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Symmetry of O-H-O and N-H-N Hydrogen Bonds in 6-Hydroxy-2-formylfulvene and 6-Aminofulvene-2-aldimines[1]

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The symmetry of the hydrogen bonds in 6-hydroxy-2-formylfulvene and two *N,N′*-diaryl-6-aminofulvene-2-aldimines is probed by the NMR technique of isotopic perturbation. Observed deuterium-induced ^{13}C NMR isotope shifts at several positions can be attributed to a combination of an intrinsic shift and the perturbation of a tautomeric equilibrium. The most dramatic are at the aldehydic or aldiminic carbon signals, where the observed isotope shift for the unlabeled carbon is +376 or +223 ppb. This large downfield shift is contrary to the small upfield shift expected for a four-bond intrinsic shift and can be attributed only to a perturbation shift. Therefore these intramolecular hydrogen bonds are asymmetric, the proton resides in a double-minimum potential surface, and each molecule exists as a pair of rapidly interconverting tautomers, regardless of solvent. The symmetry of the hydrogen bond is not governed only by the O-O or N-N distance. It is proposed that symmetric hydrogen bonds can be observed in crystalline phases but not as yet in solution because the disorder of the solvation environment induces an asymmetry of the hydrogen bond, whereas a crystal can guarantee a symmetric environment. These results provide no insight into the source of the stabilization attributed to low-barrier hydrogen bonds if they lack the special feature of symmetry.

Key Words: symmetry; hydrogen bonds; NMR; isotopic perturbation; LBHBs.

INTRODUCTION

Hydrogen bonds are a key feature of molecular structure and the focus of an enormous number of theoretical and experimental studies (*1*). Usually the motion of the hydrogen-bonded hydrogen is described by a double-well potential, but in symmetric hydrogen bonds it is a single well. Such hydrogen bonds require donor atoms of equal basicity and an unusually short O-O distance of $\leq$2.5 Å (*2*). These hydrogen bonds are unusually strong, perhaps because resonance energy is maximized when two resonance forms are of equal energy, or because of covalent character (*3*). These have been called short, strong hydrogen bonds or low-barrier hydrogen bonds (LBHBs) or centered or symmetric hydrogen bonds, depending on the observational criterion.

[1] This paper is dedicated to F. H. Westheimer, on the occasion of his 90th birthday.

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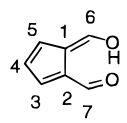
Recently LBHBs have been proposed to play a role in enzymatic catalysis (*4*). An extra stabilization is claimed to reduce the activation barrier for the formation of high-energy intermediates or transition states. Yet hydrogen-bond strengths are often considerably lower than the 10–20 kcal/mol suggested (*5*). Consequently this proposal has generated considerable controversy (*6*), and there are some enzymic reactions where LBHBs are not required (*7*). Authoritative recent reviews are available (*8*). The potential significance of symmetric hydrogen bonds has prompted us to search for examples in solution.

The question is whether the proton in the hydrogen bond resides in a single- or a double-minimum potential surface. Alternatively, the crucial distinction is between a single symmetric structure and a pair of rapidly interconverting asymmetric tautomers.

Our previous studies addressed the intramolecular O-H-O hydrogen bonds in 3-hydroxy-2-phenylpropenal (*9*) and in dicarboxylate monoanions (*10*), as well as the N-H-N hydrogen bonds in protonated 1,8-bis(dimethylamino)naphthalenes (*11*). We now extend those studies to the O-H-O and N-H-N hydrogen bonds of neutrals 6-hydroxy-2-formylfulvene (**1**), *N*,*N*′-diphenyl-6-aminofulvene-2-aldimine (**2**), and *N*,*N*′-bis(3,5-dimethylphenyl)-6-aminofulvene-2-aldimine (**3**).

These molecules are good candidates for symmetric hydrogen bonding. The short O-O and N-N distances, 2.51 and 2.79 Å, respectively (*12*), favor transformation of a double-well potential into a single-well one. The donor and acceptor basicities are necessarily matched. An unusually strong bond is indicated by ^{15}N-^{15}N and $^{15}N \cdots H$ scalar couplings across the N-H-N hydrogen bond in a desymmetrized analog (*13*). Moreover, aromaticity in the cyclopentadienyl ring may provide additional stabilization to the symmetric structure.



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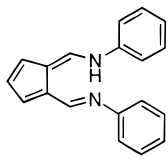

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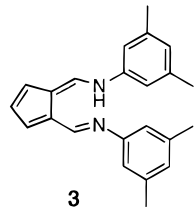

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There is considerable evidence against symmetric hydrogen bonds in these molecules, from X-ray and neutron-diffraction data (*12*), quadrupole coupling constants (*14*), UV-visible absorption (*15*), X-ray photoelectron spectroscopy (*16*), and microwave studies (*17*). A 6-31G**/MP2 calculation indicates that the symmetric structure of **1** is 1.8 kcal/mol less stable than the asymmetric one, but the stabilities reverse, by 0.5 kcal/mol, when zero-point energy is included (*18*). Although N-H-N hydrogen bonds are generally longer and thus weaker than O-H-O, the O-O distance in a fully planar 1,2-dicarboxylate monoanion (a seven-membered ring, including H) would be shorter than optimum (*19*), so that the N-N distance in **2** or **3** may be more favorable for a strong, symmetric hydrogen bond.

This study also addresses the influence of solvation on the symmetry of the hydrogen bond. Because solvation stabilizes localized charges more than delocalized ones (*20*), the hydrogen bonds in the ions studied previously may suffer from a bias toward asymmetry that is not operative with neutrals. Although previous work showed the

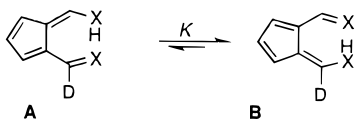
O-H-O hydrogen bond of uncharged 3-hydroxy-2-phenylpropenal to be asymmetric (*9*), this may simply be a consequence of too long an O-O distance. Besides, oxygens possess additional lone pairs that can hydrogen bond to solvent. We now study N-H-N systems that are neutral and that lack lone pairs or NH that can hydrogen bond to solvent, as well as a comparison O-H-O system.

METHODOLOGY OF ISOTOPE SHIFTS

Isotopic perturbation of equilibrium is a powerful and widely applicable NMR technique for distinguishing a single symmetric structure from a pair of asymmetric tautomers (*21*). It succeeds even when interconversion is so rapid that separate signals from individual tautomers are not seen. It relies on measuring the isotope shift $^{n}\Delta_{obs}$, the difference (Eq. (1)) between the ^{13}C chemical shifts in molecules with and without deuterium (*22*). This includes an intrinsic contribution $^{n}\Delta_{0}$, which is usually <0 (upfield) and falls off rapidly with n, the number of bonds between the ^{13}C and the D.

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

The isotopolog of **1, 2**, or **3** with exactly one deuterium at C6,7 can be synthesized by known procedures. If the hydrogen bond is asymmetric, there is an additional contribution to Δ_{obs}, arising from perturbation of the equilibrium between the two tautomers **A** and **B** (X = O, NAr). Because an enol or enamine has a higher C-H stretching frequency than an aldehyde or imine, tautomer **A** has a higher zero-point energy. Therefore the equilibrium favors the other tautomer **B**, and the time-averaged chemical shifts are displaced from those in d_0, where the two tautomers are of identical stability. This is seen as a perturbation (of equilibrium) isotope shift given by Eq. (2), where $D = \delta_{XH} - \delta_{=X}$, the chemical-shift difference between exchange-related carbons proximal and distal to the OH or NH in a static tautomer.



A B

$$^{n}\Delta_{e} = \frac{K - 1}{2(K + 1)} D \tag{2}$$

The perturbation shifts can be estimated. By analogy to 3-hydroxy-2-phenylpropenal, $^{4}\Delta_{e}$ at the aldehydic carbons of **1** is expected to be ca. +0.76 ppm (*9*). For **2** or **3** at 25°C the equilibrium constant K is ca. 1.09, from the difference of 18.3 cm^{-1} in CH vs CD zero-point energies between enamine (ν = 2990 cm^{-1}) and aldimine (ν = 2865 cm^{-1}) (*23*). The chemical shifts can be estimated (δ = 130, 160 ppm) from these same models (*24*). Then, according to Eq. (2), the aldiminic CH is expected to exhibit a $^{4}\Delta_{e}$ of +0.66 ppm, and the CD a $^{4}\Delta_{e}$ of −0.66 ppm, but shifted further upfield by $^{1}\Delta_{0}$ and observable only with ^{2}H decoupling. The perturbation shift $^{4}\Delta_{e}$ at C4 is automatically zero by symmetry. The chemical shifts for the fulvene carbons of a frozen tautomer of **1** or **2** can be estimated from the acetyl and trimethylsilyl

derivatives, and the chemical shifts for phenyl carbons in a frozen tautomer of **2** or **3** can be estimated by using *N*-benzylaniline and *N*-benzylideneaniline as models (*25*). Table 1 lists the estimated pertubation isotope shifts, all but one of which are positive (downfield for the carbon nearer H).

Isotope shifts are now used to determine the shape of the potential surface of the O-H-O hydrogen bond of **1** and the N-H-N hydrogen bonds of **2** and **3**. If the hydrogen bond is symmetric, the labeled compound will exhibit only intrinsic shifts. Instead, a combination of an intrinsic isotope shift and a shift due to perturbation of a tautomeric equilibrium is seen at several carbons. Thus each of these species exists as a pair of rapidly interconverting tautomers, and the hydrogen bond is characterized by a double-well potential.

MATERIALS AND METHODS

6-Dimethylamino-2-(N,N-dimethylformiminium)fulvene perchlorate (26). This precursor was prepared from 6-(dimethylamino)fulvene (*27*) and dimethylformamide-$POCl_3$ complex (*28*) in THF, precipitated with $NaClO_4$ in methanol, and recrystallized: 17% yield, mp. 229–233°C (lit. 235–237°C). ^{13}C NMR ([$^2H_6$]DMSO) δ 48.5, 118.4, 125.3, 128.5, 154.3.

*6-Hydroxy-2-formylfulvene (**1**) (26).* The perchlorate salt above was stirred with chloroform and aqueous NaOH. The organic material was collected, washed with water, and evaporated. The residue was stirred with aqueous NaOH at 50°C under N_2, then acidified with aqueous HCl, extracted with CH_2Cl_2, and evaporated carefully: 64% yield.

*N,N′-Diphenyl-6-aminofulvene-2-aldimine (**2**) (15).* A solution of perchlorate salt in ethanol was refluxed with aniline and cooled, and the resulting precipitate was recrystallized: 53% yield, mp 98–100°C (lit. 100°C).

*N,N′-Bis(3,5-dimethylphenyl)-6-aminofulvene-2-aldimine (**3**).* Perchlorate salt was refluxed in ethanol with 3,5-dimethylaniline and cooled, and the resulting precipitate was recrystallized: 54% yield, mp. 155–158°C. ^1H NMR ($CDCl_3$) δ 2.36 (s, 12H), 6.46 (t, J = 3.75 Hz, 1H), 6.85 (s, 2H), 6.94 (s, 4H), 7.06 (d, J = 3.5 Hz, 2H), 8.30 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 21.3, 117.1, 120.8, 122.2, 126.8, 134.3, 139.4, 145.3, 150.5.

Preparation of deuterated compounds. Labeled compounds were synthesized using

TABLE 1

Estimated Perturbation Isotope Shifts at CHX, Fulvene, and Phenyl Carbons of **1** or **2**

Carbon	Δ_{e1}, ppm	Δ_{e2}, ppm
C6,7	0.76	0.66
C1,2	0.47	0.07
C3,5	0.89	0.12
Ipso	—	0.09
Ortho	—	0.18
Meta	—	−0.01
Para	—	0.19

TABLE 2

^{1}H-Coupled ^{13}C NMR Data of **2** in [$^2H_4$]Methanol

Carbon	δ, ppm	Multiplicity	J, Hz
Ortho	120.1	ddd	157, 7.3, 6.0
4	121.9	dt	164, 4.5
1,2	124.0	m	
Para	126.0	dt	157, 8.4
Meta	130.9	ddd	152, 8.3, 2.3
3,5	136.7	dm	163
Ipso	147.1	m	
6,7	151.8	dd	160, 2.3

[$^2H_7$]dimethylformamide-$POCl_3$ complex as the source of the second formyl group. This results in exactly one deuterium and one protium on the two aldehydic or aldiminic carbons. The multiplicities and integration of the ^{1}H NMR spectra were in agreement with the expected product.

NMR Spectra and sample preparation. Spectra were recorded on a Varian Unity 500 spectrometer operating at a ^{13}C resonance frequency of 125 MHz and a ^{1}H resonance frequency of 500 MHz. Spectra are referenced to the solvent. Samples for measurement of isotope shifts were prepared by mixing equal weights of d_1 and d_0 compounds, except for 6-hydroxy-2-formylfulvene, which was synthesized as a mixture of d_1 and d_0. Decoupling of both ^{1}H and ^{2}H was achieved by sending an additional 76.85-MHz signal through the lock channel.

RESULTS

NMR signal assignments. Partially assigned NMR spectra of **2** had been reported (*14*). The full ^{1}H spectrum could be assigned on the basis of signal integrations and splitting patterns. The full ^{13}C spectrum was assigned on the basis of ^{1}H-couplings and a 2D HMQC spectrum that correlates ^{1}H and ^{13}C chemical shifts. Table 2 lists the carbon multiplicities and C-H coupling constants. Assignments for **3** were made by analogy to **2**.

6-Hydroxy-2-formylfulvene. The ^{13}C NMR data for the mixture of isotopologs of **1** in $CDCl_3$ are listed in Table 3. The second and third columns list n and n', the number of bonds between the label and the nearer or farther, respectively, of each

TABLE 3

^{13}C NMR Data from Mixture of **1** and 6-[^{2}]**1** in $CDCl_3$

Carbon	n	n'	δ_0, ppm	Δ_{down}, ppb	Δ_{up}, ppb
6,7	1	4	176.0	+376	—
1,2	2	3	126.5	+200	−279
3,5	3	4	141.2	+151	−195
4	4	4	125.2	<5	<5

set of carbons. The fourth column lists the NMR shifts for unlabeled **1**. The fifth and sixth columns list the observed downfield and upfield isotope shifts of 6-[^{2}H]**1** relative to **1**.

Without ^{2}H decoupling the only signal observed from C6,7 of 6-[^{2}H]**1** is the CH, since the CD is split into a triplet and lacks a nuclear Overhauser enhancement. The CH shows a large downfield shift of 376 ppb. For both C1,2 and C3,5 one signal of 6-[^{2}H]**1** is shifted upfield and the other downfield. The signal for C4 is a singlet, since it is too far from the label to show a resolvable $^4\Delta_0$ and since it is located symmetrically relative to the deuterated and undeuterated carbons and therefore cannot show a Δ_e.

N,N′-Diphenyl-6-aminofulvene-2-aldimine. Figure 1 shows individual NMR signals of cyclopentadienyl and CHN carbons from a 1:1 mixture of **2** and 6-[^{2}H]**2**. The spectra are aligned along the signal of unlabeled **2** and are plotted on the same scale. The signal for C4 is a singlet. Three signals are observed from some carbons, owing to isotope shifts. Because of the stoichiometry the two smaller signals can be assigned to 6-[^{2}H]**2**. For C1,2 and C3,5 of 6-[^{2}H]**1** one signal is shifted upfield and the other downfield, by unequal amounts. For ipso and ortho carbons (not shown) the signals are shifted by equal or nearly equal amounts. For meta carbons, the signals are singlets, with unresolvable isotope shifts. The para carbon shows a high-field shoulder, corresponding to a small intrinsic isotope shift.

The ^{13}C NMR chemical shifts and isotope shifts of a mixture of **2** and 6-[^{2}H]**2** in [$^2H_6$]DMSO are listed in Table 4. The results in $CDCl_3$ in Table 5 are quite similar. Table 6 lists the data in [$^2H_4$]methanol. The assignment of C6,7 was facilitated by simultaneously decoupling not only ^{1}H but also ^{2}H, since otherwise the CD signal is invisible, as demonstrated by comparing Fig. 1a with Fig. 2, which shows C6,7 in the ^{1}H- and ^{2}H-decoupled ^{13}C NMR spectrum of **2**.

N,N′-Bis(3,5-dimethylphenyl)-6-aminofulvene-2-aldimine. The assignment of C6,7 signals in 6-[^{2}H]**3** was made from a ^{1}H-coupled ^{13}C NMR spectrum. The special feature of this derivative is that it permits the assignment of the ipso carbon signals of 6-[^{2}H]**3**, and by extension that of 6-[^{2}H]**2**. The ^{1}H-coupled spectrum is simplified by 3,5-dimethyl substitution, which eliminates the $^3J_{CH}$ between ipso carbon and meta CH of **2**. Consequently the ipso carbon of 6-[^{2}H]**3** shows a well-resolved downfield 6.6-Hz doublet, due to $^3J_{CH}$ to the aldiminic CH, which must be distal. In contrast, the other ipso carbon is an upfield singlet, broadened by an unresolvable $^3J_{CD}$, so it must be proximal to the label. The ^{13}C NMR data for the mixture of isotopologs of **3** in [$^2H_6$]DMSO are listed in Table 7.

DISCUSSION

6-Hydroxy-2-formylfulvene. The isotope shifts in Table 3 are not purely intrinsic. The signal from C6,7 of 6-[^{2}H]**1** that is readily observed, without ^{2}H decoupling, is the CH. Its large downfield shift of 376 ppb, relative to **1**, is entirely contrary to the small upfield shift expected from a $^4\Delta_0$ (*22*). This must be a perturbation shift. Likewise, the isotope shifts for both C1,2 and C3,5 in 6-[^{2}H]**1** are too large to be intrinsic. The inequality of upfield and downfield isotope shifts for each of these carbons means that intrinsic isotope shifts are not negligible. The combination of intrinsic and perturbation shifts could not be separated, but the data are consistent