Symmetry of the Hydrogen Bond in Malonaldehyde Enol in Solution

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Abstract: A fundamental question about the hydrogen bond is whether the hydrogen is located in the middle of the two electronegative atoms, in a single-well potential, or else is closer to one of them and jumping between them, in a double-well potential. This question has been of interest recently because short, strong hydrogen bonds have been proposed to provide stabilization in some enzyme-catalyzed reactions. The NMR method of isotopic perturbation of equilibrium is now used to get an unambiguous answer for the intramolecular hydrogen bond of the enol of 2-phenylmalonaldehyde-α-*d* in $CDCl_3$ and pyridine-d_5. The equilibrium isotope shift, which is large, downfield, and dependent on temperature, was measured in both ^1H and ^{13}C NMR spectroscopy. This result shows that the intramolecular hydrogen bond of 2-phenylmalonaldehyde enol is asymmetric, corresponding to the presence of two equilibrating tautomers.

Introduction

Hydrogen Bonding. The hydrogen bond is generally considered to be an electrostatic interaction between a proton donor A−H and a proton acceptor B, with an energy that is usually about 5 kcal/mol.[1] It is important in determining the structure and reactivity of a wide range of organic and inorganic molecules and biomolecules. Recently ab initio molecular orbital theory has become quite reliable in assessing the strengths, geometry, and other properties of hydrogen bonds.[2]

Symmetry of Hydrogen Bonds. The question of the symmetry of hydrogen bonds is an old one. Many studies have relied on crystallographic data.[1,3] Usually a hydrogen bond is asymmetric, with the hydrogen closer to the more basic atom (**1a**). Even if the two atoms have the same basicity, the hydrogen may be of lower energy when it is closer to one atom than centered between them. Such hydrogen bonds are described by a double-well potential. If the two atoms are of identical basicity, the potential is a symmetric one, but the hydrogen is jumping back and forth (**1b**).

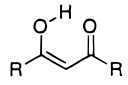
A−H··B A−H··B ⇌ A··H−B A··H··B

1a **1b** **1c**

If the hydrogen is centered between the two atoms (**1c**), then its motion is described by a single-well potential. Such a hydrogen bond is often called a symmetric one. It is also found to be unusually strong. An example is bifluoride ion, FHF^-, whose hydrogen-bond energy is 40 kcal/mol.[4] For OHO hydrogen bonds, if the O−O distance is less than 2.4 or 2.5 Å, then the double-well potential becomes a single-well potential.[5] Other features associated with a strong hydrogen bond are low fractionation factors for selectivity of deuterium over protium[6] and ^1H NMR signals far downfield.[7]

A centered hydrogen bond is quite remarkable, since it requires >20 kcal/mol to stretch a 3500 cm^{-1} O−H bond from the normal 1.0 Å to the 1.2 Å midway between the two oxygens. One rationalization for a compensating stabilization is that a symmetric hydrogen bond has "covalent character" or resonance assistance that confers an extra strength.[8] Strong, low-barrier hydrogen bonds have received considerable attention recently because it has been proposed that they can provide additional stabilization to the transition state or intermediate in some enzyme-catalyzed reactions.[9] This proposal has generated some controversy.[10]

Enols of β-Dicarbonyl Compounds. The intramolecular hydrogen bonds of the enol forms of malonaldehyde (**2**, R═H) or acetylacetone (**2**, R═CH_3) are strong, with a stabilization



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estimated as 10−12 kcal/mol.[11] Even though these hydrogen

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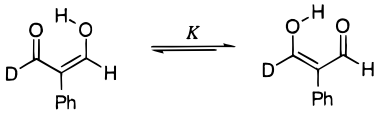
bonds are strong, photoelectron[12] and microwave spectroscopy,[13] as well as conflicting X-ray crystallographic[14] and electron diffraction evidence[15] generally indicate that they are asymmetric, with a double-well potential. The unequal O_{1s} energies seen in the photoelectron spectrum have been verified by calculation.[16] For these molecules the O−O distance seems to be too long to favor a single-well potential.

Yet according to recent high-level calculations, the symmetry of such hydrogen bonds is less certain. To be reliable, calculations must account for electron correlation, which stabilizes the symmetric structure.[17] For maleate and oxalate monoanions the barrier to proton transfer is lower than the zero-point energy.[18] In contrast, ab initio calculations on malonaldehyde enol (**2**, R═H) usually show a double-well potential with a small barrier,[19] although there are some exceptions,[20] especially when the zero-point energy is included.[11b] It is clear that the potential energy for motion of the hydrogen is very sensitive to the O−O distance, which is not always calculated reliably. A recent review concluded that a double-well potential is well supported by experiment but that calculations do not give a reliable energy barrier.[21]

Proposed Experiment. The symmetry of the hydrogen bond is a basic question about an important feature of molecular structure. The method of isotopic perturbation of equilibrium[22] can unequivocally distinguish symmetric structures from asymmetric ones. It is an NMR method that is applicable even when interconversion from one asymmetric structure to another is extremely fast. Saunders successfully applied this method to carbocations, including the controversial norbornyl cation,[23] and McMurry applied it to *in*-bicyclo[4.4.4]-1-tetradecyl cation.[24]

Subsequently Perrin and Thoburn used isotopic perturbation to investigate the symmetry of the intramolecular hydrogen bonds in the monoanions of some dicarboxylic acids.[25] On the basis of ^{18}O-induced ^{13}C NMR isotope shifts at the carboxyl carbon they concluded that the hydrogen bonds are symmetric in organic solvents but asymmetric in aqueous solution, in contrast to some early results from diffraction studies. Yet further studies of isotope shifts at ipso carbons showed that these hydrogen bonds are asymmetric not only in aqueous solutions but also in organic solvents.[26] The asymmetry was attributed to a disorder of the local solvation environment around the anion. This is consistent with ab initio MO calculations on maleate and malonate monoanions, where the barrier to hydrogen transfer is low but increased when the ion is embedded in a polarizable medium.[27]

We therefore sought to study the symmetry of the hydrogen bond in an uncharged species, the enol of malonaldehyde (**2**, R═H). More suitable is the enol of 2-phenylmalonaldehyde (**3**), with a phenyl group at C2 simply for ease of synthesis and to avoid the conformational flexibility and the polymerization of the parent.[28] If the hydrogen of 2-phenylmalonaldehyde enol is in a double-well potential, then there are two tautomers in equilibrium. Monodeuterium substitution will perturb this equilibrium between **3-*d*$_1$(enol)** and **3-*d*$_1$(ald)**, differing in whether the H is on the enol or aldehyde carbon, whereas there is no perturbation for **3** or **3-*d*$_2$**, which serve as a comparison.



3-*d*$_1$(enol) **3-*d*$_1$(ald)**

Deuterium has the further advantage that its isotope effect is potentially much larger than that in our previous studies with ^{18}O.[25,26]

Isotope Shifts. The isotope shift is the change of the NMR chemical shift δ of a reporter nucleus X due to isotopic substitution n bonds away (eq 1).[22,29] The heavier isotope

$$ {}^{n}\Delta = \delta X_{\text{heavier}} - \delta X_{\text{lighter}} \qquad (1) $$

usually produces an upfield shift, corresponding to $\Delta < 0$. There are small intrinsic shifts associated with the presence of the isotope, and these decrease with distance from the site of substitution. For example, in ^{13}C NMR a deuterium-induced one-bond intrinsic isotope shift ($n = 1$) is about −300 ppb, for $n =$ 2 it is about −100 ppb, and for $n \geq 3$ it is between −100 and 0 ppb.

Besides the intrinsic isotope shift there is possibly an equilibrium isotope shift Δ_{eq} detectable at the aldehyde carbon of **3** and also at its CH. If the two tautomers are in rapid equilibrium, separate signals are not seen, but only an average, a 50:50 one, if they are degenerate. If isotopic substitution perturbs the degeneracy, it can be manifested as an equilibrium isotope shift given by eq 2,

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$$\Delta_{eq} = \delta_{CHD} - \delta_{CHH} = D(K - 1)/2(K + 1) \qquad (2)$$

where K is the equilibrium constant [**ald**]/[**enol**] and D is the difference between chemical shifts of =CH−O and −CH=O. This can readily be derived by comparing the chemical shift of **3**, where the equilibrium constant is 1, with the weighted average of the chemical shifts for =CH−O and −CH=O, respectively, in **3-*d*$_1$(enol)** and **3-*d*$_1$(ald)**. The additional factor of 2, absent in the customary equation,[22d,25] is because the comparison is between CH signals of **3-*d*$_1$** and undeuterated **3**, rather than with the deuterated carbon of **3-*d*$_1$**.

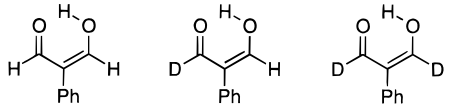
The CH stretching frequency of an aldehyde is 2770 cm^{-1} and that of an enol is 3020 cm^{-1}.[30] The zero-point energy for **3-*d*$_1$(enol)** is then $^1/_2$[2770 + (1/$\sqrt{2}$)3020] cm^{-1} and that for **3-*d*$_1$(ald)** is $^1/_2$[3020 + (1/$\sqrt{2}$)2770] cm^{-1}. From the energy difference of 37 cm^{-1}, K is estimated to be 1.2 at 25 °C. The equilibrium favors the tautomer **3-*d*$_1$(ald)**, with H on the lower frequency bond and D on the higher. Moreover, the separation between aldehyde and enol ^{13}C chemical shifts is ca. 20 ppm, as judged from the chemical shifts of **3** in the solid state.[31] Therefore, Δ_{eq} is expected to be ca. +1 ppm. Similarly, in the ^{1}H NMR spectrum, where the separation between chemical shifts of =CH−O and −CH=O is ca. 2 ppm, we may expect a Δ_{eq} of ca. 0.1 ppm.

The observed isotope shift between the CH signals of **3-*d*$_1$** and of undeuterated **3** is actually a sum, not only of any Δ_{eq} but also including an intrinsic $^3\Delta_0$ or $^4\Delta_0$. The sign of Δ_{eq} is positive, opposite to that of $^3\Delta_0$ or $^4\Delta_0$. Moreover, the magnitude of Δ_{eq} is expected to be substantially larger than that of $^3\Delta_0$ or $^4\Delta_0$. Therefore, if there are two asymmetric tautomers, a large positive (downfield) isotope shift will be observed. However, if there is a single symmetric structure, then only a small normal (negative) isotope shift should be observed. Thus, the sign and magnitude are both diagnostic.

Experimental Section

Instrumentation. NMR spectra were recorded on a Varian Unity 500 MHz spectrometer. Chemical shifts for ^{13}C spectra are relative to $CDCl_3$ (δ 77.0), C_6D_6 (δ 128.0), or pyridine-d_5 (δ 123.5). The temperature was measured from methanol chemical shifts.[32] Mass spectra were obtained on a Hewlett-Packard 5988 GC/MS.

For ^{13}C NMR with ^{2}H-decoupling a synthesized signal generator was fixed to the appropriate deuterium frequency and a spectrum of a mixture of **3**, **3-*d*$_1$**, and **3-*d*$_2$** (0.1 g in 1 mL of $CDCl_3$) was run while selectively decoupling aldehyde deuteriums. That frequency was converted from the aldehyde frequency in a ^{1}H NMR spectrum that was taken with the lock turned off after normal locking and shimming.



3 **3-*d*$_1$** **3-*d*$_2$**

2-Phenylmalonaldehyde Enol and Its Isotopologues. Established syntheses were followed.[33] Dimethylformamide (DMF, 1 mL, 13 mmol) was added dropwise to $POCl_3$ (1.2 mL, 13 mmol). The temperature was maintained below 25 °C by intermittent cooling in ice. After the solution stirred for five minutes, phenylacetic acid (0.7 g, 5.1 mmol) in DMF (1.6 mL, 21 mmol) was added. The mixture was held at 70 °C for 18 h and then cooled, and ethanol (7 mL) was added. After 4 h the mixture was poured into water, and the 1,3-bis(dimethylamino)-2-phenylpropenyl cation was precipitated with sodium perchlorate. Recrystallization from ethanol produced a white salt (1.1 g, 3.63 mmol, 70% yield). This salt (0.30 g, 0.99 mmol) was added to sodium hydroxide (0.13 g), water (2 mL), and methanol (2 mL). The resulting solution was refluxed for 30 min. The solvent was distilled off until less than 2 mL remained, and the solution was filtered, diluted with water, and acidified with 1 mL of 3M HCl. The next day white crystals (0.075 g, 0.52 mmol, 50% yield) were collected, washed, and dried: mp 93−94 °C (lit.[33b] 92−95 °C); ^{1}H NMR (acetone-d_6) δ 14.3 ppm (s, OH, 1H), 8.6 ppm (s, CHO, 2H), 7.2−7.5 ppm (m, Ph, 5H).

Preparation of the deuterated enol (a mixture of **3**, **3-*d*$_1$**, and **3-*d*$_2$**) utilized DMF-d_7 as source of deuterium. In preparation 1, the synthesis as described above for **3** was followed except that DMF-d_7 (1.0 g, 13 mmol) was used at the first step. In preparation 2, 1 g of DMF-d_7 was used at the first step, and 1 mL of DMF at the second. In preparation 3 1.040 g of DMF and 1.018 g of DMF-d_7 were mixed and used in equal amounts in both the first and second steps.

The mass spectrum of partially deuterated 2-phenylmalonaldehyde enol (preparation 1) showed molecular ion peaks (M^+) at m/e 148 for **3**, 149 for **3-*d*$_1$**, and 150 for **3-*d*$_2$**. Their relative intensity was 75.49: 69.56:18.29. With correction for natural isotopic abundances this corresponds to 50.7% **3**, 41.7% **3-*d*$_1$**, and 7.65% **3-*d*$_2$**. Preparation 2 gave 31.0% **3**, 49.1% **3-*d*$_1$**, and 19.9% **3-*d*$_2$**. Preparation 3 gave 27.4% **3**, 49.0% **3-*d*$_1$**, and 23.7% **3-*d*$_2$**. These are statistical mixtures that correspond to the proportions of DMF and DMF-d_7 used.

Results

NMR Spectra of 2-Phenylmalonaldehyde. The ^{1}H NMR spectrum of the enol of 2-phenylmalonaldehyde in $CDCl_3$ shows an OH signal at δ 14.5, an aldehyde signal at δ 8.6, and phenyl signals at δ 7.2−7.6. In the ^{13}C NMR spectrum the aldehyde carbon is at δ 181.3. In C_6D_6 the ^{1}H and ^{13}C spectra again show sharp OH and aldehyde signals, but in DMSO-d_6 the OH signal at δ 12 is very broad, and the aldehyde signal at δ 8.6 is also broad. The aldehyde signal in the ^{13}C NMR spectrum was too broad to be observed in DMSO-d_6. In pyridine-d_5 the width of the aldehyde signal in the ^{1}H NMR spectrum is smaller than that in DMSO-d_6.

Signal Assignments of Isotopologues. The ^{1}H NMR spectrum of the enol of 2-phenylmalonaldehyde (mixture of **3**, **3-*d*$_1$**, and **3-*d*$_2$**) in $CDCl_3$ shows two aldehyde signals, at 8.698 and 8.648 ppm. Because **3-*d*$_2$** has no aldehyde proton, it is invisible. Of the two observable signals, the downfield one is assigned as **3-*d*$_1$**, and the upfield as **3** since the relative intensity of the latter is increased by adding pure **3**.

Two ^{13}C NMR signals were observed in the carbonyl region of a mixture of **3**, **3-*d*$_1$**, and **3-*d*$_2$** under the usual ^{1}H-decoupling condition. From the relative amounts of **3**, **3-*d*$_1$**, and **3-*d*$_2$**, determined by mass spectrometry, the taller signal is assigned as **3**. This is confirmed by the observation that its intensity is increased by adding pure **3**. The other signal is assigned as the CH carbon of **3-*d*$_1$**.

Four signals appear in the carbonyl region in the ^{1}H- and ^{2}H-decoupled ^{13}C NMR spectrum of the statistical mixture of **3**, **3-*d*$_1$**, and **3-*d*$_2$** (Figure 1). The two signals furthest downfield are the same as those visible without ^{2}H decoupling. The other two signals are from carbons attached to ^{2}H. On the basis of the relative amounts, the taller of these can be assigned as the CD carbon signal of **3-*d*$_1$**. The weakest signal, not always visible, is assigned as **3-*d*$_2$**.

Isotope Shifts of 2-Phenylmalonaldehyde (3). Chemical shifts and isotope shifts for 2-phenylmalonaldehyde enol at room temperature are listed in Table 1. Some of these results were

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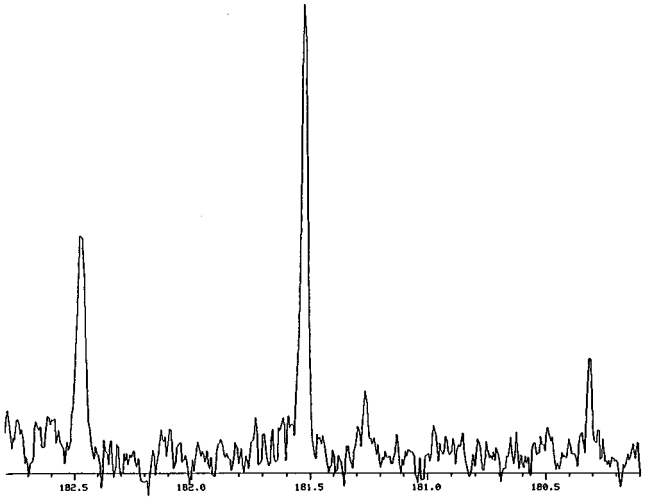

Figure 1. ^{1}H and ^{2}H decoupled ^{13}C NMR spectrum of the statistical mixture of **3**, **3-*d*$_1$**, and **3-*d*$_2$** in $CDCl_3$ at −37.9 °C.

Table 1. Chemical Shifts and Isotope Shifts for 2-Phenylmalonaldehyde Enol (**3**)

solvent	δ, ppm	$\Delta_{eq} + {}^3\Delta_0$, ppb	${}^1\Delta_0 + {}^3\Delta_0$, ppb	$\Delta_{eq} + {}^4\Delta_0$, ppb[a]
$CDCl_3$	181.3	759	−261	50
C_6D_6	181.1	753		
pyridine-d_5	180.4	560		

[a] ^{1}H δ 8.6.

presented at the discussion meeting on Hydrogen Transfer: Experiment and Theory (Berlin, September, 1997).[34]

The chemical shift difference between **3** and **3-*d*$_2$** is −261 ppb. This value is the sum of two intrinsic isotope shifts, ${}^1\Delta_0$ and ${}^3\Delta_0$. It is because this is so large that we compare **3-*d*$_1$** with undeuterated **3**, rather than comparing the two carbons of **3-*d*$_1$**. The former chemical shift difference, or equivalently the difference between the deuterium-bearing carbons of **3-*d*$_1$** and **3-*d*$_2$**, is large, 759 ppb in $CDCl_3$. In C_6D_6 solution it is the same, but it is significantly lower in pyridine. These values represent the sum of Δ_{eq} and ${}^3\Delta_0$. Similarly, the peak separation in the ^{1}H NMR spectrum is 50 ppb, which is the sum of Δ_{eq} and ${}^4\Delta_0$.

The temperature dependence of the isotope shifts for 2-phenylmalonaldehyde enol in $CDCl_3$ is shown in Figure 2. It is clear that the values of ${}^1\Delta_0 + {}^3\Delta_0$ are constant, whereas the magnitudes of both $\Delta_{eq} + {}^3\Delta_0$ from the ^{13}C spectrum and $\Delta_{eq} + {}^4\Delta_0$ from the ^{1}H spectrum increase with decreasing temperature. A temperature dependence of $\Delta_{eq} + {}^3\Delta_0$ was also observed in pyridine-d_5, increasing from +558 ppb at 25 °C to +662 ppb at −39 °C.

Discussion

Configurational Interconversion. In the solid state the configuration of 2-phenylmalonaldehyde enol is (E)-anti, with the two oxygens as far apart as possible and with an intermolecular hydrogen bond.[35] In solution in $CDCl_3$ and C_6D_6 the configuration changes to (Z)-syn, with the two oxygens in close proximity, to permit intramolecular hydrogen bonding. The downfield chemical shift of the OH, at 14.5 ppm, is consistent with a strong intramolecular hydrogen bond.

Generally, the activation energy for C═C rotation is so high that interconversion between (E)-anti and (Z)-syn configurations

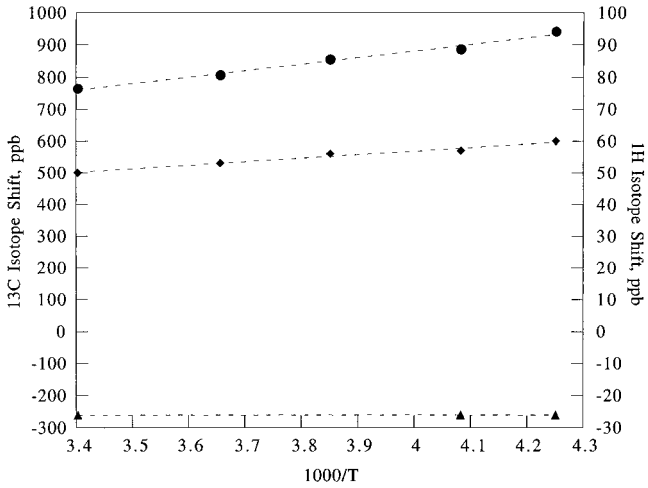

Figure 2. Temperature dependence of isotope shifts for 2-phenylmalonaldehyde: ^{13}C $\Delta_{eq} + {}^3\Delta_0$ (○), ^{13}C ${}^1\Delta_0 + {}^3\Delta_0$ (△), ^{1}H $\Delta_{eq} + {}^4\Delta_0$ (◇).

is very slow at room temperature. Therefore, it is not obvious how the solid-state (E)-anti form dissolves to produce the (Z)-syn. We propose that this change occurs via the anion (or possibly the cation) by proton exchange catalyzed by trace base (or acid). The partial double bond should facilitate rotation, as seen with the anion of acetylacetone, where the activation energy is only 13.7 kcal/mol.[36] The line broadening in DMSO-d_6 or pyridine-d_5 might be due to the slow configurational exchange. Since DMSO-d_6 and pyridine-d_5 are more polar and more basic solvents, there may be a small amount of (E)-anti anion in an equilibrium that is slow on an NMR time scale. The line broadening is temperature dependent, which was also observed by Imashiro and co-workers but attributed to proton exchange with solvent molecules.[31]

Isotope Shifts and Hydrogen-Bond Symmetry. The NMR method of isotopic perturbation of equilibrium demonstrates well how to judge the symmetry of the intramolecular hydrogen bond of the enol of 2-phenylmalonaldehyde. The experimental value for the isotope shift in the ^{13}C NMR spectrum, 0.7 ppm, is close to the expected 1 ppm from eq 2. Likewise, the ^{1}H isotope shift of 50 ppb is reasonably close to the 0.1 ppm expected. This is direct evidence that the H-bond of 2-phenylmalonaldehyde enol is asymmetric, with two equilibrating tautomers.

The hydrogen bond of 2-phenylmalonaldehyde enol is also asymmetric in pyridine-d_5 as judged from the large positive isotope shift and its temperature dependence. The isotope shift $\Delta_{eq} + {}^3\Delta_0$ is significantly smaller than in $CDCl_3$. This difference is probably due to an averaging over the enol and its anionic conjugate base, $PhC(CHO)_2^-$. Since this latter is a symmetric resonance hybrid, without any Δ_{eq}, the net isotope shift is reduced.

The isotope shifts are observed to be greater at lower temperature, indicating that they are a consequence of a chemical equilibrium governed by a free-energy difference, rather than something intrinsic. This is conclusive evidence for a mixture of two species, rather than a single symmetric one.

The temperature dependence provides quantitative information about the equilibrium. Since eq 2 expresses the relation between Δ_{eq} and K, and since the temperature dependence of K is given as $\exp(-\Delta G°/RT)$, series expansion of the exponential and differentiation leads to eq 3,

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$$d\Delta_{eq}/d(1/T) = D\Delta H°/4R \quad (3)$$

where $\Delta H°$ is the enthalpy difference between the two tautomers. The slope of $\Delta_{eq}+{}^3\Delta_0$ in Figure 2 is 202 ppb-K. If the chemical shift difference D is taken as 20 ppm, $\Delta H°$ is 27 cm^{-1}. The slight discrepancy between this value and the 37 cm^{-1} expected above is probably due to the hydrogen bonding, which reduces D relative to the aldehyde and enol model. Likewise, the ^1H isotope shift of +50 ppb at 20.7 °C or +60 ppb at −37.9 °C is only slightly lower than the 0.1 ppm estimated above. The overestimate presumably arises because the CH frequencies of aldehyde and enol, as observed,[37] do not differ by as much as those above.

The intercept of Figure 2 is the intrinsic shift Δ_0 since Δ_{eq} must approach 0 as T approaches infinity. Thus, the ^{13}C $^3\Delta_0$ is estimated as +74 ± 55 ppb, with a large uncertainty. The positive $^3\Delta_0$ is unusual but has precedent.[38] From the observed $^1\Delta_0 + {}^3\Delta_0$ in Table 1 and this $^3\Delta_0$, $^1\Delta_0$ is found to be −335 ppb, which is reasonable.[29] The isotope shift Δ_{eq} is then +691 ppb at 20.7 °C and +867 ppb at −37.9 °C. These values are too large to be intrinsic. Moreover, they are positive (downfield), which is quite unusual. Therefore, these isotope shifts are unequivocal evidence for an asymmetric hydrogen bond.

It is necessary to dispel the thought that the isotopic perturbation itself creates the asymmetry that we have inferred. There are actually two such perturbations, not only the deuterium substitution but also the rare ^{13}C for NMR spectroscopy. However, it follows from the Born−Oppenheimer approximation[39] that the potential-energy surface governing nuclear motion, whether single-well or double-well, is independent of nuclear mass. Therefore, isotopic substitution can distinguish these.

We therefore assert unequivocally that 2-phenylmalonaldehyde in solution is asymmetric, with hydrogen motion described by a double-well potential. Might this be single-well in the gas phase, with the double-well potential imposed by the disorder of solvation, as for monoanions of dicarboxylates?[26] We consider this unlikely, since malondialdehyde is a neutral species and thus not strongly solvated. Our method does permit the conclusion of a double-well potential but without providing any estimate of the height of the barrier. However, we have no reason to doubt the upper limit of 6 kcal/mol or a lifetime of picoseconds for tautomeric interconversion.[12,40]

Conclusions

The NMR method of isotopic perturbation of equilibrium can give a clear answer to the question of whether a hydrogen bond is symmetric or asymmetric. This method is applied to the enol of 2-phenylmalonaldehyde and unequivocally shows that in organic solvents its hydrogen bond is asymmetric, with a double-well potential.

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