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Hydrogen-Bond Symmetry in Difluoromaleate Monoanion

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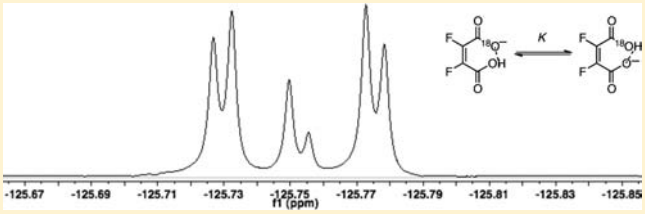
Supporting Information

ABSTRACT: The symmetry of the hydrogen bond in hydrogen difluoromaleate monoanion is probed by X-ray crystallography and by the NMR method of isotopic perturbation in water, in two aprotic organic solvents, and in an isotropic liquid crystal. The X-ray crystal structure of potassium hydrogen difluoromaleate shows a remarkably short O−O distance of 2.41 Å and equal O−H distances of 1.206 Å, consistent with a strong and symmetric hydrogen bond. Incorporation of ^{18}O into one carboxyl group allows investigation of the symmetry of the H-bond in solution by the method of isotopic perturbation. The ^{19}F NMR spectra of the mono-^{18}O-substituted monoanion in water, CD_2Cl_2, and CD_3CN show an AB spin system, corresponding to fluorines in different environments. The difference is attributed to the perturbation of the acidity of a carboxylic acid by ^{18}O, not to the mere presence of the ^{18}O, because the mono-^{18}O dianion shows equivalent fluorines. Therefore, it is concluded that the monoanion exists as an equilibrating pair of interconverting tautomers and not as a single symmetric structure not only in water but also in organic solvents. However, in the isotropic liquid crystal phase of 4-cyanophenyl 4-heptylbenzoate, tetrabutylammonium hydrogen difluoromaleate-^{18}O shows equivalent fluorines, consistent with a single symmetric structure. These results support earlier studies, which suggested that the symmetry of hydrogen bonds can be determined by the local environment.



INTRODUCTION

Hydrogen-Bond Symmetry. A fundamental structural question is whether the hydrogen in a hydrogen bond (H-bond) between two donor atoms of equal basicity is centered between the two donors ("symmetric" H-bond) or is closer to one and jumping between them.[1] This is the distinction between a single-well and a double-well potential. Centered hydrogens are associated with short heavy-atom distances, and with "strong" H-bonds, although these associations have been questioned.[2] Centered hydrogens can be observed in crystalline phases, but they are elusive in solution, both protic and aprotic.[3] Previous studies suggested that the symmetry of the H-bonds can be disrupted by the instantaneous local solvation environment,[4] which is disordered, leading to solvatomers (isomers that differ in solvation).[5] The disorder of solvation renders the two donor atoms instantaneously unequal, whereupon the hydrogen attaches to the less well solvated donor.[6]

Recently, the results of those studies were reinterpreted in terms of the desymmetrizing effect of isotopic substitution on an otherwise symmetrical potential-energy surface.[7] The desymmetrization arises from anharmonic coupling between a desymmetrizing vibrational mode and other modes whose zero-point energies are isotope-dependent. Calculated trajectories of hydrogen motion then lead to H-bond asymmetries and time-averaged NMR chemical shifts for the ipso carbon of phthalate monoanion that are comparable to experimental ones, at least in organic solvents. Therefore, it was concluded that the asymmetry of an aprotic organic solvent environment is not strong enough to disrupt the symmetry of the H-bond, although such a disruption was accepted for aqueous solution.

Liquid Crystals. If the difference in H-bond symmetry is due to the difference between the order of a crystal and the disorder of solution, an intermediate environment might be a good test of this interpretation. Such an intermediate environment can be realized by dissolving the solute molecule to be studied in a liquid crystalline solvent.[8] Among different types of liquid crystals, nematic phases are the least ordered and the most mobile. A nematic phase is composed of rod-shaped molecules that are aligned parallel to each other and that orient solute molecules relative to their long axis.[9] After some exploration, 4-cyanophenyl 4-heptylbenzoate was chosen for this study. It is a nematic liquid crystal between 40 and 53 °C, and becomes isotropic above 53 °C.[10]

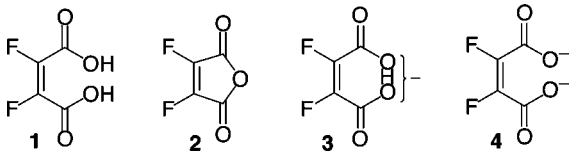
For the purposes of this study, the isotropic phase of this material was used at 55 °C. It avoids the dipolar couplings that appear in the nematic phase.[11] Although the long-range order of the nematic phase is absent (as is the alignment relative to the applied magnetic field in an NMR spectrometer), the isotropic phase retains short-range order.[12] The hope of this study is that the short-range order is sufficient that the two carboxyls are in the same environment, similar to the situation in a crystal.

To avoid submerging the NMR signals of the substrate under the dominant signals of the ^1H or ^{13}C nuclei of a liquid crystal solvent, and to avoid the necessity of decoupling ^1H, ^{19}F NMR is especially convenient. Besides, ^{19}F NMR chemical shifts are quite sensitive to chemical environment, a property that was

Received: December 27, 2011
Published: April 21, 2012

   dx.doi.org/10.1021/ja2117848 | J. Am. Chem. Soc. 2012, 134, 7766−7772

useful for measuring secondary deuterium isotope effects.[13] Therefore, difluoromaleic acid (**1**) has been chosen for this study. It has an exceedingly simple NMR spectrum. The availability of the anhydride (**2**) makes possible the incorporation of one ^{18}O into the diacid,[14] for the purpose of isotopic perturbation.

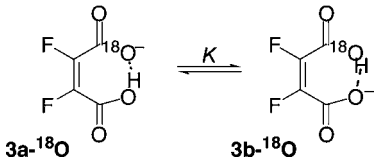


Isotope Shifts and Isotopic Perturbation of Equilibrium. Asymmetric structures can be distinguished experimentally from symmetric ones by the NMR method of isotopic perturbation. This was originally applied to carbocations,[15] and it succeeds even when signals are coalesced by rapid exchange. The method depends on measuring the isotope shift (isotope effect on chemical shift) $^{n}\Delta$, due to a heavier isotope n atoms away from the reporter nucleus (eq 1).[16] There are two contributions to the observed isotope shift (eq 2), an intrinsic shift, Δ_0, owing simply to the presence of an isotope, and a shift, Δ_{eq}, induced by isotopic perturbation of an equilibrium.

$$^{n}\Delta = \delta_{heavy} - \delta_{light} \quad (1)$$

$$\Delta_{obs} = \Delta_0 + \Delta_{eq} \quad (2)$$

Our task is to distinguish whether difluoromaleate monoanion has a centered hydrogen (**3**) or is a mixture of two tautomers, with an asymmetric H-bond between the OH and the O^-. To do so, we use mono-^{18}O-substituted difluoromaleate monoanion. Either this has a centered hydrogen (**3**-^{18}**O**) or it is an equilibrium mixture of two tautomers, **3a**-^{18}**O** and **3b**-^{18}**O**. (The presence of additional isotopomers with ^{18}O in the carbonyl instead of in the H-bond halves the observed isotope effect but can be ignored.). Owing to vibrational frequencies and zero-point energies, an ^{18}O-labeled carboxylic acid is ~1% less acidic than an ordinary carboxylic acid.[17] Consequently, the tautomeric equilibrium is shifted slightly toward **3b**-^{18}**O**, with an equilibrium constant $K \sim 1.01$.



This perturbation of the equilibrium by an isotope then results in a chemical-shift inequivalence between the two fluorines. In tautomer **3a**-^{18}**O**, the upper F is adjacent to a carboxylate, and the lower F is adjacent to a carboxylic acid. In tautomer **3b**-^{18}**O**, these are reversed. If the ^{19}F NMR chemical shift of a fluorine adjacent to a carboxylate is designated as $\delta_{CO_2^-}$ and the chemical shift of a fluorine adjacent to a carboxylic acid group as δ_{COOH}, then the chemical shifts of the upper and lower fluorines are $X_{3a}\delta_{CO_2^-} + X_{3b}\delta_{COOH}$ and $X_{3a}\delta_{COOH} + X_{3b}\delta_{CO_2^-}$, respectively, where X_{3a} and X_{3b} are mole fractions. The difference between these two chemical shifts is then an equilibrium isotope shift, given by eq 3, where $D = \delta_{COOH} - \delta_{CO_2^-}$.[18] Strictly, this isotope shift is $^{3}\Delta - {}^{4}\Delta$, because both fluorines are subject to the influence of the ^{18}O, but their relationship to the ^{18}O differs. The parameters δ_{COOH} and $\delta_{CO_2^-}$ can be estimated from the ^{19}F NMR chemical shifts of difluoromaleic acid **1** (or less reliably of the monoanion **3**) and difluoromaleate dianion **4**, respectively. These are very crude estimates because fluorine adjacent to carboxylate is also opposite to a carboxylic acid and vice versa, and because the H-bond between the OH and the O^- affects the chemical shifts. It is also necessary to measure Δ_0, the intrinsic isotope shift due to the proximity to ^{18}O, but this can be modeled by diacid **1** or dianion **4**. Nevertheless, the signature of a tautomeric mixture is a difference between the chemical shifts of the upper fluorine, adjacent to ^{18}O, and the lower fluorine, adjacent to ^{16}O. Indeed, such a difference was seen in the ^{13}C NMR spectrum of aqueous mono-^{18}O-labeled succinic acid,[19] and the dipolar couplings of this monoanion in a liquid crystal were measured and used to evaluate the conformation.[20]

$$\Delta_{eq} = \frac{K-1}{K+1}D \quad (3)$$

We therefore have undertaken a study of the symmetry of the H-bond in difluoromaleate monoanion by X-ray diffraction in a crystalline solid and by the method of ^{18}O-induced isotopic perturbation of ^{19}F NMR chemical shifts in water, in two organic solvents, and in a nematic liquid crystal as solvent. We now report that this H-bond is symmetric in the crystal and in the isotropic liquid crystal, but not in aqueous or organic solution.

EXPERIMENTAL SECTION

Synthesis. Difluoromaleic anhydride (**2**) was obtained by the literature procedure, starting from 1,1,2-trichloro-2,3,3-trifluorocyclobutane or from trifluorosuccinic acid.[21]

Hydrolysis of anhydride **2** in water produced difluoromaleic acid (**1**), free of the stereoisomeric fumaric acid. Incorporation of ^{18}O could be achieved by stirring 0.1−0.2 mmol of anhydride with 10−15 μL of $H_2{}^{18}O$ plus 50−100 μL of tetrahydrofuran for solubility. The extent of mono-^{18}O-labeling was monitored by mass spectrometry, and a reaction time of 2 h at room temperature was found suitable. At longer times, further equilibration occurred, and additional ^{18}O could be incorporated. Alternatively, to favor a high yield of mono-^{18}O-acid, the anhydride was hydrolyzed in $H_2{}^{18}O$ containing >2 equiv of $Na^{16}OH$, such that the ^{18}O content was ~85%, to produce the dianion (**4**-^{18}**O**). The excess hydroxide is necessary because with only one equivalent the resulting monoanion would neutralize another equivalent of hydroxide.

Incorporation of ^{18}O was confirmed by mass spectrometry. The diacid isolated from one reaction of the anhydride with $H_2{}^{18}O$ was 1:1 unlabeled and mono-^{18}O-labeled, plus a small amount of doubly labeled (Figure S1, Supporting Information). Diacid from another reaction was a 1:2 mixture (Figures S3, S4). Mass spectrometric analysis was unsuccessful for the nonvolatile dianion (**4**-^{18}**O**), even after conversion to the diacid, owing to ^{18}O exchange in 20% H_2SO_4. A more reliable measure of the ^{18}O content is 85%, from intensities in the ^{19}F NMR spectrum shown and analyzed below.

The potassium salt of the unlabeled monoanion (**3**) was generated by treating the diacid with 1 equiv of potassium hydroxide. Potassium hydrogen difluoromaleate was then isolated by concentrating the solution to dryness and recrystallizing the salt from water. The 50%-labeled diacid served as a sample of the monoanion because this is such a strong acid that it is fully ionized in dilute aqueous solution. The sodium salt of the mono-^{18}O-difluoromaleate monoanion was obtained from the solution of the dianion by adding small amounts of acetic acid until the chemical shifts remained constant. The tetrabutylammonium salt of the partially labeled monoanion (1:1 or 1:2 **3** + **3**-^{18}**O**) was prepared by dissolving the partially labeled diacid in water containing 1 equiv of tetrabutylammonium hydroxide and removing the water under high vacuum to give a white solid. To confirm that the sample was the monoanion, the intensity of the ^{1}H

dx.doi.org/10.1021/ja2117848 | J. Am. Chem. Soc. 2012, 134, 7766−7772

signal at 20.08 ppm in CD_3CN was compared with the intensities of the n-butyl signals.

The tetrabutylammonium salt of 1:2 **3** + **3**-^{18}O was dissolved in 4-cyanophenyl 4-heptylbenzoate to produce a 2−3 wt % solution. The sample was homogenized by repeated heating to the isotropic phase and then cooling back to the nematic phase, with physical shaking or vortex mixing. The ^{19}F NMR spectrum was then obtained for the isotropic phase.

NMR Spectroscopy. NMR spectra were recorded at 18 °C on a JEOL-500 FT-NMR spectrometer (470 MHz ^{19}F). In aqueous solutions, $NaBF_4$ was used as internal standard, with two sets of peaks in a 1:4 ratio at −151.04 ppm (br) and −151.10 ppm (q).[22] In organic solvents and in liquid crystal, $CFCl_3$ (0 ppm) was used as internal standard.

RESULTS

Crystal Structure. Crystallographic data for potassium hydrogen difluoromaleate are summarized in Table S1. The structure of hydrogen difluoromaleate monoanion (**3**) within a crystal of potassium hydrogen difluoromaleate is shown in Figure 1. According to the X-ray data, the O−O distance in the

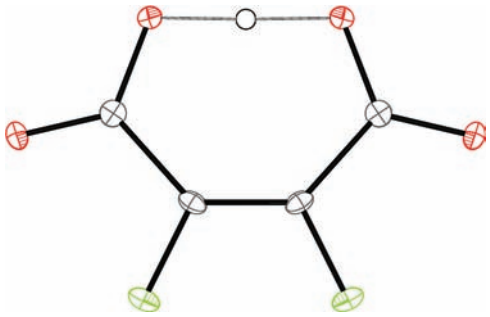


Figure 1. X-ray structure of hydrogen difluoromaleate monoanion in the crystal of its potassium salt.

hydrogen difluoromaleate monoanion is 2.41 Å, and the hydrogen is placed exactly in the middle of two oxygen atoms, with equal O−H distances of 1.206 Å. The centering of the hydrogen is a consequence of its position on a crystallographic mirror plane. The alternative of a hydrogen disordered across the mirror plane is less likely, in view of the neutron-diffraction data that exclude this possibility for the similar salt, potassium hydrogen chloromaleate.[23]

Chemical Shifts. The ^{19}F NMR chemical shift of the difluoromaleate dianion (**4**) could be obtained from the product of hydrolysis of the anhydride in excess NaOH. The chemical shift of the monoanion (**3**) could be obtained from the aqueous solution of the diacid because this is such a strong acid that it is fully ionized in dilute aqueous solution. The chemical shift of difluoromaleic acid (**1**) could be obtained only in 20% H_2SO_4, where it is likely that the chemical shift of the standard has changed, inasmuch as the chemical shift of BF_4^- is quite sensitive to solvent.[24] Table 1 lists ^{19}F chemical shifts for

Table 1. ^{19}F Chemical Shifts (ppm) for Difluoromaleic Acid (1), Its Monoanion (3), and Its Dianion (4)

1	3	4
−126.43	−125.26	−139.60

difluoromaleic acid and its conjugate bases in aqueous media. As expected, ^{19}F chemical shifts are quite sensitive to the state of protonation, especially for the dianion. However, the apparent irregularity with proton number may be due to uncertainty in the chemical shift of the BF_4^- standard.

If the parameters δ_{COOH} and $\delta_{CO_2^-}$ are estimated from the ^{19}F NMR chemical shifts of **1** and **4**, respectively, and if the equilibrium constant between tautomers **3a**-^{18}**O** and **3b**-^{18}**O** is taken as 1.01, then eq 3 predicts a chemical-shift difference between the two fluorines of mono-^{18}O-difluoromaleate monoanion of 0.07 ppm. Of course, this is a crude estimate, inasmuch as the models for *K* and *D* lack the H-bond, which is likely to decrease the values of these parameters. Nevertheless, the sensitivity of ^{19}F chemical shifts to the state of protonation is what makes this experiment feasible.

^{19}F NMR Spectra and Signal Assignments. The NMR spectrum of mono-^{18}O-labeled difluoromaleate dianion (**4**-^{18}**O**) in D_2O is shown in Figure S2. The NMR spectrum of mono-^{18}O-labeled difluoromaleate monoanion (**3**-^{18}**O**) in D_2O is shown in Figure 2. For comparison, the NMR spectrum of a 1:2 mixture of unlabeled and mono-^{18}O-labeled difluoromaleate monoanion in D_2O is shown in Figure S3. The NMR spectrum of the tetrabutylammonium salt of a 1:2 mixture of unlabeled and mono-^{18}O-labeled difluoromaleate monoanion in CH_3CN is shown in Figure 3. The NMR spectrum of the tetrabutylammonium salt of a 2:1 mixture of mono-^{18}O-labeled and unlabeled difluoromaleate monoanion in CD_2Cl_2 is shown in Figure S4. The NMR spectrum at 55 °C of a 1:2 mixture of unlabeled and mono-^{18}O-labeled tetrabutylammonium hydrogen difluoromaleate-^{18}O (**3** + **3**-^{18}**O**) in 4-cyanophenyl 4-heptylbenzoate liquid crystal as solvent is shown in Figure 4.

The simplest ^{19}F NMR spectra are those of the mono-^{18}O-labeled difluoromaleate dianion in D_2O (Figure S2) and of the tetrabutylammonium salt of the partially ^{18}O-labeled monoanion in 4-cyanophenyl 4-heptylbenzoate liquid crystal (Figure 4). Those spectra show only singlets. The diacid (**1**), produced in 20% H_2SO_4 from the ^{18}O-labeled difluoromaleic acid, also showed a singlet, but it is likely that the H_2SO_4 catalyzed ^{18}O exchange with solvent, so that this spectrum is inconclusive.

The most complicated spectra are those of the mono-^{18}O-labeled difluoromaleate monoanion in D_2O (Figure 2) and of the 2:1 mixture of mono-^{18}O-labeled and unlabeled difluoromaleate monoanion in D_2O (Figure S3). Each of them is six lines. Because they differ only in the extent of ^{18}O incorporation, comparison permits the strong signals at 125.263 ppm to be assigned to unlabeled difluoromaleate monoanion (**3**). Unlabeled material is a necessary consequence of the presence of $H_2{}^{16}O$ in the hydrolysis.

The four ^{19}F NMR signals at −125.240, −125.245, −125.286, and −125.291 in Figure 2, two upfield and two downfield of the signal due to **3**, can then be recognized as a pair of doublets constituting an AB spin system, arising from the mono-^{18}O-labeled difluoromaleate monoanion (**3**-^{18}**O**). Likewise, the outer four signals in Figure S3 are an AB pattern. The chemical-shift separation between the two fluorines is 0.046 ppm, and the scalar coupling constant ^3J between them is 2.4 Hz. This coupling constant is unusually small, even for cis fluorines,[25] but a 5-Hz coupling constant was observed for the monobenzyl ester of difluoromaleic acid.[26] The weak signal at −125.268 ppm in Figure 2 or at −125.272 ppm in Figure S3 can then be assigned to doubly ^{18}O-labeled difluoromaleate monoanion (**3**-^{18}**O**$_2$), with one ^{18}O in each carboxyl. Incorporation of a second ^{18}O **is a** consequence of the further equilibration of the acid formed from hydrolysis of the anhydride in $H_2{}^{18}O$. However, incorporation of a second ^{18}O into the dianion formed by hydrolysis of the anhydride with

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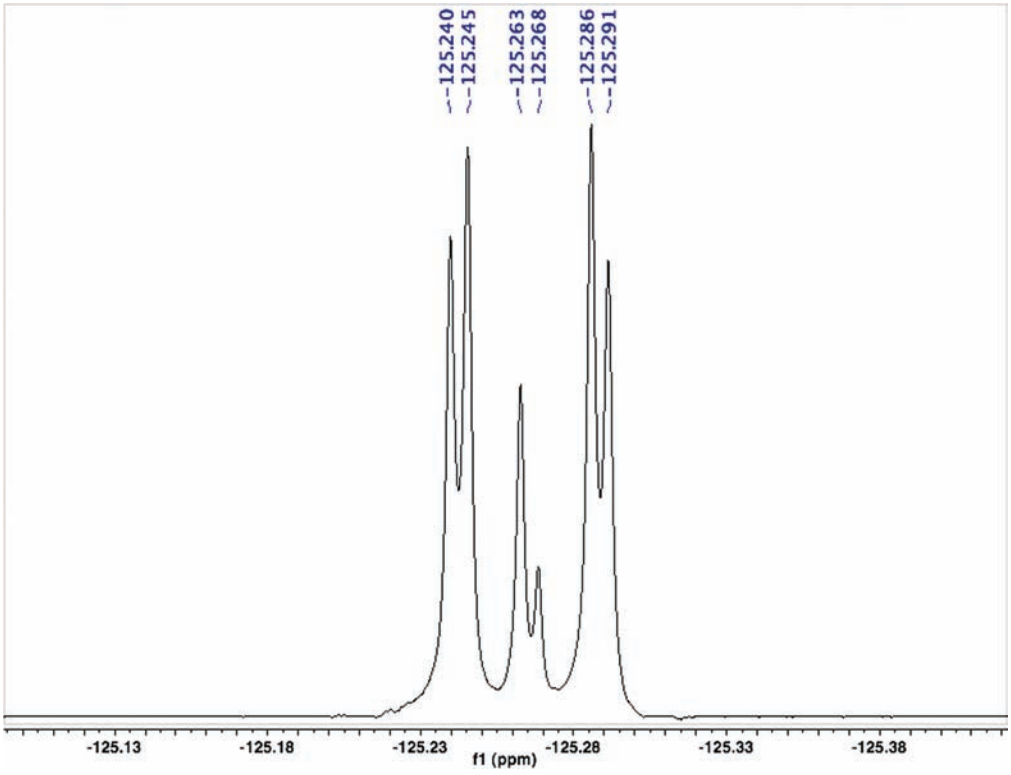

Figure 2. ^{19}F NMR spectrum of mono-^{18}O-labeled difluoromaleate monoanion (**3**-^{18}**O**) in D_2O.

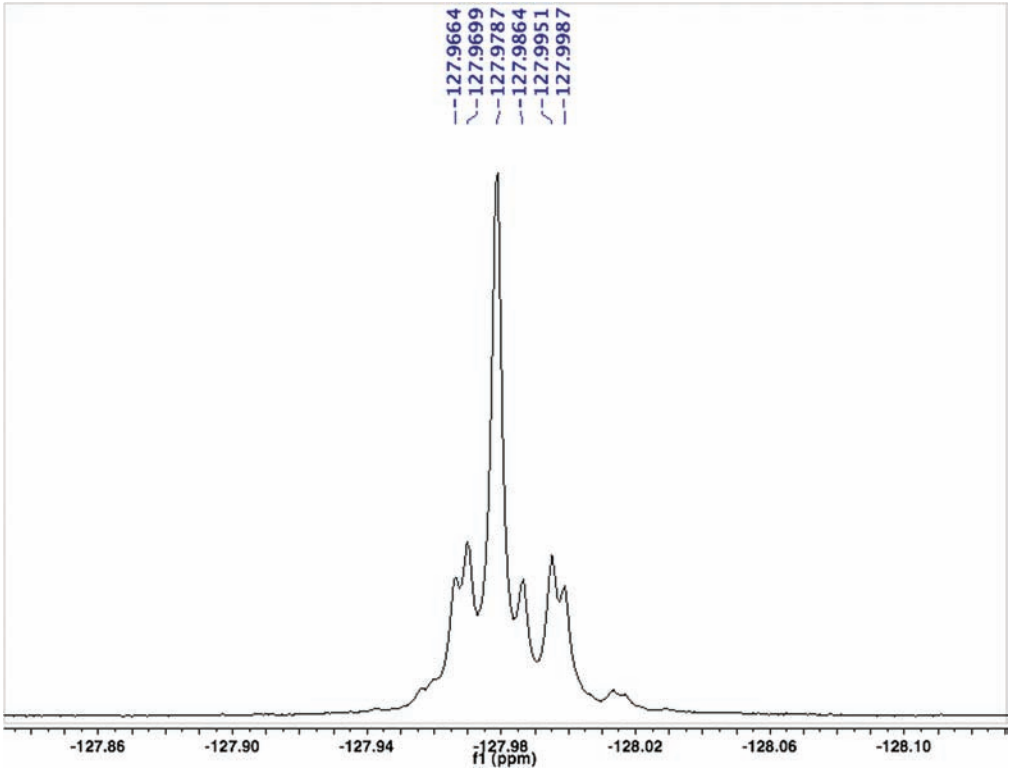

Figure 3. ^{19}F NMR spectrum of the tetrabutylammonium salt of a 1:1 mixture of unlabeled and mono-^{18}O-labeled difluoromaleate monoanion (**3** + **3**-^{18}**O**) in CD_3CN.

NaOH is more problematic. The mechanism for this incorporation is proposed below.

The ^{19}F NMR spectrum of the ^{18}O-labeled monoanion in CH_3CN (Figure 3) also shows an AB pattern, although the signal for unlabeled **3** is more prominent. The coupling constant is still 2 Hz, but the chemical-shift separation is lower, 0.029 ppm. In CD_2Cl_2 (Figure S4), the AB pattern is still present, with the same lower chemical-shift separation, along

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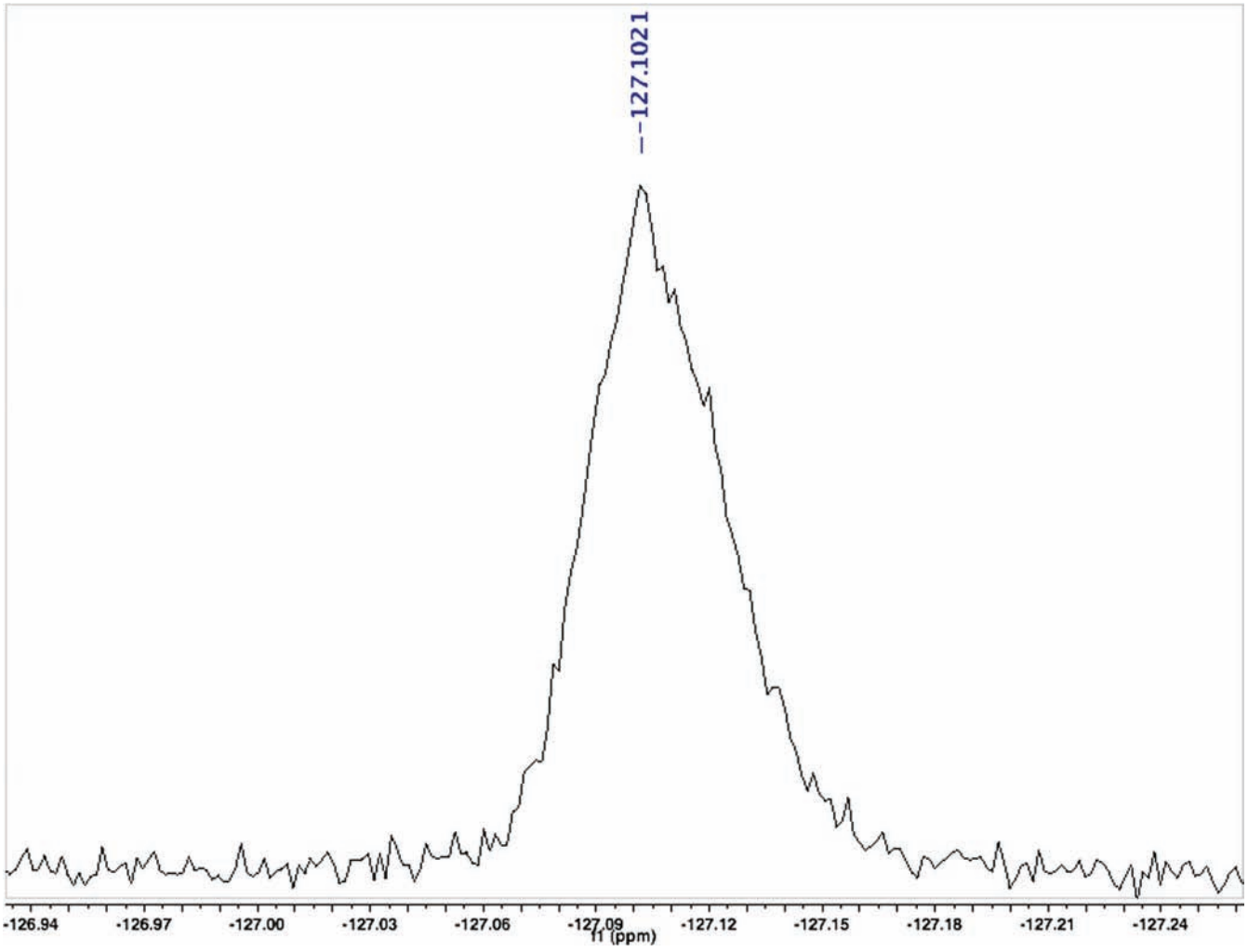


Figure 4. ^{19}F NMR spectrum at 55 °C of a 1:2 mixture of tetrabutylammonium hydrogen difluoromaleate and difluoromaleate-^{18}O (**3** + **3**-^{18}**O**) in 4-cyanophenyl 4-heptylbenzoate isotropic liquid crystal.

with a prominent signal for unlabeled **3**, but the coupling constant is not resolvable.

Isotope Shifts. The ^{19}F NMR singlet for the mono-^{18}O-labeled difluoromaleate dianion (**4**-^{18}**O**) (Figure S2) shows that there is no resolvable intrinsic isotope shift Δ_0 due to ^{18}O substitution per se. The two middle ^{19}F NMR peaks of the difluoromaleate monoanion in Figures 2 and S3, due to **3** and **3**-$^{18}O_2$, are offset slightly upfield and downfield relative to the center of the AB pattern of **3**-^{18}O. This offset represents a very small intrinsic isotope shift Δ_0 of 0.0025 ppm per ^{18}O, and it seems to be the same (or unresolvably different) regardless of whether the ^{18}O is separated from the ^{19}F by 3 or 4 bonds.

The key result is the AB pattern for the ^{18}O-labeled difluoromaleate monoanion (**3**-^{18}O) in D_2O (Figure 2), in CD_3CN (Figure 3), and in CD_2Cl_2 (Figure S3). *The two fluorines are inequivalent, with different chemical shifts, and they can split each other.* The chemical-shift separations are 0.046, 0.029, and 0.028 ppm, respectively. These are not due to an intrinsic isotope shift Δ_0 because no Δ_0 was resolvable in the dianion (**4**). Moreover, if these were intrinsic, they would be the difference between three-bond and four-bond isotope shifts, whereas each of these in the monoanion is only 0.0025 ppm per ^{18}O and the same for $^3\Delta_0$ and $^4\Delta_0$, so that the difference would be far less than what is observed. Therefore, these are equilibrium isotope shifts, Δ_{eq}, due to perturbation of an equilibrium, as in eq 3.

Values of Δ_{eq} are summarized in Table 2. According to the estimate based on eq 3, Δ_{eq} ought to be >0. This means that

Table 2. Equilibrium ^{19}F Isotope Shifts (ppm) for Mono-^{18}O-Labeled Difluoromaleate Monoanion (3-^{18}O)

solvent	Δ_{eq}, ppm
D_2O	0.046
CD_3CN	0.029
CD_2Cl_2	0.028

the fluorine adjacent to ^{18}O is predicted to be downfield of the fluorine adjacent to ^{16}O. However, it is not possible to verify this because the fluorines cannot be assigned relative to the position of the ^{18}O.

A further result is that no isotope shift is seen in Figure 4 for the tetrabutylammonium salt of difluoromaleate-^{18}O monoanion in 4-cyanophenyl 4-heptylbenzoate liquid crystal solvent at 55 °C. Although the signal is broader than the signals in isotropic solutions, it is a singlet, with no sign of separation into an AB multiplet. For comparison, Figure S5 is an adaptation of Figure S4, with the same 1:2 composition as that of Figure 4, but with an additional line-broadening of 6 Hz to match the

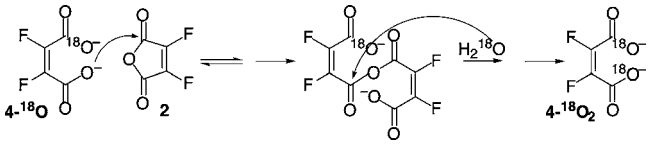
dx.doi.org/10.1021/ja2117848 | J. Am. Chem. Soc. 2012, 134, 7766–7772

line-width of Figure 4. This is graphic evidence that difluoromaleate-^{18}O monoanion in liquid crystal does not display an AB pattern within the broadened signal.

DISCUSSION

Mechanism for Incorporation of Two ^{18}O into Difluoromaleate Dianion (4). The weakest signals in Figure 2 and Figure S3 are assigned to doubly ^{18}O-labeled difluoromaleate monoanion (**3-^{18}O$_2$**), with one ^{18}O in each carboxyl group. The second ^{18}O in the sample of Figure S3 is a consequence of the further equilibration of the acid formed from hydrolysis of the anhydride in $H_2{}^{18}O$. However, the second ^{18}O in the sample of Figure 2 is more problematic because in excess NaOH the dianion ought to be inert to further exchange. Consequently, it is still necessary to account for the second ^{18}O, in order to justify the signal assignment. We propose the mechanism in Scheme 1 to account for this

Scheme 1. Mechanism for Incorporation of a Second ^{18}O into Difluoromaleate Dianion (4)



incorporation. It requires dianion **4** to be weakly competitive with OH^- as a nucleophile toward the anhydride (**2**), a reactivity that is not impossible.

It is also possible, although half as probable, for both ^{18}O to appear in the same carboxylate. Upon neutralization with acetic acid, this isotopomer would show double the Δ_{eq} of the mono-^{18}O-labeled difluoromaleate monoanion (**3-^{18}O**) and would appear as an AB pattern with twice the separation of the prominent AB pattern in Figure 2 and with half the total intensity of the weak singlet of **3-^{18}O**. Some samples did show this additional AB pattern.

H-Bond Symmetry in Crystal. According to the X-ray structure in Figure 1, the O−O distance in difluoromaleate monoanion (**3**) is 2.41 Å, which qualifies it as having a "short" H-bond. Moreover, structure refinement places the hydrogen exactly in the middle of the two oxygen atoms, with equal O−H distances of 1.206 Å. These distances fit exactly the correlation of OHO distances in so-called "strong" H-bonds, as corrected for zero-point vibrational effects.[27] Therefore, in this salt, where the crystalline environment appears to be symmetric, the H-bond of the monoanion is symmetric. This contrasts with the X-ray structures of several salts of (±)-α,α′-di-*tert*-butylsuccinate monoanion, where the hydrogen is closer to one oxygen than to the other.[28]

Isotope Shifts and H-Bond Symmetry. Not only in aqueous solution but also in the aprotic organic solvents CD_3CN and CD_2Cl_2 the ^{19}F NMR spectrum of difluoromaleate monoanion (**3-^{18}O**) exhibits an AB spin system. The ^{18}O renders the two fluorines inequivalent, with chemical shifts that differ by 0.046 or 0.028 ppm. This is adequately close to the 0.07 ppm predicted by eq 3, which is recognized as an overestimate, owing to the crudeness of the models for evaluating *K* and *D*. The chemical-shift difference is not merely due to the presence of the ^{18}O, because it is not seen in the dianion (**4-^{18}O**) or in the diacid (**1-^{18}O**), although the spectrum of the latter is inconclusive, owing to ^{18}O exchange with solvent. This chemical-shift difference is thus an isotope shift attributable to the perturbation of an equilibrium by the isotopic label and indicates that the H-bonded monoanion exists as a pair of tautomeric structures. Its H-bond is not symmetric.

In contrast, in the isotropic phase of the liquid crystal 4-cyanophenyl 4-heptylbenzoate as solvent, the tetrabutylammonium salt of hydrogen difluoromaleate-^{18}O (**3-^{18}O**) appears as a single peak, albeit broadened, and does not show any isotope shift. In principle, this result could be due to a smaller *D* (eq 3) than in the other two aprotic organic solvents. However, the near identity of the observed isotope shifts in those two solvents (Table 2) suggests that a similar AB pattern would have been seen in this liquid crystal. Subject to this uncertainty in *D*, the absence of an isotope shift indicates that in this environment the monoanion exists as a single structure, with a symmetric H-bond. We conclude that the partial ordering of this isotropic liquid crystal is sufficiently close to the order in a crystal, where the H-bond is also symmetric.

These results are evidence that the symmetry of H-bonds can be determined by the disorder of the instantaneous solvation environment. They counter the conclusions that the asymmetry of an aprotic organic solvent environment is not strong enough to disrupt the symmetry of the H-bond and that observed isotope shifts are due to isotopic desymmetrization on an otherwise symmetrical potential-energy surface.[7] That isotopic desymmetrization ought to have been the same in a liquid crystal as in an aprotic organic solvent. Yet the observed isotope shift disappears in the liquid crystal, consistent with an H-bond that has become symmetric because the partial ordering of this liquid crystal allows the two donor oxygens to be in the same environment.

Would the calculated trajectories of hydrogen motion on a symmetrical potential-energy surface again lead to unequal time-averaged NMR chemical shifts for difluoromaleate-^{18}O monoanion (**3-^{18}O**),[7] as are seen experimentally in Table 2? Moreover, would the calculated isotope shifts depend on solvent? Here the distance between the reporter nucleus and the isotope is one bond greater than that for the ipso carbon in phthalic acid. This is a challenge to computation.

CONCLUSIONS

The short O−O distance of 2.41 Å and equal O−H distances in the X-ray structure of potassium hydrogen difluoromaleate (K^+**3**) support a symmetric, short, H-bond in the crystal. The ^{19}F NMR spectra of the difluoromaleate-^{18}O monoanion (**3-^{18}O**) in water and in two aprotic organic solvents show an AB pattern, indicating that the two fluorines are inequivalent, with different NMR chemical shifts. The inequivalence is not seen in the diacid (**1-^{18}O**), so it is not due simply to the presence of ^{18}O. Instead the chemical-shift difference is attributed to perturbation of the acidity constant of a carboxylic acid by ^{18}O substitution. Therefore, hydrogen difluoromaleate monoanion **3** exists in solution as a pair of interconverting tautomers rather than as a single symmetric structure. However, the absence of any isotope shift for **3** in 4-cyanophenyl 4-heptylbenzoate is taken as evidence for a symmetric H-bond in this isotropic liquid crystal.

We therefore affirm the role of solvation in determining the symmetry of H-bonds. In water and in an aprotic organic solvent, the disorder of the local environment renders the two oxygens of **3** inequivalent, leading to an asymmetric H-bond. In contrast, the order in the crystal and in the isotropic liquid

dx.doi.org/10.1021/ja2117848 | J. Am. Chem. Soc. 2012, 134, 7766−7772

crystal allows the two donor oxygens to be in the same environment, permitting a symmetric H-bond.

■ ASSOCIATED CONTENT

Supporting Information

Instrumentation. Diffraction Techniques. Materials. Figure S1: mass spectrum of the diacid isolated from reaction of difluoromaleic anhydride (**2**) with $H_2{}^{18}O$. Figure S2: ^{19}F NMR spectrum of mono-^{18}O-labeled difluoromaleate dianion (**4**-^{18}O) in D_2O. Figure S3: ^{19}F NMR spectrum of a 1:2 mixture of unlabeled and mono-^{18}O-labeled difluoromaleate monoanion (**3** + **3**-^{18}O) in D_2O. Figure S4: ^{19}F NMR spectrum of the tetrabutylammonium salt of a 1:2 mixture of unlabeled and mono-^{18}O-labeled difluoromaleate monoanion (**3** + **3**-^{18}O) in CD_2Cl_2. Figure S5: Simulated ^{19}F NMR spectrum of a 1:2 mixture of unlabeled and mono-^{18}O-labeled difluoromaleate monoanion (**3** + **3**-^{18}O) in CD_2Cl_2, as in Figure S4, but with 6 Hz additional line broadening. Table S1 summarizing crystallographic data for potassium hydrogen difluoromaleate (K^+**3**). X-ray crystallographic file in CIF format for potassium hydrogen difluoromaleate. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by NSF Grant CHE07-42801 to CLP and by Instrumentation Grant CHE97-09183. A.L.R. gratefully acknowledges NSF Grant CHE-0634989 for purchase of the X-ray diffractometer.

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