] The substitution pattern forces the nitrogens into proximity, and a short N−N distance favors a single-well potential. *N*-Methylation avoids NH hydrogen bonds to solvent and helps shield the nitrogens from solvent and counterion.

Most evidence indicates that the N−H−N hydrogen bonds of **1·H⁺** are asymmetric. According to a Hartree−Fock 6/31G calculation, the structure with an asymmetric hydrogen bond is ~5 kcal/mol lower in energy than the symmetric,[14] but electron correlation reverses this order, and both higher-order electron correlation and solvation reverse it again.[15] X-ray studies have been inconclusive. According to several reviews and compilations that have addressed this question, there are both asymmetric structures and symmetric ones, often with the proton on a two-fold axis.[16] In recent years the majority of structures have been found to be asymmetric,[17] but others appear to be symmetric.[18] The hydrogen bond is asymmetric according to primary isotope shifts,[11] dipolar $^{15}N-^{2}H$ couplings,[19] ESCA ionization potentials,[20] and neutron diffraction.[21] Much less information is available on the symmetry of **2·H⁺**, where the methoxy groups markedly increase the basicity. Thus, this may be symmetric even though **1·H⁺** is often found to be asymmetric.

Our interest is in the structure of hydrogen bonds. Previous studies of dicarboxylate monoanions and of malonaldehyde showed that their O−H−O hydrogen bonds are asymmetric in solution,[22] even though the former class includes prime examples that are symmetric in crystals. It was suggested that the disorder of solvation or of counterion association induces the asymmetry. Regardless of the energetic implications for enzyme catalysis, the symmetry of hydrogen bonds is a fundamental question about molecular structure.

Methodology of Isotope Shifts

Isotopic perturbation of equilibrium is a powerful and widely applicable NMR technique for distinguishing a single static structure from a pair of tautomers.[23] It succeeds even if equilibration causes signals from the individual structures to coalesce. It relies on measuring the isotope shift $^{n}\Delta_{obs}$, the difference between ^{13}C chemical shifts of molecules with and without deuterium (eq 1).[24] This includes an intrinsic contribution $^{n}\Delta_{o}$, which is usually <0 (upfield) and falls off rapidly with *n*, the number of bonds between the reporter carbon and the deuterium.

$$^{n}\Delta_{obs} = \delta_{C(D)} - \delta_{C(H)} \quad (1)$$

If the hydrogen bond in a species such as **1·H⁺** is asymmetric, and if an *N*-CH_3 is replaced by an *N*-CD_3, then there is an additional contribution to Δ_{obs}. Alpha deuteration perturbs the tautomeric equilibrium (Figure 2b) because it increases amine basicity.[25] As a result, the time-averaged ^{13}C chemical shift is displaced. This is seen as a perturbation isotope shift Δ_e given by eq 2, where $D = \delta_{BH^+} - \delta_B$, the chemical-shift difference between exchange-related carbons proximal and distal to the

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Table 1. Estimated (eq 2) Perturbation Isotope Shifts for Carbons Proximal to a CD_3

	δ_B (ppm)	δ_{BH+} (ppm)	Δ_e^{est} (ppb)
N-CH_3	40.55	48.0	185
ipso	150.6	143.4	−180
ortho	112.6	121.4	219
meta	129.0	131.6	64
para	116.6	131.3	368

protonated nitrogen in a static tautomer.[22,23]

$$^{n}\Delta_e = \frac{K-1}{2(K+1)} D \qquad (2)$$

This perturbation shift can be estimated. The equilibrium constant K is modeled by the ratio of acidity constants for *N*,*N*-dimethylanilinium ion and its mono-CD_3 isotopolog ($K_a^H/K_a^D = 1.105$).[26] The paired chemical shifts δ_B and δ_{BH^+} in a static tautomer are modeled by the various carbons of *N*,*N*-dimethylaniline and of its conjugate acid.[27] Table 1 lists these chemical shifts and the estimated perturbation shift for each carbon proximal to CD_3. The perturbation shift for the corresponding distal carbon is of equal magnitude but opposite sign.

The synthesis of a single isotopolog of **1** or **2** presents a severe challenge, although there is precedent for asymmetric substitution patterns.[28] Fortunately, the synthesis of a statistical mixture of all of the isotopologs is feasible. Besides, the mixture provides multiple peaks for comparisons.

The number of NMR signals in that mixture and their relative intensities, depending on the deuterium content, can be calculated. In a 50% labeled mixture the distribution is 6.25% d_0 or d_{12}, 25% d_3 or d_9, 12.5% *N*,*N*-d_6, and 25% *N*,*N*′-d_6. The bridgeheads C9 and C10 can experience only an intrinsic shift, which depends on the total number of CD_3 groups. A quintet results, with d_0 at one extremity and d_{12} at the other.

The splittings for the nonbridgehead aromatic carbons C1−C8 depend on whether the isotope shifts are due to perturbation of an equilibrium or are intrinsic. If the latter, each carbon appears as a triplet of triplets. The larger splitting is the result of a 1:2:1 statistical mixture of non-, mono-, and bis-CD_3 groups on the proximal nitrogen. The smaller splitting is from distal CD_3. If these shifts have the same sign, then the d_0 and d_{12} signals are again at the extremities.

In contrast, a quintet results if the isotope shifts are due solely to perturbation of an equilibrium. Isotopologs with the same number of CD_3 groups on each nitrogen (d_0, d_{12}, and *N*,*N*′-d_6) experience no perturbation. They appear at the center of the quintet. The d_3 and d_9 isotopologs experience a perturbation due to one CD_3. One signal of each is shifted upfield and the other downfield to an equal extent, producing two signals flanking the central one. The *N*,*N*-d_6 isotopolog is shifted doubly, and its signals appear at the extremities of the quintet. With 50% labeling the relative intensities are 1:4:6:4:1.

A more complicated situation arises if there are both intrinsic and perturbation isotope shifts. Nine peaks appear, with separations and pattern of intensities that depend on both isotope shifts. Thus the pattern—triplets of triplets versus quintet or more complicated—may distinguish whether there are perturbation shifts.

Quintets due to perturbation shifts can be further distinguished from those due to intrinsic shifts by adding unlabeled material. In a quintet caused by perturbation isotope shifts, the central peak will be enhanced, whereas in a quintet caused by fortuitously equal intrinsic shifts, a peak at the extremity will be enhanced. Moreover, if there is any intrinsic shift, the enhanced peak reveals its sign. We now report that both **1**·H^+ and **2**·H^+ unambiguously show perturbation isotope shifts at several carbons, that each of these is a mixture of two tautomers, and that their hydrogen bonds are asymmetric.

Experimental Section

Materials. 1,8-Bis(dimethylamino)naphthalene was prepared from 1,8-diaminonaphthalene and dimethyl sulfate with NaH,[29] bp 95−97°/0.4 Torr. The free base could be obtained by extraction from aqueous NaOH and precipitated and recrystallized as the thiocyanate (**1·HSCN**), mp 204−208 °C, lit.[28a] 220−224 °C. ^{1}H and ^{13}C NMR spectra agree with published spectra.[30] 2,7-Dimethoxy-1,8-dinitronaphthalene was prepared from 2,7-dimethoxynaphthalene and nitric/sulfuric acid,[31] mp 235−245 °C (lit. 227−230). ^{1}H NMR (DMSO-d_6) δ 4.04 (s, 6H), 7.69 (d, J = 9.5 Hz, 2H), 8.36 (d, J = 9.5 Hz, 2H), ^{13}C NMR (DMSO-d_6) δ 57.6, 113.0, 126.3, 134.5, 160.1. This was reduced to 2,7-dimethoxy-1,8-diaminonaphthalene·HCl with $SnCl_2$,[32] dec 165−170 °C (lit. 170 °C). ^{1}H NMR (D_2O) δ 4.02 (s, 6H), 7.32 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), ^{13}C NMR (D_2O) δ 56.5, 111.5, 128.7, 152.3. This was methylated to 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene·HBF_4 (**2·HBF$_4$**) with dimethyl sulfate and NaH, chromatographed, precipitated with HBF_4, and recrystallized,[32] mp 233−237 °C (lit. 227−230 °C). ^{1}H NMR (DMSO-d_6) δ 3.18 (d, J = 2.5 Hz, 12H), 4.05 (s, 6H), 7.53 (d, J = 9 Hz, 2H), 8.06 (d, J = 9 Hz, 2H), ^{13}C NMR (DMSO-d_6) δ 42.4, 56.7, 113.4, 122.1, 124.5, 126.0, 130.9, 155.1. This could be converted to 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene·$HBPh_4$ (**2·HBPh$_4$**) by precipitation with sodium tetraphenylborate, yield 83%. ^{1}H NMR (DMSO-d_6) δ 3.16 (d, J = 2.5 Hz, 12H), 4.04 (s, 6H), 6.78 (t, J = 7.0 Hz, 4H), 6.92 (t, J = 7.3 Hz, 8H), 7.18 (m, 8H), 7.51 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), ^{13}C NMR (DMSO-d_6) δ 42.4, 56.7, 113.3, 121.6, 122.1, 124.5, 125.4 (q, J_{CB} = 2.8 Hz), 126.0, 130.9, 135.6, 155.1, 163.5 (q, J_{CB} = 49.1 Hz). The statistical mixture of isotopologs of **1** or **2** was synthesized using a 1:1 mixture of dimethyl sulfate-d_6 and -d_0 in the methylation step, analogous to the preparation of **1**-d_{12}.[33] Further details are available.[34]

NMR Spectroscopy. Spectra were recorded on a Varian Unity 500 spectrometer operating at a ^{13}C frequency of 125 MHz and a ^{1}H frequency of 500 MHz. For assignment of signals to isotopologs, approximately 20% w/w d_0 material was added to the 50% CD_3 mixture.

Results

^{13}C Signal Assignments. All of the NMR signals for **1** and **1**·H^+ have been assigned.[30] The two bridgehead signals of **2**·H^+ were assigned as those that were approximately half the intensity of the other signals in a ^{1}H-decoupled spectrum acquired with a 5-s delay. Of these C10 was assigned by its large $^3J_{CH}$ of 8.4 Hz and a smaller $^2J_{CH}$ of 1.9 Hz in a ^{1}H-coupled spectrum. The two pairs of CH carbons were distinguished from the others by their large $^1J_{CH}$'s and from each other by an additional $^3J_{CH}$ of 4.5 Hz for C4,5. The assignments of C1 and C2 were made by analogy to *N*,*N*-dimethylaniline (δ = 151 ppm) and anisole (δ = 160 ppm).[35] A summary of these results and assignments is given in the Supporting Information.

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Table 2. ^{13}C NMR Data for **1** in $CDCl_3$

carbon	δ (ppm)	multiplicity	Δ_0 (ppb)
N-CH_3	44.4	d	−110
1,8	151.3	brs	<5
2,7	113.5	t,t	−74, −15
3,6	125.5	s	<5
4,5	122.3	t	−52
9	121.2	qn	18
10	137.9	s	<5

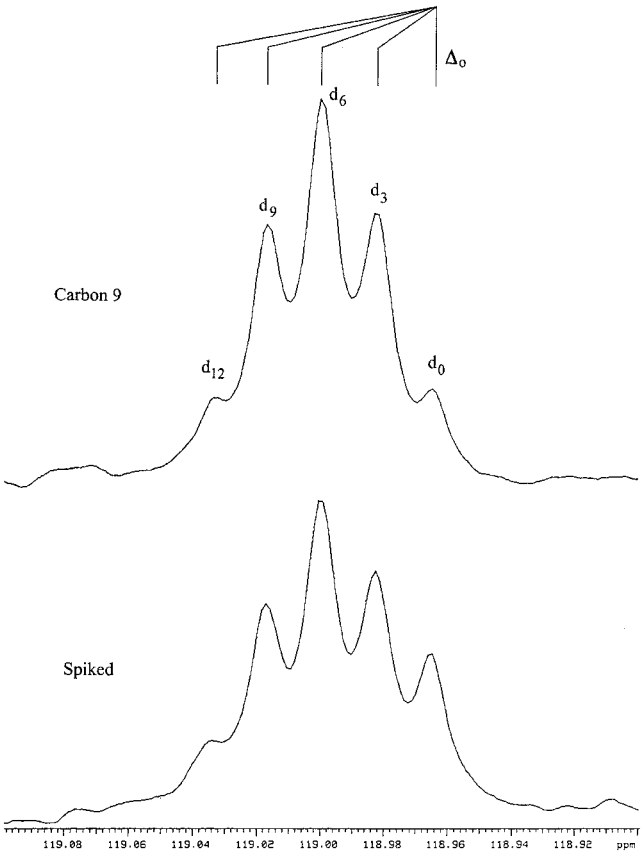

Figure 3. C9 region of ^{13}C NMR spectrum of **1·HSCN** in DMSO-d_6; below with added d_0.

Free Base Bis(dimethylamino)naphthalene. All isotope shifts are intrinsic, since addition of d_0 increases an extremity peak. The signal of C2,7 appears as a triplet of triplets, owing to a $^4\Delta_0$ of −74 ppb and a $^6\Delta_0$ of −15 ppb. The signal of C9 appears as a quintet, owing to a single $^4\Delta_0$ of +18 ppb. The signal of C4,5 appears as a triplet due to only one $^6\Delta_0$ of −52 ppb. These data are summarized in Table 2.

1,8-Bis(dimethylamino)naphthalene·H$^+$. Figure 3 shows the signal of C9 in **1·HSCN**; it is a 1:4:6:4:1 quintet, with d_0 upfield. The enhancement of an extremity peak indicates that the splitting pattern is the result of purely intrinsic isotope shifts, as required for bridgehead carbons. However, the enhancement of the upfield peak means that $^4\Delta_0 > 0$. Figure 4 shows the signal due to C2,7; it, too, is a 1:4:6:4:1 quintet, but with d_0 in the center. This is an especially clear demonstration of a perturbation shift $^4\Delta_e$. Figure 5 shows the signal of C1,8; it is a nine-line pattern, with d_0 as the fourth line. This corresponds to a combination of a larger $^3\Delta_e$ and a smaller $^3\Delta_0$, which splits d_3 from d_9 and d_0 from N,N'-d_6 from d_{12}. Each upfield signal is broadened relative to its corresponding downfield signal. This is due to an unresolved $^3J_{CD}$ that broadens the signal proximal to a CD_3. Thus, all C1,8 signals can be assigned, as indicated in Figure 5. Moreover, these assignments mean that the perturbation shift $^3\Delta_e$ must be negative. The nine-line pattern of C4,5 is similar, with both a $^6\Delta_e$ and a $^6\Delta_0$, but no $^6J_{CD}$ to guide assignment of the sign of the former.

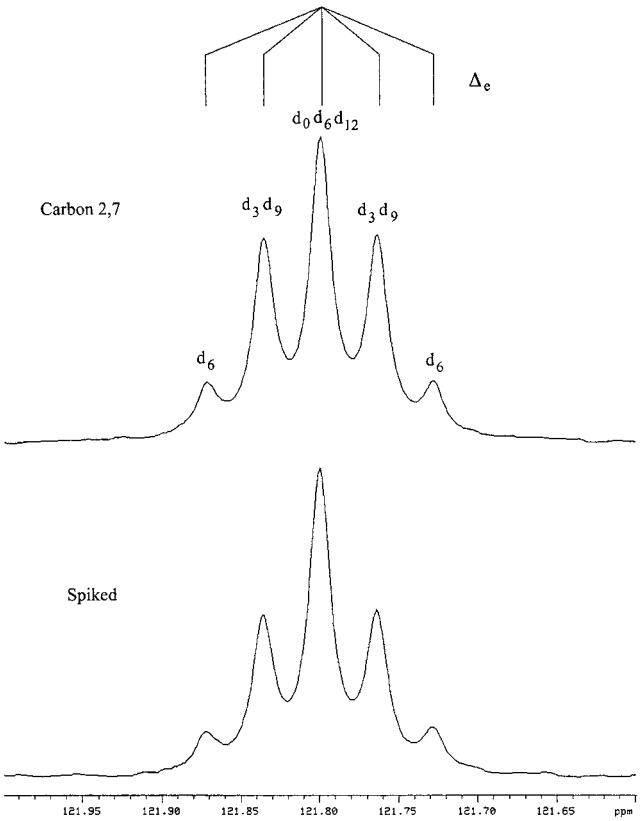

Figure 4. C2,7 region of ^{13}C NMR spectrum of **1·HSCN** in DMSO-d_6; below with added d_0.

The ^{13}C NMR chemical shifts, multiplicities, and isotope shifts for each carbon of **1·HSCN** in DMSO-d_6 are listed in Table 3. Intrinsic isotope shifts Δ_0 range from −78 to +18 ppb. The magnitudes of the perturbation shift Δ_e range up to 120 ppb. Except for the special case of C1,8, with its $^3J_{CD}$, the sign of the perturbation shift cannot be determined experimentally. Therefore, two possible values for the other carbons are included in Table 4. According to the estimates in Table 1, Δ_e is expected to be positive at those carbons. Therefore the less likely possibility of a negative shift is indicated in parentheses. The data for **1·HSCN** in methanol-d_4 and $CDCl_3$ are presented in the Supporting Information. The only difference is that C4,5 is a quintet, without detectable $^6\Delta_0$, and the isotope shifts of the C1,8 multiplet could not be resolved.

2,7-Dimethoxy-1,8-bis(dimethylamino)naphthalene·H$^+$. Figure 6 shows that the *N*-methyl groups of **2·**HBF_4 appear as a doublet of doublets. The multiplicity of C1,8 and its isotope shifts could not be determined because of poor resolution. The signal of C9 is a quintet with a single intrinsic shift $^4\Delta_0$ of +15 ppb. The quintet for C2,7 is due to a $^4\Delta_e$. The isotope shift at C3,6 is smaller than in **1·H**$^+$ and results only in signal broadening. Signals of C4,5 again exhibit both $^6\Delta_e$ and a $^6\Delta_0$ in DMSO-d_6 but only $^6\Delta_e$ in methanol-d_4 and $CDCl_3$. Table 4 lists the chemical shifts, multiplicities, and perturbation and intrinsic shifts of **2·**HBF_4 in DMSO-d_6. Data for **2·**HBF_4 in methanol-d_4 and $CDCl_3$ and for **2·**$HBPh_4$ in DMSO-d_6, which are qualitatively similar to those from **2·**HBF_4, are presented in the Supporting Information.

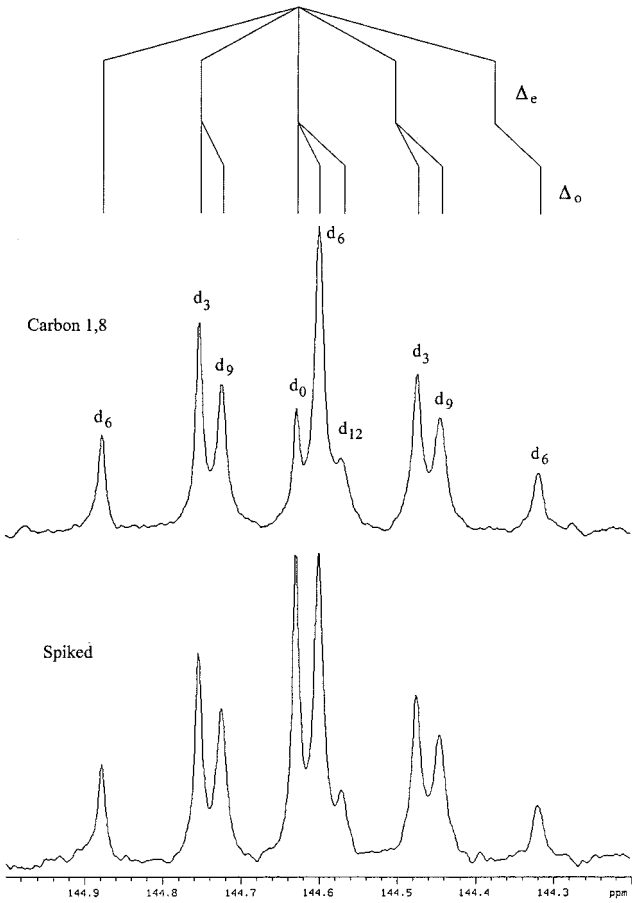

Figure 5. C1,8 region of ^{13}C NMR spectrum of **1·HSCN** in DMSO-d_6; below with added d_0.

Table 3. ^{13}C NMR Chemical Shifts and Isotope Shifts of **1·HSCN** in DMSO-d_6

carbon	δ (ppm)	multiplicity	Δ_o (ppb)	Δ_e (ppb)
1,8	144.6	m	−29	−120
2,7	121.8	qn	|<5|	35 (−35)[a]
3,6	127.0	qn	|<5|	18 (−18)[a]
4,5	128.9	m	−13	32 (−45)[a]
9	119.0	qn	18	0
10	134.8	brs	|<5|	0
N-CH_3	45.7	d	−78	|<5|

[a] Direction uncertain. Values in parentheses are for the less likely possibility of a negative shift.

Table 4. ^{13}C NMR Chemical Shifts and Isotope Shifts of **2·HBF$_4$** in DMSO-d_6

carbon	δ (ppm)	multiplicity	Δ_0 (ppb)	Δ_e (ppb)
1,8	126.0	m	—	—
2,7	155.1	qn	|<5|	47 (−47)[a]
3,6	113.4	brs	|<5|	|<5|
4,5	131.0	m	−12	14 (−26)[a]
9	122.1	qn	15	0
10	124.6	brs	|<5|	0
N-CH_3	42.4	d,d	−80, −25	|<5|
O-CH_3	56.7	s	|<5|	|<5|

[a] Direction uncertain. Values in parentheses are for the less likely possibility of a negative shift.

Discussion

1,8-Bis(dimethylamino)naphthalene. In the free base there is no N−H−N hydrogen bond and thus no tautomeric equilibrium. There are conformational equilibria that might have been subject to isotopic perturbation, to the extent that CH_3 and CD_3 differ sterically. Nevertheless, the splitting patterns (Table 2) are consistent with purely intrinsic shifts.

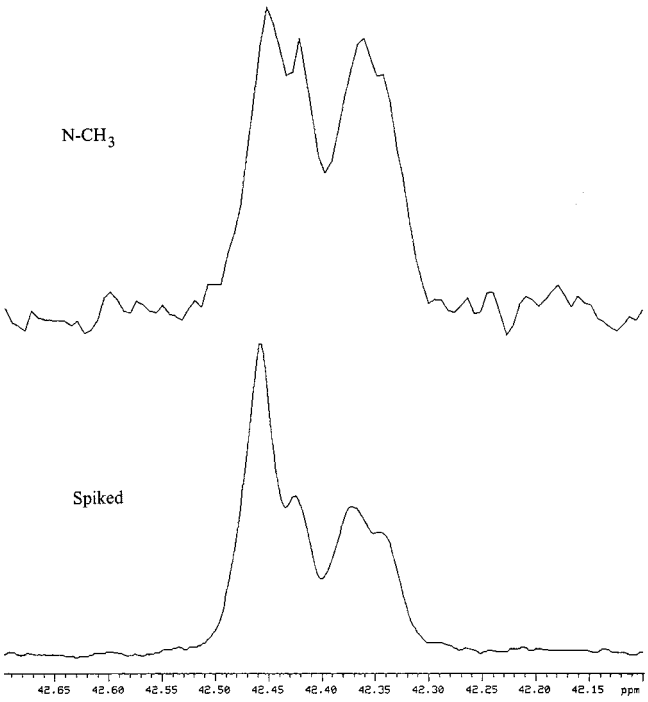

Figure 6. *N*-methyl region of ^{13}C NMR spectrum of **2·HBF$_4$** in DMSO-d_6; below with added d_0.

1,8-Bis(dimethylamino)naphthalene·H$^+$. The ^{13}C NMR spectrum of the mixture of isotopologs of **1·HSCN** (Table 3) indicates intrinsic isotope shifts for some carbons, perturbation isotope shifts for others, and a combination of both for still others. The $^3\Delta_0$ at *N*-methyl is −78 ppb, consistent with previously reported values.[24] The quintet for C9 is due to an intrinsic shift. There is even a detectable $^6\Delta_0$ at C4,5. In contrast, the quintets for C2,7 and C3,6 must be attributed to a perturbation shift, because d_0 is the central peak of each. The signals of C1,8 and C4,5 exhibit a combination of both intrinsic and perturbation isotope shifts, since the signal due to d_0 is neither the central peak nor an extremity.

The positive $^4\Delta_0$ of C9 is unusual. Previous examples of positive $^2\Delta_0$ and $^3\Delta_0$ involve carbocationic systems with isotopic perturbation of hyperconjugation or resonance,[36] but these are not analogous. Regardless of the origin of the downfield shift, it is small.

Also anomalous is the absence of a $^4\Delta_0$ at the other *ortho* position, C2,7. A possible explanation is that intrinsic isotope shifts are larger at carbons that have an anti relationship to a CD_3. A relation between $^3\Delta_0$ and ^3J has been noted, and the latter increases with dihedral angle.[37] Indeed, the $^6\Delta_0$ at distant C4,5 may be detectable because the CD_3s are doubly anti (CNC1C9, C1C9C10C5).

For C1,8 the broadenings due to the unresolved $^3J_{CD}$ lead to assignments that show the perturbation shift to be negative. This agrees in sign with the estimate for the ipso carbons in Table 1. This further supports the estimate of positive signs for perturbation shifts at C2,7, C3,6, and C4,5. Therefore, of the two possible values included in Table 3, the negative shifts in parentheses are indeed less likely.

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2,7-Dimethoxy Derivative. The behavior of $\mathbf{2{\cdot}H^+}$ (Table 4) is quite similar to that of $\mathbf{1{\cdot}H^+}$, with qualitatively similar isotope shifts at the ring carbons. The quintet for C9 is due simply to an intrinsic isotope shift $^4\Delta_0$, whereas the quintet for C2,7 is due to a perturbation shift $^4\Delta_e$. Signals of C4,5 exhibit both perturbation and intrinsic shifts in DMSO-d_6. A minor difference is that isotope shifts at C1,8 and C3,6 are unresolvable.

The only significant difference is in the *N*-methyl signals. For $\mathbf{2{\cdot}H^+}$ they are two doublets (Figure 6), with separations of 80 and 25 ppb. The most downfield signal is due to the d_0 isotopolog. This pattern corresponds to two unequal intrinsic shifts. The −80 ppb shift is consistent with a $^3\Delta_0$ from a geminal CD_3, quite close to that seen in $\mathbf{1{\cdot}H^+}$. The other shift is remarkable in that it appears only as a doublet, not as a triplet. Therefore only one of the methyl positions on the other nitrogen is responsible for the shift, and deuteration at the other position has no effect.

There is an interesting stereochemical implication of the observation that only one methyl on the other nitrogen produces an intrinsic isotope shift. It requires that the cis/trans relationship of methyls be preserved on the NMR time scale. If not, both methyls would produce isotope shifts, and a triplet would have resulted. Equivalencing cis and trans could well be slow because it requires not only rotating the dimethylamino group in a congested environment but also breaking the hydrogen bond.

No second doublet splitting could be resolved for $\mathbf{1{\cdot}H^+}$. The resolution was too poor to exclude the possibility of a 12-ppb triplet splitting, which would result from averaging cis and trans isotope shifts. However, this would require rapid $C_{aryl}-N$ rotation to equivalence cis and trans, and this rotation is slow in protonated *N*,*N*′-dibenzyl-*N*,*N*′-dimethyl-1,8-naphthalenediamine.[38] It is likely that the isotope shift across the hydrogen bond is a feature of the crowding in $\mathbf{2{\cdot}H^+}$.

It is not clear whether the additional isotope shift in $\mathbf{2{\cdot}H^+}$ is due to the trans methyl or to the cis. Although intrinsic isotope shifts (like coupling constants) are generally larger for carbons that are anti to a deuterium, the cis methyl might act through space, especially since the methoxy groups may force the *N*-methyls toward each other and facilitate the transmission of an intrinsic shift across the hydrogen bond.

Perturbation Isotope Shifts. The key result is that the observation of perturbation isotope shifts Δ_e at all four ring carbons of $\mathbf{1{\cdot}H^+}$ and at two carbons of $\mathbf{2{\cdot}H^+}$ indicates that the isotopes do perturb a tautomeric equilibrium. In solution the hydrogen-bonded proton resides in a double-well potential surface, and the ion exists as a pair of rapidly converting tautomers. These ions are unequivocally asymmetric. Even though the N−N distance is short enough to allow a single-well potential, the NHN path is longer. The role of a reduced NHN angle in favoring an asymmetric hydrogen bond has been noted.[15]

Equal basicity of the two nitrogens is a necessary condition for a symmetric hydrogen bond.[3] Yet the essence of the perturbation method is the use of CD_3 groups to render the basicities unequal. Might the isotopic substitution itself destroy a symmetry that might have been present without isotopes? There are actually two such substitutions, both the deuterium and the ^{13}C required for NMR. However, it follows from the Born−Oppenheimer Approximation[39] that the potential-energy surface governing nuclear motion is independent of nuclear mass. Therefore, the isotopic substitution cannot have converted a single-well potential into a double-.

The magnitudes of the perturbation isotope shifts in Tables 3-4 are markedly lower than the estimates in Table 1. Despite this discrepancy, the relative magnitudes do parallel the estimates, in that the *meta* carbons C3,6 exhibit the smallest shifts. The major discrepancy is that only intrinsic shifts are observed for the *N*-methyl carbons of both $\mathbf{1{\cdot}H^+}$ and $\mathbf{2{\cdot}H^+}$, even though a substantial perturbation shift, comparable to that at C2,7, is expected. The reduction of the magnitudes and the absence of any detectable perturbation shift at *N*-methyl may be due to the inadequacies of dimethylaniline as a model for **1** and **2**, which are twisted, and of dimethylanilininium ion as a model for $\mathbf{1{\cdot}H^+}$ or $\mathbf{2{\cdot}H^+}$, with its hydrogen bond (Figure 2b).

Environmental Effects. The results are essentially independent of solvent. In DMSO, chloroform, and methanol each of these cations exists as a pair of rapidly converting tautomers. The magnitude of the perturbation isotope shift seems to be slightly smaller in nonpolar solvents. This may be due to variation of *K* or *D* in eq 2. The difference in isotope shifts between $\mathbf{2{\cdot}HBF_4}$ and $\mathbf{2{\cdot}HBPh_4}$ is also negligible. Thus, neither solvent nor counterion affects the shape of the potential surface.

Why are these ions symmetric in some crystals but asymmetric in solution? In a nonpolar medium the diffuse charge of a symmetric hydrogen bond ought to be favored over the localized charge of an asymmetric one, as is demonstrated by calculations.[40] A crystal is a highly polar environment, owing to the strong electric fields of nearby ions, so that it might have favored an asymmetric hydrogen bond. Yet only in crystals is a symmetric hydrogen bond found. A further difference though is that in solution the local environment is disordered, with the two nitrogens subject to unequal solvation. Such a dynamic disorder can induce a further asymmetry in the hydrogen bond.[41] Even though this cationic hydrogen bond is shielded from solvent and counterions, the results indicate that it nevertheless is asymmetric.

If the asymmetry in solution can be induced by unequal solvation, then any stabilization due to resonance stabilization cannot be large. There still remains the question of why these ions appear to be symmetric in some crystals. It may be that the X-ray results are misleading and that these ions are always asymmetric but sometimes appear symmetric, owing to averaging over a static or dynamic disorder. Indeed there are ions that are asymmetric at low temperature but symmetric at higher.[42]

Origin of the Enhanced Basicity. Why are bis(dimethylamino)naphthalenes so basic? Relative to *N*,*N*-dimethylaniline the basicity is enhanced 10^8-fold, and 10^{12}-fold for the 2,7-dimethoxy derivative.[10] If $\mathbf{1{\cdot}H^+}$ and $\mathbf{2{\cdot}H^+}$ are not symmetric, then they are not stabilized by resonance involving two identical resonance forms, nor is there sufficient stabilization from reduction of zero-point energy when a double-well potential is converted to single-, since this could contribute at most 3.6 kcal/mol (from an ordinary hydrogen-bonded N−H at 2500-cm^{-1}).

We therefore conclude that the hydrogen bonds are not strong in themselves. Instead we return to the long-standing interpreta-

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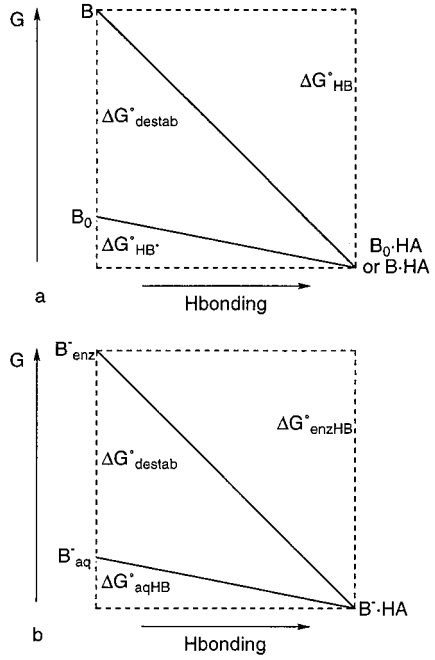

Figure 7. Hydrogen-bond energy and strain relief (a) in bis(dimethylamino)naphthalenes and (b) in enzymes.

tion that the basicity of bis(dimethylamino)naphthalenes arises from relief of strain upon protonation.[7,10] There are several sources of strain in the free base, not only steric but also electronic. One is the loss of conjugation between the lone pair and the aromatic pi system, owing to the steric requirements of the *N*-methyls. Another is the enforced overlap of the nitrogen lone pairs, which repel, especially with 2,7 methoxy groups, which restrict the conformational flexibility. Still other strains arise from distortions to restore conjugation or to relieve lone-pair repulsions. When the lone pairs accept a proton, these sources of strain are eliminated.

This is not inconsistent with the conclusion from some recent calculations that stabilization is due primarily to the hydrogen bond and only minimally to strain relief.[15,43] Specifically, it was concluded that relief of strain contributes only about half the observed increase of basicity, and considerably less than half in the gas phase. However, N−H−N$^+$ hydrogen bonds are stronger in the gas phase, and calculations may overestimate the strength, inasmuch as a single-well potential was derived by B3LYP. A key result is that the calculated hydrogen-bond energies in water, as offset by strain in the cations, hardly differ among protonated 1,8-diaminonaphthalene, **1·H**$^+$, and **2·H**$^+$. Therefore the strength of the hydrogen bond itself is nearly constant and is not responsible for the variation of pK_a. Indeed, the normal basicity of 1,8-diaminonaphthalene shows that the hydrogen bond itself cannot be responsible for the enhanced basicity of the more strained derivatives.

Figure 7a illustrates how relief of strain can make the hydrogen bond appear to be unusually strong. For a model base, B_0, formation of a hydrogen bond with HA is assumed to lower the energy by $\Delta G°_{HB°}$. If another base, B, is destabilized by an additional $\Delta G°_{destab}$, then formation of a hydrogen bond with HA, with relief of the destabilization, lowers the energy by $\Delta G°_{HB}$. This is greater than $\Delta G°_{HB°}$, but not because of a stronger hydrogen bond.

Significance for LBHBs in Enzyme Catalysis. In accounting for the role of unusual hydrogen bonds in some enzymatic catalysis, there may be no need to invoke an LBHB or any extra stabilization due to the hydrogen bond itself. Figure 7b illustrates how relief of strain can lower energy. It is patterned after Figure 7a, but it also resembles a figure attributing an increased hydrogen-bond strength to the greater variability of pK_a in DMSO.[44] If a basic group, B$^-$, in aqueous medium were to form a hydrogen bond with HA, the energy would be lowered by $\Delta G°_{aqHB}$. However, if B$^-$ in an enzyme active site is destabilized by $\Delta G°_{destab}$, then formation of a hydrogen bond with HA lowers the energy by $\Delta G°_{enzHB}$, which is greater than $\Delta G°_{aqHB}$. This destabilization can arise either by forcing the lone pairs of B$^-$ to overlap with other lone pairs or by placing B$^-$ in an aprotic environment, where it lacks stabilization due to hydrogen bonding with solvent. The first possibility is like **1** and **2**, and the second is justified by the observation that hydrogen bonds appear stronger in aprotic solvents such as DMSO.[6] However, the stabilization is not due to any unusual strength of the hydrogen bond itself but to relief of a destabilization.

The extra stabilization of $\Delta G°_{enzHB}$, relative to $\Delta G°_{aqHB}$, can be utilized to lower the energy of the transition state. Although enzymes usually reduce activation energies by stabilizing the transition state, it is not a new idea that they may also do so by introducing strain into the enzyme−substrate complex.[45] In the context of LBHBs this requires that the energy of substrate binding be sufficient to desolvate an anionic group or to force it against another anion. If the strain is relieved on passing to the transition state, by inserting a proton and forming a hydrogen bond, then k_{cat} can be increased.

Summary and Conclusions

The protons in the intramolecular hydrogen bonds of cations **1·H**$^+$ and **2·H**$^+$ reside in a double-well potential surface. The ^{13}C NMR spectrum of **1·H**$^+$ shows splitting patterns that are consistent with perturbation isotope shifts. The spectrum of **2·H**$^+$ is qualitatively similar, except for an intrinsic isotope shift at *N*-methyl that is transmitted across the hydrogen bond from only one CD_3. Perturbation shifts appear in the spectra in all solvents and with all counterions. The magnitudes of perturbation shifts are slightly sensitive to environment. The presence of perturbation isotope shifts establishes the existence of an equilibrium between a pair of rapidly interconverting asymmetric tautomers.

Since these ions are not symmetric, symmetry cannot be the source of an unusual strength for their hydrogen bonds. Instead the high basicity of bis(dimethylamino)naphthalenes is attributed to the relief of strain on protonation. A similar relief of strain may be involved in enzymatic reactions, without invoking a special role for an unusually strong LBHB.

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Supporting Information Available: Tables of ^{1}H-coupled ^{13}C NMR data for **2·HBF$_4$** in DMSO-d_6 and ^{13}C NMR chemical shifts and isotope shifts for **1·HSCN** and **2·HBF$_4$** in methanol-d_4 and $CDCl_3$ and for **2·HBPh$_4$** in DMSO-d_6 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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