Gas-phase CO has a ^{13}C chemical shift of 184 ppm, and it usually shifts downfield upon forming strong metal carbonyl complexes. In the case of weak complexes, however, upfield shifts are more common. Cu(I) carbonyl compounds[38–40] are among the weakest carbonyl complexes ever isolated, and the ^{13}C chemical shifts are in the vicinity of 172 ppm.[41] Zn carbonyls have not been investigated by NMR, but they are also expected to involve weak bonding.[42–44] We speculate that the 172-ppm resonance in Figure 9c is a mobile CO on the surface weakly interacting with either copper or zinc.

Summary

The in situ NMR studies presented here enable us to comment on the questions posed in the introduction.

1. Both CO_2 and CO interact with the catalyst surface at low pressure, but CO_2 is taken up more readily to form the carbonate species observed during methanol decomposition on $Cu/ZnO/Al_2O_3$. CO_2 is also formed when the carbonate species formed from methanol is heated to 523 K.

2. ^{13}C T_1 relaxation time measurements provide indirect evidence that paramagnetic Cu(0) atoms or clusters are dispersed into the oxide phase(s) in $Cu/ZnO/Al_2O_3$. This result does not disprove the claim that only the metal surface is important, but the possibility of a role for dispersed clusters and/or a synergistic effect between the metal and oxide phases should not be overlooked.

3. Pure ZnO, pure Al_2O_3, and ZnO/Al_2O_3 were shown to be fairly reactive in this contribution. A terminal methoxy group forms on Al_2O_3, and a bridging methoxy forms on ZnO. Formaldehyde readily disproportionated to formate and methoxy on any of the above catalysts. Copper was essential for the oxidation of formate to carbonate and the oxidation of methoxy to formaldehyde and/or formate at 523 K. Methanol synthesis clearly cannot proceed at 523 K without a metal component, but the oxide phases appear to be more reactive than necessary for a mere support role. Copper alone may be capable of catalyzing all of the steps in methanol synthesis; but under the in situ conditions used in this investigation, several adsorbed species are present on the ZnO and Al_2O_3 components.

4. The most significant results of the present study pertain to the reaction mechanism. The terminal bridging methoxy on Al_2O_3 and the bridging methoxy on ZnO form from either formaldehyde decomposition or methanol adsorption. Formaldehyde is too reactive to be detected as a free species using our in situ protocol, but the paraformaldehyde decomposition studies are consistent with formaldehyde having an intermediary role, possibly as a surface-bound dioxymethylene species. Formate is a ubiquitous intermediate in many catalysis reactions, and it was easily generated and thoroughly characterized in the present investigation. The formate on $Cu/ZnO/Al_2O_3$ and related catalysts is best described as a symmetrical bidentate or bridging species which is rigid at 298 K but exhibits anisotropic motion on the surface on a time scale of ca. 1 ms at 493 K. Surface carbonate is produced readily by oxidation of formate on $Cu/Zn/Al_2O_3$, and the carbonate is in equilibrium with free CO_2.

This study has also reported extensive data on the principal components of the ^{13}C chemical shift tensors of various species on the catalysts studied.

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Registry No. Al_2O_3, 1344-28-1; ZnO, 1314-13-2; Cu, 7440-50-8; MeO, 2143-68-2; HCO_2H, 64-18-6; CH_3OH, 67-56-1; $(CH_2O)_x$, 30525-89-4; HCHO, 50-00-0; CO_2, 124-38-9; CO, 630-08-0.

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Symmetries of Hydrogen Bonds in Monoanions of Dicarboxylic Acids

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Abstract: The NMR method of isotopic perturbation of degenerate equilibrium was used to distinguish between single- and double-well potentials in intramolecularly hydrogen-bonded monoanions of ^{18}O-labeled succinic, maleic, and phthalic acids. The observed isotope shift on the ^{13}C spectra demonstrates that these monoanions exist as two equilibrating tautomers in aqueous solution but as a single symmetric structure in a nonpolar solvent. This difference is attributed to the disorder of the aqueous environment.

In the study of hydrogen bonds one of the fundamental questions is whether the potential energy for motion of the hydrogen has a single minimum ("well") or two. If single, the hydrogen is fixed between the two donor atoms (**1**). If there are two minima, the hydrogen will be found closer to one donor than to the other. There are then two tautomeric forms, in rapid equilibrium (**2**), and the symmetric structure is the transition state for interconversion of the tautomers. Both situations have been observed, by a variety of experimental methods.[1] Often there are two forms, even if the donor atoms are identical, as in $CH_3C(OH){=}CH\text{-}COCH_3$, the enol of acetylacetone. The single, symmetric form is seen in hydrogen maleate (**3**) and hydrogen phthalate (**4**)

$$\underset{\mathbf{1}}{-O\cdots H\cdots O-} \qquad \underset{\mathbf{2}}{-O{-}H\cdots\cdots O- \rightleftharpoons -O\cdots\cdots H{-}O-}$$

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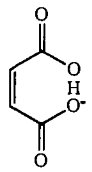
monoanions. One empirical generalization is that the symmetric form becomes favored only for "strong" hydrogen bonds, those where the oxygen–oxygen distance is less than ca. 2.5 Å. This is reasonable, since as two potential-energy wells move toward each other, eventually the barrier between them disappears and there remains only a single well.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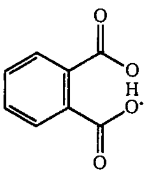
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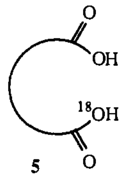
Previous methods for answering this question include microwave spectroscopy, which is applicable only in the gas phase, and X-ray or neutron diffraction, which is applicable only in crystalline materials. Most studies in solution have used infrared spectroscopy, but that is indirect and relies on empirical correlation, which may be misleading. Besides, infrared is difficult to apply to aqueous solutions, which are of special interest for hydrogen bonding. Two other methods applicable to nonaqueous solutions utilize the chemical shifts of hydrogen-bonded protium and deuterium (and tritium)[2] or quadrupole coupling constants of deuterium,[3] but these require independent knowledge of how the magnetic shielding or the electric-field gradient varies with position along the O–O axis. Even molecular-orbital calculations[4] are not always reliable, since the potential-energy surface can be soft and the location of the minimum is sensitive to the basis set and to the correction for correlation energy. Fortunately there is a new, direct method for determining the symmetry of hydrogen bonds in solution, even aqueous ones, without the need for input parameters.

The familiar NMR (nuclear magnetic resonance) methods are incapable of answering this question. Even if there are two forms, they will interconvert so rapidly that separate NMR signals will not be seen, but only an averaged signal that ordinarily would be indistinguishable from that of a symmetric structure. The ability to probe the symmetry of a hydrogen bond depends on a clever NMR method, the method of isotopic perturbation of equilibrium. Saunders[5] has applied this method extensively to the determination of the structure of carbocations, including the controversial norbornyl cation, and it has recently been applied to demonstrate the symmetry of *in*-bicyclo[4.4.4]-1-tetradecyl cation.[6]

Since the method is subtle and since the assumptions must be made explicit, it is advisable to explain how it operates for the dicarboxylic acids of interest here. The ^{13}C NMR spectrum of a mono-^{18}O-substituted diacid (**5**) shows two peaks, separated by 26 ppb, near δ 170, due to the carbonyl carbon. The doubling of the peaks occurs because there are intrinsic isotope shifts in the ^{13}C NMR.[7] The dianion (**6**) also shows two peaks, with the same 26-ppb separation, but near δ 176. The 6-ppm change of chemical shift reflects the sensitivity of ^{13}C NMR to environment.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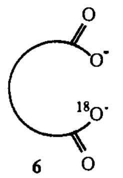
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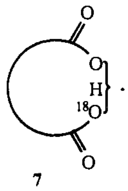
The question then is whether the monoanion exists as a single structure (**7**) or as a mixture of two forms (**8a** and **8b**). If it is a single structure, there are no further complications, and only the intrinsic isotope shift will be seen. If there are two forms, they differ by protonation of either the ^{16}O or ^{18}O carboxyl. (Actually, **8b** includes another tautomer, with the proton of the ^{16}O of the ^{18}O-containing carboxyl, but it is shown below that this complication merely decreases the observed effect by a factor of 2.) Separate signals are not seen for the two forms, since they interconvert too rapidly. Instead, only an averaged signal is seen, near δ 173. Ordinarily that would be a 50:50 average of the two tautomers. However, the isotope perturbs the equilibrium so that the two carboxyls have different acidities.[8] The isotope changes the vibrational frequencies of a carboxylic acid and of a carboxylate, and thereby changes their zero-point energies. As a result, tautomers **8a** and **8b** have different energies, and K_T, the equilibrium constant between them, is greater than 1. The effect is small, but the sensitivity of ^{13}C NMR to environment is sufficient to detect the slightly greater amount of **8b**. Since the ^{16}O acid is stronger, the carbon attached to ^{16}O is more likely to be a carboxylate, and the carbon attached to ^{18}O is more likely to be a carboxylic acid. Consequently, in the averaging, the chemical shift of the former is slightly nearer to δ 176 and that of the latter is slightly nearer to δ 170. This represents a small upfield shift for the carbon attached to ^{18}O and a small downfield shift for the carbon attached to ^{16}O. Therefore, there is an additional isotope shift in the monoanion, beyond the intrinsic shift, due to isotopic perturbation of the equilibrium.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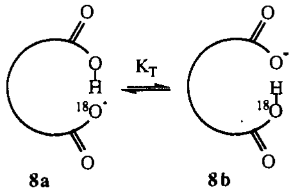
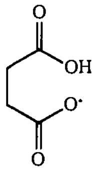


8a 8b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We now report such an isotope shift not only for formic acid and the monoanion **9** of succinic acid, where it was expected, but also for the monoanions of maleic (**3**) and phthalic acid (**4**), which had been considered the canonical examples of a symmetric hydrogen bond. A preliminary report of these results has been published.[9]

Experimental Section

Materials and Sample Preparation. A mixture of formic acid, formic acid-^{18}*O*, and formic acid-^{18}*O*$_2$ was prepared by stirring 5 μL of formic acid (Fischer, 88%, 0.13 mmol) in a mixture of 10 μL of $H_2{}^{16}O$ (0.56 mmol) and 10 μL of $H_2{}^{18}O$ at 40–50 °C overnight. Maleic anhydride (Aldrich) was recrystallized twice from chloroform. Succinic and phthalic anhydrides (Aldrich) were sublimed at 1 Torr. The ^{18}O dicarboxylic acids were prepared by adding 0.1 mmol of anhydride to 20 μL of 98% $H_2{}^{18}O$ (Icon) and warming in a bath at 40 °C for several

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hours. Since phthalic anhydride is only sparingly soluble in water, 10 μL of dioxane was used as a cosolvent. With excess $H_2{}^{18}O$ and longer reaction times, more than one ^{18}O could be incorporated into succinic and maleic acids.

After incorporation of ^{18}O, each solution was diluted with H_2O containing 10–20% D_2O for spectrometer lock. Approximately 10 μmol of disodium ethylenediaminetetraacetate (Na_2EDTA, Eastman) was added to chelate traces of metal species that otherwise may lead to paramagnetic line broadening of ^{13}C carbonyl resonances. Dioxane was used as an internal NMR standard (δ 66.5).

Titrations and Spectroscopic Studies in Aqueous Solution. ^{13}C spectra were obtained on a General Electric QE-300 FT-NMR spectrometer operating at 7.05 T (75 MHz ^{13}C), with broadband ^1H decoupling. The temperature was controlled at 26 °C. Typically 8K data points (real + imaginary) were collected for each spectral region using a spectral width of ±256 Hz and zero-filled to 16K for a final resolution of 16 points/Hz. The signal-to-noise ratio was maximized by pulsing at the Ernst angle,[10] which in this case is about 45°. Even at natural abundances of ^{13}C, only 100–500 transients were necessary. Additional line broadening of 0.2 Hz was imposed. Chemical shifts and isotope shifts were read from the digitized peak positions. (Measurement of small isotope shifts is obviously limited to peaks that are resolvable, so small values are uncertain.) Assignments of ^{13}C signals as either ^{16}O or ^{18}O were made by adding an authentic sample of the ^{16}O carboxylic acid.

Each acid was titrated with 5-μL aliquots of 4.9 M KOH, and ^{13}C NMR spectra were obtained after each addition. For maleic and phthalic acids, which are more acidic and dissociate appreciably in water, the final sample was reacidified with excess 12 M HCl. Aqueous samples of sodium hydrogen phthalate-^{18}O and disodium phthalate-^{18}O were prepared by neutralization with 1.00 and 2.00 equiv of NaOH, respectively, and the ^{13}C NMR spectra were recorded at 2, 62, and 98 °C.

For ^{18}O-labeled maleic acid an additional run was done in 99% D_2O, titrated with 40% NaOD (Aldrich) and reacidified with 37% DCl (Aldrich). Samples of sodium hydrogen phthalate-^{18}O and disodium phthalate-^{18}O prepared as above were lyophilized overnight, and the spectra of the labeled diacid, monoanion, and dianion in 99% D_2O were recorded.

The amount of base added did not accurately reflect the amount of carboxylic acid neutralized, especially for a stronger acid such as maleic, which is partially dissociated to its monoanion even without addition of base. The chemical shifts of the carbonyl peaks relative to the internal standard, dioxane, proved to be a more accurate measure of the extent of neutralization. Separate, large-scale titrations of unlabeled succinic and phthalic acids showed that the chemical shift of the monoanion is indeed the average of those of the diacid and the dianion. However, the chemical shift of hydrogen maleate monoanion is 174.0 ppm, significantly different from the 173.6-ppm average. Therefore the titration scale was adjusted so as to be linear across the two separate halves of the titration.

Studies in Nonaqueous Solvents. The ^{18}O-labeled acids were prepared as above. One equivalent of 1.00 M KOH was added to the maleic or phthalic acid to make the monoanion, which was then dried overnight at 1 Torr. Further sample preparation was done in a drybox. Alternatively, 1 equiv of benzyltrimethylammonium hydroxide (Aldrich, 40% in methanol) was used to prepare a solution of hydrogen maleate anion, and the solvent was lyophilized. The sample was then dissolved in dimethylsulfoxide-d_6 or acetonitrile-d_3 (Aldrich, 1 mL ampules).

Anhydrous samples in THF were prepared in a slightly different manner. Tetrabutylammonium hydroxide in water (Aldrich, 40%, 75 mg, 0.1 mmol) was added to 0.1 mmol of ^{18}O maleic or succinic acid. After removal of water at 1 Torr, these salts (as well as their corresponding acids) were transferred to flame-dried NMR tubes in a drybox. Tetrahydrofuran-d_8 stored over Na was vacuum-transferred to the NMR tubes, which were then sealed under a nitrogen atmosphere. Spectra were recorded on a Varian Unity 500 spectrometer operating at a ^{13}C resonance frequency of 125 MHz. The efficient WALTZ-16 decoupling scheme was used.[11]

In each case it was possible to verify that the monoanion had indeed been made by the presence of a characteristic broad peak near δ 20 in the ^1H NMR spectrum. This corresponds to a strongly hydrogen-bonded proton.

Calculation of K_T. At any point along the titration there are four species in equilibrium as shown in Figure 1. It follows from thermodynamics that $K_T = {}^{16}K_1/{}^{18}K_1 = {}^{16}K_2/{}^{18}K_2$; the equilibrium constant between the two tautomers of the monoanion must equal the isotope effect on the acidity constants. As n, the extent of neutralization, increases from 0 to 2, f_i, the fraction of acid present as the ith species, is readily derived. In particular, the n-dependence of f_B, the fraction with only the labeled carboxyl protonated, is given by eq 1, where $r = K_2/K_1 = 4K_{a2}/K_{a1}$. The statistical factor of 4 relating the microscopic acidity constants to the macroscopic constants K_{a1} and K_{a2} (within 1% of the tabulated[12] acidity constants for ^{16}O acids) arises because $K_{a1} = {}^{16}K_1 + {}^{18}K_1$ and $1/K_{a2} = 1/{}^{18}K_2 + 1/{}^{16}K_2$. For formic acid the competition between ^{16}O and ^{18}O acids is intermolecular, corresponding to $r = 1$.

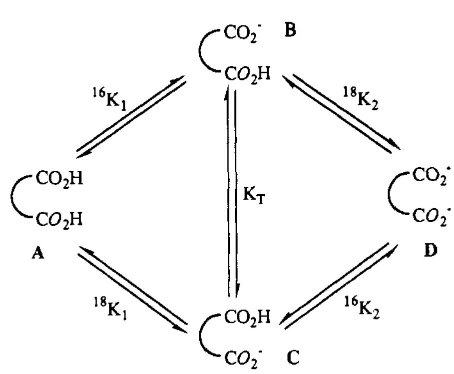

Figure 1. Acid–base equilibrium of an ^{18}O-labeled dicarboxylic acid, O = di-^{16}O-labeled, *O* = mono-^{18}O-labeled.

$$f_B = \frac{(K_T + 1) - \{(n-1)^2[(K_T+1)^2 - 4rK_T] + 4rK_T\}^{1/2}}{(K_T+1)^2 - 4rK_T} \tag{1}$$

Owing to rapid proton exchange between the carboxyl and the carboxylate, individual ^{13}C NMR resonances of separate CO_2H and CO_2^- groups cannot be observed. The observed chemical shift δ is the average of the chemical shifts of the protonated and unprotonated forms, weighted by their relative amounts (eqs 2 and 3). This assumes that

$$\delta_{16} = (f_A + f_C)\delta_{CO_2H} + (f_B + f_D)\delta_{CO_2^-} \tag{2}$$

$$\delta_{18} = (f_A + f_B)\delta_{CO^{18}OH} + (f_C + f_D)\delta_{CO^{18}O^-} \tag{3}$$

δ_{CO_2H} and $\delta_{CO_2^-}$, the chemical shifts of the diacid and the dianion, are suitable models for the chemical shifts of the carboxylic acid and carboxylate groups of the monoanion. This assumption is a good one for succinic acid, but not for maleic or phthalic acid, where the internal hydrogen bond is likely to change the chemical shifts relative to the models. It is especially poor for the ipso, ortho, and meta carbons of phthalic acid, since it assumes that the chemical shift depends on the state of protonation of only the nearer carboxyl.

The isotope shift Δ (strictly, ${}^N\Delta_{^{13}C}(^{18}O)$, where N is the number of bonds between the perturbing ^{18}O and the observed ^{13}C) is defined as $\delta_{18} - \delta_{16}$. (Since substitution by a heavier isotope almost always results in an upfield shift, isotope shifts are usually negative numbers.[7]) This can be related to the extent of neutralization n through f_B (eq 4), where Δ_0

$$\Delta = \Delta_0 + f_B(K_T - 1)D \tag{4}$$

is the intrinsic isotope shift, $\delta_{CO^{18}OH} - \delta_{CO_2H}$ or $\delta_{CO^{18}O^-} - \delta_{CO_2^-}$, and D is the chemical-shift difference between CO_2H and CO_2^-, $\delta_{CO_2H} - \delta_{CO_2^-}$. Both of these parameters were measured independently. For the ipso carbon of phthalic acid two different values of Δ_0 were taken, one for the diacid and another for the dianion.

At either end of the titration ($n = 0$ or 2) the numerator of f_B (eq 1) goes to zero, so that Δ reduces to the intrinsic isotope shift, as it should. Also Δ properly reaches its maximum at half-neutralization; at $n = 1$ eq 4 reduces to eq 5. For $r \ll 1$ eq 5 simplies to the well-known eq 6 (usually seen as solved for K_T) for isotopic perturbation of equilibrium.[5,7bd]

$$\Delta_{max} = \Delta_0 + \frac{(K_T - 1)D}{(K_T + 1) + (4rK_T)^{1/2}} \tag{5}$$

$$\Delta_{max} = \Delta_0 + \frac{K_T - 1}{K_T + 1}D \tag{6}$$

The best fit of the titration data was determined by iteratively varying K_T to minimize the sum of the squares of the deviations between observed isotope shifts and shifts calculated according to eq 1 and 4 (eq 7).

$$\partial \sum_{\text{points}} (\Delta_{obsd} - \Delta_{calcd})^2/\partial K_T = 0 \tag{7}$$

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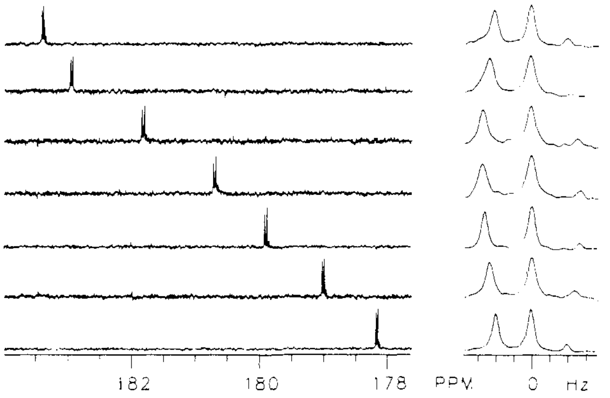

Figure 2. Titration of succinic acid monitored by carbonyl ^{13}C NMR.

Table I. Isotope Shifts, Chemical Shifts, and Isotope Effects on Acidity Constants of Carboxylic Acids in 10–20% D_2O

acid[a]	$-\Delta_0$[b], ppb	δ_{CO_2H}, ppm	$\delta_{CO_2^-}$, ppm	K_T[b]
formic	25	166.9	172.0	1.0108 ± 0.0005
succinic	27	178.2	183.4	1.0060 ± 0.0001[c]
maleic	26	170.8	176.3	1.0044 ± 0.0001[d]
maleic[e]	26	169.5	175.3	1.0053 ± 0.0002
phthalic	26	172.9	178.5	1.0091 ± 0.0002
phthalic[f]	≤5	133.0	138.7	1.0201 ± 0.0002
phthalic[g]	<4	129.8	128.2	1.0121 ± 0.0008
phthalic[h]	<4	132.3	129.7	1.0128 ± 0.0003
phthalic[e]	26	172.8	178.6	1.0130 ± 0.0003

[a] Carbonyl carbon except where indicated otherwise. [b] per ^{18}O. [c] 1.0060 ± 0.0001 from di-^{18}O acid. [d] 1.0043 ± 0.0002 from di-^{18}O acid. [e] In 99% D_2O. [f] Ipso carbon. [g] Ortho carbon. [h] Meta carbon.

Statistical errors were calculated from the quality of the fit according to propagation of errors, except for phthalic acid in D_2O, where the errors in δ and D were taken as 1 ppb. Further details are available.[13]

Results

^{13}C Spectra and Peak Assignments. The ^{13}C NMR spectra of partially ^{18}O-labeled formic, maleic, and succinic acids show three resolvable peaks in the carbonyl region, corresponding to $C^{16}O_2H$, $C^{16}O^{18}OH$, and $C^{18}O_2H$, with the carbons bearing the ^{18}O appearing upfield. (For phthalic acid-^{18}O, which resisted incorporation of additional ^{18}O, only the first two peaks were observed.) This agrees with the well-established generalization that heavy isotopes produce upfield intrinsic isotope shifts.[7] Figure 2 shows the three peaks of succinic acid.

Titrations in Aqueous Solution. As the acid is titrated, the carbonyl peaks (and the ipso peak of phthalic acid, but not its ortho or meta peaks) shift downfield. This corresponds to $D > 0$ in eqs 4–6. It is opposite to what might be expected on the basis of electron density, but it is well established.[14] Figure 2 shows the successive shifts for succinic acid. Limiting chemical shifts (δ_{CO_2H} and $\delta_{CO_2^-}$) at both ends of the titration are listed in Table I.

At either end of the titration an intrinsic isotope shift (Δ_0) of about 26 ppb/^{18}O is observed for carbonyl carbons. However, at the more distant ipso, ortho, and meta carbons of phthalic acid the intrinsic shifts are zero, within experimental error, except perhaps for the ipso carbon of the diacid. Intrinsic shifts are listed in Table I.

The isotope shift increases upon addition of base, reaches a maximum at half-neutralization, and then decreases back to the initial intrinsic isotope shift at 2 equiv of base. Figure 2 shows how the isotope shift of succinic acid varies with the extent of neutralization. This is in good agreement with the isotope shifts observed by Mega and Van Etten.[15] Figure 3 shows the isotope shifts for all four reporter carbons of phthalic acid. The fits to eq 4 are good. Data on the meta and ortho carbons are less reliable because the isotope shift was often barely resolvable above the line width. With the linearization of the titration scale for maleic acid (plot not shown) its maximum isotope shift also occurs at its monoanion.

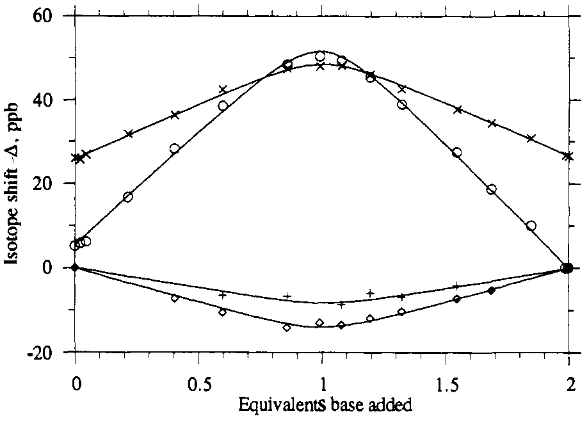

Figure 3. Observed isotope shifts for phthalic acid-^{18}O (negative shift upfield) vs n, number of equivalents of base added (× = carbonyl, ○ = ipso, ◇ = meta, + = ortho, — = best fit to eqs 1 and 4).

Table II. Temperature Dependence of ^{13}C Isotope Shifts of Aqueous Hydrogen Phthalate Monoanion and Phthalate Dianion

T, °C	$-\Delta_{HPhth^-}$,[a] ppb	$-\Delta_{HPhth^-}$,[b] ppb	$-\Delta_{Phth^{2-}}$,[a] ppb
2	57	64	27
26	48	50	27
62	39	37	
98	34	32	25

[a] Carbonyl carbon. [b] Ipso carbon.

The tautomeric equilibrium constants K_T obtained by fitting the isotope shifts to eq 4 are listed in Table I. Since more than one ^{18}O could be incorporated into succinic and maleic acids, this allowed for two separate determinations of K_T. Both are reported, but that for the doubly labeled carboxyl has been converted to a per-^{18}O basis. The value for formic acid agrees well with the 1.0117 (interpolated to 20% D_2O) measured by Ellison and Robinson.[8a]

Temperature Dependence of the Isotope Shift. The result of the temperature dependence studies are shown in Table II. The isotope shift in hydrogen phthalate monoanion decreases with increasing temperature whereas in disodium phthalate it remains nearly constant over the temperature range.

Deuterium Dependence of the Isotope Shift. The results of the titration of ^{18}O-labeled maleic and phthalic acids in D_2O are included in Table I. Compared to H_2O as solvent, the maximum isotope shift (Δ_{max}) and the derived equilibrium constant K_T increase in D_2O by a detectable amount.

Studies in Nonaqueous Solvents. The change to less polar organic solvents precluded a full titration. It was, however, necessary only to prepare the monoanion since it had already been observed from aqueous titrations that the maximum isotope shift occurs in the monoanion. Where possible, spectra of the acids were also recorded to verify that the intrinsic isotope shift remains unchanged in these solvents. Unfortunately, it was not possible to obtain good spectra of maleic and succinic acid in THF-d_8, owing to broadening of the carbonyl resonances. It is not possible to dissolve the dianions in these solvents. The organic cation used in these studies, tetrabutylammonium ion, is necessary to pull the monoanion into solution at a high enough concentration for ^{13}C NMR. The potassium salts, even with 18-crown-6, or the lithium salts, even with cryptand, are not soluble in THF. This contrasts with ordinary carboxylate or enolate anions, presumably because the negative charge here is spread over two carboxyl groups and does not coordinate the counterion well.

Isotope shifts of the various acids and their monoanions are listed in Table III, along with their chemical shifts. In DMSO-d_6 and CD_3CN the observed isotope shift of the monoanions is greatly diminished, and for hydrogen maleate and hydrogen succinate

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Table III. Chemical Shifts and Isotope Shifts in Organic Solvents

acid	counterion	solvent	δ_0,[a] ppm	δ,[b] ppm	Δ_0,[a] ppb[c]	Δ,[b] ppb[c]
phthalic	K^+	DMSO-d_6	167.9	168.6	26	29
phthalic[d]	K^+	DMSO-d_6	132.8	135.0	5	16
maleic	K^+	DMSO-d_6	166.7	167.2	25	26
maleic	$PhCH_2NMe_3^+$	CD_3CN	167.0	168.8	25	26
maleic	nBu_4N^+	THF-d_8	166.7	168.4	*e*	27
succinic	nBu_4N^+	THF-d_8	173.7	176.2	*e*	27

[a] Diacid. [b] Monoanion. [c] ±1 ppb. [d] Ipso carbon. [e] Not determined owing to excessively broad peaks.

in THF-d_8 only the intrinsic isotope shift is observed.

Discussion

Assertion. The key result shown in Figure 3 and in the derived K_T values listed in Table I is the increased isotope shift in the monoanions of maleic and phthalic acids. This result is consistent with the assertion that hydrogen maleate (**3**) and hydrogen phthalate (**4**) anions exist as a pair of asymmetric equilibrating tautomers. However, this contradicts well-established evidence that they have symmetric hydrogen bonds.[1] It is necessary to document the new evidence and to show that it is not consistent with a symmetric structure.

It is firmly established that the intramolecular hydrogen bonds seen in crystalline hydrogen maleate and hydrogen phthalate monoanions persist in solution. In aprotic solvents that hydrogen appears in the ^1H NMR spectrum below δ 20,[2] corresponding to unusually strong hydrogen bonding. In aqueous solution the ΔpK_a values for phthalic and maleic acid of 1.58 and 3.48,[12] between first and second acidity constants, corrected for the statistical factor of 4, have been taken as manifestations of the stabilization of the monoanions by intramolecular hydrogen bonding. For comparison, succinic acid has a corrected ΔpK_a of only 0.64, so that this and formic acid are good controls that do not have a symmetric hydrogen bond.

It might be thought that the method of isotopic perturbation is doomed to yield the answer that any structure is asymmetric. Even if the fully ^{16}O-substituted maleate or phthalate monoanion (or a doubly ^{12}C- or ^{13}C-substituted monoanion, rather than with the single ^{13}C NMR probe nucleus) is symmetric, perhaps it is the isotopic substitution itself that creates the asymmetry. However, it is a corollary of the Born–Oppenheimer approximation[16] (which holds here to a very high degree) that the potential in which the nuclei move is determined solely by the electrons and not by the nuclear masses. Therefore isotopic substitution does probe whether the hydrogen bond is symmetric or asymmetric.[5] However, it must be recognized that this is the distinction, rather than between single- and double-well potentials, since there is only a single structure when the double-well barrier lies below the zero-point energy.

Isotopic Perturbation of Equilibrium. The *qualitative* result, that there is an increased isotope shift in the monoanions, is consistent with perturbation of an equilibrium between two species. Stronger evidence is the *quantitative* agreement between the tautomeric equilibrium constant K_T derived from that shift and other measures of K_T. Thus all the values in Table I are quite close to the K_T for formic acid[8a] and for phosphoric acid and alkyl phosphates.[8c] Analogous results, but of larger magnitude, have been obtained for deuterium isotope effects on acidities of anilinium ions.[17] All these are certainly due to isotopic perturbation of proton-transfer equilibria, but they were measured by this same NMR method. Independent corroboration comes from acidity-constant comparisons on ^{18}O benzoic acids and ^{15}N anilines, determined by a chromatographic technique[8b] that does not rely on NMR methods, which also give K_T around 1.01. Since equilibrium constants of very similar magnitude are seen not only for succinic acid but also for maleic and phthalic acids, it would be exceedingly fortuitous if the increased isotope shifts in these monoanions were due to some other phenomenon.

Table IV. Vibrational Frequencies of RCOOH, $RC^{18}O^{18}OH$, RCO_2^-, and $RC^{18}O_2^-$

mode	$\nu(^{16}O)$, cm^{-1}	$\nu(^{18}O)$, cm^{-1}	$\Delta\nu$, cm^{-1}
$C{=}O$	1760[a]	1718	42
$C{-}OH$	1300[a]	1271	29
$O{-}H$	3000[a]	2990	10
$C\overset{\cdots}{-}O^{\delta-}$	1500[a,b] (×2)	1464 (×2)	36 (×2)
sum[c]	3060	3051	9

[a] From ref 19. [b] Average of symmetric and asymmetric stretches. [c] $\nu_{C=O} + \nu_{C-OH} + \nu_{O-H} - 2\nu_{C\overset{\cdots}{-}O^{\delta-}}$.

It is also possible to compare the experimental K_T in Table I with an estimate from known vibrational frequencies of carboxylic acids and carboxylate anions,[18] listed in Table IV. For simplicity we calculate the equilibrium constant for proton transfer between unlabeled and doubly ^{18}O-labeled acids (eq 8). The corresponding

$$RCOOH + RC^{18}O_2^- \rightleftarrows RC^{18}O^{18}OH + RCO_2^- \qquad (8)$$

frequencies of the labeled species can be calculated by correcting for the changes in reduced mass, and these are also listed in Table IV. The net difference of 9 cm^{-1} is equivalent to a zero-point energy difference of 4.5 cm^{-1} for the two sides of eq 8. This then corresponds to an equilibrium constant of 1.022 at 26 °C, with the di-^{18}O acid weaker.

This calculation assumes ^{12}C acids and doubly labeled oxygens, but these simplifications do not matter. For ^{13}C-substituted acids, the net $\Delta\nu$ is still calculated to be 9 cm^{-1}. For a mono-^{18}O-labeled acid the proton can be on either of its oxygens, and a calculation for the mixture of two tautomers gives $K_T = 1.011$, or simply half the effect due to double labeling. The experimental values in Table I are in good agreement with the calculated 1.011. Also, we find experimentally that the doubly ^{18}O-labeled acids show twice the isotope shifts of the corresponding singly labeled ones.

There is a further complication from the presence of the doubly ^{18}O-labeled diacid with one ^{18}O in each carboxylic acid group. This shows an intrinsic isotope shift but no isotope shift due to perturbation of equilibrium. Since its concentration is low, its peak is not resolvable but represents only an undetectable shoulder on the downfield side of the peak of the singly labeled carboxyl. To the extent that this broadens the peak, it reduces the measured isotope shift, so that the observed value is a lower limit.

A similar calculation for $RC^{18}O^{18}OD$ leads to $K_T = 1.024$ for eq 8, or $1.012/^{18}O$. The increase of K_T in D_2O solvent has been seen with formic acid.[8a] Moreover, the results in Table I correspond to isotope shifts of the monoanions of maleic and phthalic acids that are greater in D_2O. This is further evidence that these isotope shifts are due to perturbation of an equilibrium.

Variations in K_T. Why do the K_T values in Table I vary among the different acids and among the various reporter nuclei? The zero-point energy difference for eq 8 is a small difference between two large numbers, so that the estimated equilibrium constant K_T is quite sensitive to the choice of vibrational frequencies. Since these frequencies may vary with acid, so may K_T.

A more serious variation in K_T is found among the different reporter nuclei of phthalic acid. This is a consequence of the simplifying assumption, for eqs 2 and 3, that δ_{CO_2H} and $\delta_{CO_2^-}$ are suitable models for the chemical shifts of the carboxylic acid and carboxylate groups of the monoanion. This assumption cannot be valid for maleic or phthalic acid, with their internal hydrogen bond. Indeed, the observed chemical shift of hydrogen maleate monoanion is not equal to the average of maleic acid and maleate dianion $(\delta_{CO_2H} + \delta_{CO_2^-})/2$. What is needed for eq 4, however, is the difference D, or $\delta_{CO_2H} - \delta_{CO_2^-}$, proper for the monoanion, and only the approximate value is available. This is especially approximate for the ipso, ortho, and meta carbons of phthalic acid. However, it seems unlikely that either D or the deviation of K_T from unity, derived therefrom, would be in error by more than

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3-fold. Therefore the discrepancies are not serious. Nevertheless the reported tautomeric equilibrium constants for acids with an intramolecular hydrogen bond should be regarded only as approximations.

Possible Variability of Intrinsic Isotope Shifts. Might the observed isotope shifts in the monoanions of maleic and phthalic acids be due simply to an increased intrinsic isotope shift? The increase need not be large, only from 26 ppb to 38 or 50 ppb. No such increase is seen for succinic acid, but this lacks the internal hydrogen bond, which might produce an unusual isotope shift. Previous applications of the method of isotopic perturbation of equilibrium do not suffer from this ambiguity because K_{T} is generally larger (for ^{2}H substitution rather than ^{18}O) and so is the parameter D (up to 200 ppm for carbocations). As a result the isotope shifts observed for asymmetric structures are generally much larger than the intrinsic shifts and cannot be attributed to that alternative.

Isotope shifts are observed even for a symmetric structure, since the isotope can perturb the relative contributions of resonance forms to a resonance hybrid. The magnitude of such an ^{18}O isotope shift can be estimated from deuterium-induced isotope shifts in carbocations. The ^{13}C spectra[5] demonstrate that Δ/D is always less than 0.0035 for such hybrids, in contrast to the 10–50-fold larger Δ/D for perturbation of an equilibrium. If these ratios can be transferred to ^{18}O effects, where Δ/D for perturbation of an equilibrium is considerably smaller, then the isotope shift due to perturbation of resonance in a symmetric monoanion will be vanishingly small. Besides, it would be extremely fortuitous if this perturbation would so closely match the magnitude of K_{T} predicted from acidity constants or vibrational frequencies.

The inverse dependence on temperature of the ipso and carbonyl isotope shifts in hydrogen phthalate monoanion (Table II) is further evidence against a variability of an intrinsic isotope shift. Intrinsic isotope shifts are known to be temperature independent[19] (unless there are thermally excited vibrational levels[20]), and we find that phthalate dianion shows no significant variation of isotope shift with temperature. Yet the isotope shifts for hydrogen phthalate monoanion are strongly temperature dependent. Actually, the temperature dependence of K_{T} and ΔH° derived therefrom are too large, but this is a consequence of the approximations in eqs 2 and 3. It is the qualitative result that is good evidence that the isotope shifts are a thermodynamic phenomenon, governed by a free-energy difference.

The most convincing evidence that the asymmetry of the hydrogen bonds is due to an equilibrium phenomenon is the isotope shifts at the ipso, ortho, and meta carbons of phthalic acid (Figure 3). As expected from other cases,[7] the intrinsic isotope shifts in the diacid and the dianion are zero (or nearly zero) since these carbons are so distant from the site of isotopic substitution. Only in the monoanion are shifts seen at these distant carbons, notably the 50 ppb for the ipso carbon. Moreover, the ^{18}O-induced ^{13}C NMR isotope shifts of the ortho and meta positions of hydrogen phthalate monoanion are *downfield*. This is opposite to the upfield intrinsic shifts seen nearly universally, and it is also opposite to the upfield shift seen at all other carbons, which we are attributing to isotopic perturbation of the equilibrium. However, this downfield shift is exactly what is expected from isotopic perturbation, since in contrast to all the other carbons that we have investigated, which shift downfield on deprotonation of the acid, the ortho and meta carbons shift upfield on deprotonation. Therefore we conclude that the isotope shifts in the monoanion cannot be intrinsic shifts, but must have another origin, namely perturbation of an equilibrium.

The Role of the Environment. The surprising result is that hydrogen maleate (**3**) and hydrogen phthalate (**4**) monoanions also show an isotopic perturbation of equilibrium. We therefore conclude that even these hydrogens are in double-well potentials. Yet the hydrogen bonds of these anions have long been considered examples of symmetric hydrogen bonds.[1]

How can the discrepancy between our results and previous ones be rationalized? Previous X-ray and neutron-diffraction results are definitive, but ours are incontrovertible. We propose that the discrepancy arises because our study is the first to be carried out in aqueous solution. Water is a special environment, in that it hydrogen bonds to the carboxylate group. On the average, both carboxyls are equally solvated. However, water is a disorganized solvent, and it would require considerable negative entropy for both carboxyls to be identically solvated at every instant. If one carboxyl group is more strongly solvated than the other, it becomes the carboxylate and the proton is preferentially attached to that other carboxyl. Then as the solvent fluctuates, the proton oscillates between the two carboxyls, but at any instant the hydrogen bond itself is asymmetric. Indeed, there are examples of hydrogen maleate monoanions with asymmetrically placed counterions that show an asymmetric hydrogen bond,[21] and it has long been recognized[1] that strong crystal forces can create sufficient asymmetry to favor an asymmetric hydrogen bond. Nevertheless it is unexpected that the seemingly minor change from crystal to water is also sufficient to do so. Thus even though the single-well potential may be favored in the symmetric environment of maleate and phthalate crystals, we propose that the disorder of an aqueous environment makes the hydrogen bond asymmetric. This proposal is similar to a suggestion by Kreevoy and Liang[22] that solvation lengthens the O–O distance and thereby favors the asymmetric hydrogen bond.

Recent MO calculations by Hadži on hydrogen maleate and hydrogen malonate monoanions strongly support this proposal.[23] At all levels of calculation the effect of solvation, as modeled by a continuous dielectric, is to raise the energy of the symmetric structure relative to the asymmetric one. Therefore we infer that aqueous solution can indeed make asymmetric a hydrogen bond that is otherwise symmetric.

To investigate this possibility, spectra were recorded in organic solution, first in non-hydrogen-bonding solvents (DMSO and CH_3CN) and then in a nonpolar solvent THF. The results are listed in Table III. The intrinsic isotope shifts in the control diacids are independent of solvent. This is in keeping with the observation that in aldehydes and ketones no solvent effect is seen on the one-bond $^{1}\Delta_{^{13}\mathrm{C}}(^{18}\mathrm{O})$ isotope shifts.[24] This observation is quite general,[7d] except in cases where an equilibrium phenomenon might contribute to the observed shift.

In both DMSO-d_6 and CD_3CN the isotope shift of potassium hydrogen maleate (**5**) or potassium hydrogen phthalate (**6**) is diminished from that in aqueous solution. However, D also decreases, so K_{T} is closer to unity but inaccurate. The weaker solvation results in an instantaneous environment that is effectively more symmetric. The small isotope shift may be due to residual water in the DMSO-d_6 and CD_3CN, perhaps leading to an equilibrium between structures with symmetric and asymmetric hydrogen bonds.

In the still less polar anhydrous THF-d_8 only the intrinsic isotope shift remains, indicating that hydrogen maleate reverts to a single-well potential in nonpolar solvents. This results restores the agreement with previous results in crystals, as well as with results in CH_2Cl_2.[2,3] Moreover, *this result shows that the isotopic substitution itself is not responsible for creating the asymmetry that is seen in aqueous solution.*

That the symmetry seen in crystals or nonpolar solvents is broken in aqueous solution demonstrates the importance of the local environment in determining the symmetry of the hydrogen

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bond. *This is a remarkably simple counterexample to the prevailing hope that a crystal structure describes the solution structure.*

There is no intramolecular hydrogen bond in aqueous hydrogen succinate monoanion (**9**). Yet in THF this shows only the intrinsic isotope shift. Therefore the conformation must have changed, to permit a hydrogen bond that is not only intramolecular but also symmetric. In such a nonpolar solvent, the best solvation for the carboxylate anion is hydrogen bonding to a carboxylic acid. Moreover, the symmetry of this hydrogen bond in THF is further evidence for a role for solvation in determining the symmetry of hydrogen bonds.

These results do not distinguish whether hydrogen bonds become asymmetric in water because of its polarity or because of its disorder. Certainly a polar environment ought to stabilize the asymmetric structure, with its concentrated negative charge, relative to the symmetric one, with delocalized charge. The MO calculations mentioned above[23] show that polarity does favor the asymmetric structure, but Hadži suggests that if the dynamic and discrete properties of water are included, this structure would be even more favored. It seems to us that polarity alone is not sufficient, since the crystal, with its counterions, is also quite polar, and yet the hydrogen bond is symmetric. Therefore we infer that the hydrogen bonds become asymmetric in water because of its disorder, which makes it improbable for both carboxyls to be identically solvated at each instant.

Conclusions

The hydrogen bonds in aqueous hydrogen succinate (**9**), maleate (**5**), and phthalate (**6**) monoanions are asymmetric, corresponding to a potential-energy surface having two minima. This conclusion is based on the values of K_T calculated from observed isotope shifts, the temperature dependence of the isotope shift, and the unusual isotope shifts of the aromatic carbons of phthalic acid, which are not subject to an intrinsic shift. The results on hydrogen maleate and phthalate are especially surprising since they had previously been observed to have symmetric hydrogen bonds. This difference is attributed to the disorder of the aqueous environment. In contrast, in nonpolar solvents single-well potentials are observed, not only for hydrogen maleate and phthalate monoanions, but also for hydrogen succinate.

Whether a hydrogen bond is symmetric or asymmetric is not simply inherent in the molecular structure, dependent only on the oxygen–oxygen distance, but can depend on solvent. The technique of isotopic perturbation of equilibrium has demonstrated itself to be a useful and effective technique in the study of hydrogen bonding, and it provides definitive answers to the question of the symmetry of the hydrogen bond.

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Theoretical Secondary Kinetic Isotope Effects and the Interpretation of Transition State Geometries. 1. The Cope Rearrangement

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Abstract: Theoretical secondary kinetic and equilibrium deuterium isotope effects for the Cope rearrangement of 1,5-hexadiene were calculated using RHF/3-21G, RHF/6-31G*, UHF/6-31G*, CASSCF/3-21G, and MP2/6-31G* levels of theory and the Bigeleisen–Mayer method. Isotope effects for transition structures, corresponding to a concerted process of bond reorganization, several different cyclohexane-1,4-diyl-like species, and two allyl radicals, were examined and compared with the experimentally determined values. The theoretical isotope effects calculated for the concerted pathway are in best agreement with experiment. Similar calculations were used to examine the 1,5-heptadiene and 3-methyl-1,5-hexadiene Cope rearrangements. The transition structure with methyl in the equatorial position is 1–2 kcal/mol more stable than that with the axial methyl. These results are analyzed in the framework of Gajewski's More O'Ferrall–Jencks diagrams for the Cope rearrangement, correlating kinetic isotope effects and bond order.

Introduction

The Cope [3,3]-sigmatropic rearrangement has been the subject of extensive theoretical and experimental investigations.[1-3] This class of reactions is generally thought to proceed by a concerted mechanism, but this point is still debated. Even those who agree that the rearrangement is concerted sometimes disagree regarding the geometry of the transition state. Some investigators favor a cyclohexane-1,4-diyl-like structure (bottom of Figure 1), while others support a so-called "aromatic" transition state consisting of two partially bonded three-carbon units (center of Figure 1). Two separated allyl radicals (top of Figure 1) are known to be too high in energy to qualify as participants in this reaction but do represent another limiting structure useful to this discussion. The best computational evidence available predicts a potential surface with two pathways, one via an aromatic transition state, the other through a cyclohexanediyl intermediate. Both pathways have identical energies.[2g] Calculation of free energies leads to the prediction that both pathways are concerted and that the

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