Structure of a Dihydrated, Strongly Hydrogen-Bonded Crystal

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The C-1 carbon of the dihydrated sodium salt of hydrogen bis(4-nitrophenoxide) gives rise to a single, unsplit, unbroadened signal in the solid-state, magic-angle spinning ^{13}C NMR spectrum of a crystalline powder even at 12 K. The results of rotational-echo, double-resonance ^{13}C NMR experiments with ^2H dephasing for the single ^{13}C-1 resonance, when combined with the observation of a large isotropic *J* coupling for this carbon and other information, led to the conclusion that the bridging hydrogen (or deuterium) oscillates rapidly between the two basic oxygen sites. The average lifetime of a proton in one of these sites must be $<10^{-4}$ s even at 12 K. The bridge hydrogen therefore occupies a low-barrier, double-well potential with a ground vibrational level below the central maximum. These conclusions are consistent with the crystal structure, in which the two phenoxide units are related by a rotational axis of symmetry, and the oxygen−oxygen distance is only 2.452 Å. The conclusions are also consistent with the unusual isotropic chemical shift of the bridge deuterium of 16.8 ppm relative to external tetramethylsilane. An apparent isotopic fractionation factor of 0.63 has been determined for the bridge hydrogen in the dihydrated sodium salt. This value appears to be too high in view of the other characteristics of the bridge hydrogen in the crystalline solid, which suggests that the solid was not in isotopic equilibrium with the solvent from which it was precipitated.

Introduction

Sodium hydrogen bis(4-nitrophenoxide) crystallizes with 2 mol of water per mole of salt,[1] resulting in the sharing of a single proton between two phenoxide oxygens (Figure 1). The O−H−O bridge bond is short, 2.452 Å,[1,2] and a half-hydrogen appears to be bonded to each of the two oxygens.[2] Hydrogen bonds in such systems are unusually strong,[3] and their formation may be part of the scheme that allows an enzyme to bind an intermediate or a transition state more tightly than a substrate.[4,5]

Neither X-ray nor neutron diffraction has been able to characterize the distribution function of the bridging hydrogen unambiguously in systems such as sodium hydrogen bis(4-nitrophenoxide).[2,5,6] These studies cannot distinguish with confidence between an elongated distribution along the O−O line, with a single maximum at the center, and a double-maximum distribution, with the two maxima separated by a few tenths of an angstrom. If one assumes that potential energy is a double-minimum function of the displacement of the proton from the midpoint of the O−O line, the incompletely answered question is whether or not the central maximum projects above the lowest allowed vibrational level.

In this paper, we report the use of rotational-echo, double-resonance (REDOR) NMR[7] to characterize the distribution of the bridging hydrogen. During the past few years, REDOR has been developed as an analytical spectroscopic technique for measuring inverse-r^3-weighted average interatomic distances in solids spinning at the magic angle.[8] REDOR provides a direct measure of dipolar coupling between isolated pairs of hetero-
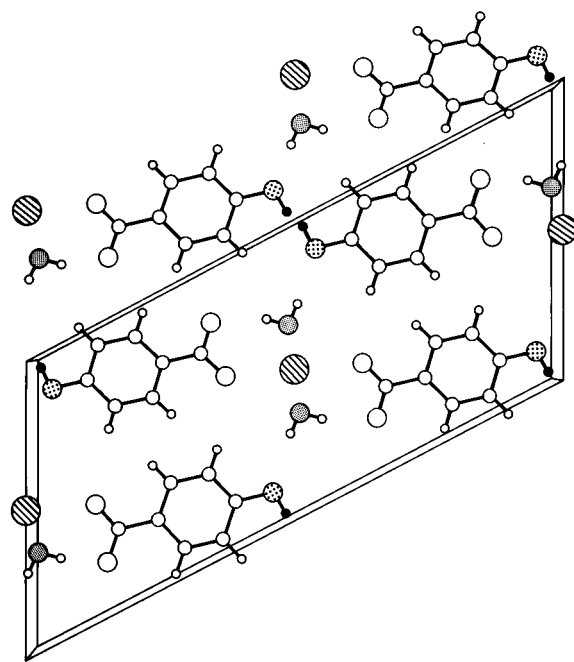
Figure 1. Crystal structure of sodium hydrogen bis(4-nitrophenoxide). A single proton bridges two phenoxy oxygens which are separated by 2.452 Å.

nuclear spins. For a 4-nitrophenoxide crystallized from D_2O, the natural-abundance ^{13}C of the ring C-1 carbon, for example, and the bridge ^2H form such a pair. The ^{13}C rotational echoes that occur each rotor period following a ^1H−^{13}C cross-polarization transfer are prevented from reaching full intensity by insertion of ^2H π pulses (Figure 2). The diminution of echo intensity has a strong dependence on the ^{13}C−^2H dipolar coupling[7] and hence on the distance from the C-1 carbon to the bridge deuterium. REDOR is described as double resonance even though more than two radio frequencies are generally used

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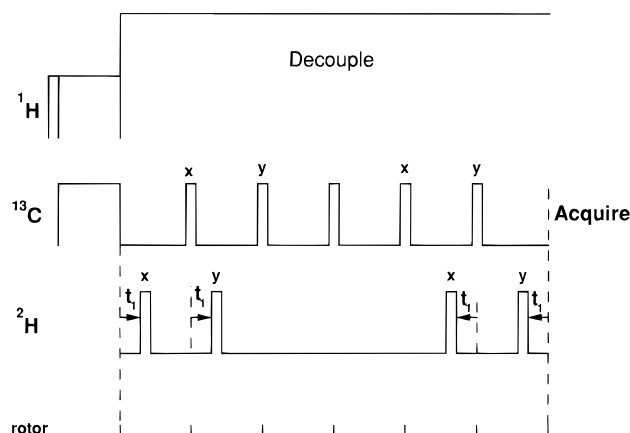
Figure 2. Pulse sequence for REDOR ^{13}C NMR with ^{2}H dephasing. The carbon magnetization is produced by a matched spin-lock, cross-polarization transfer from the protons, which are then removed from the experiment by resonant decoupling. Carbon π pulses occur on the rotor period and deuterium π pulses at t_1. The carbon π pulse in the middle of the evolution period refocuses isotropic chemical shifts. The phases of both carbon and deuterium pulses are varied by a simple *XY* alternation scheme. The illustration is for four rotor cycles of dephasing with symmetric placement of the deuterium pulses. An asymmetric version of this sequence is obtained by reversing the symmetry of the sequence about the carbon π pulse in the middle of the evolution period and placing dephasing pulses at times, t_1, measured from the beginnings of the rotor periods.

(three in this case: ^{1}H, ^{13}C, and ^{2}H) because only two heteronuclear spins are involved in the important dipolar evolution part of the experiment. The dephasing of magnetization in REDOR arises from a local dipolar ^{13}C$-^2$H field gradient and involves no polarization transfer. REDOR has no dependence on ^{13}C or ^{2}H chemical shift or quadrupolar tensors and does not require resolution of a ^{13}C$-^2$H coupling in the chemical shift dimension.[9]

Experiments

Sample Preparation. The sodium hydrogen bis(4-nitrophenoxide) was prepared following previously described procedures.[1] The [10% ^{13}C-1]-labeled sample was prepared by David D. McSherry (Vitasyn, Inc., Minneapolis, MN). After preparation of the acidic salt from H_2O, the solid was taken up in a large excess of D_2O or D_2O/H_2O mixture and subsequently precipitated by cooling and evaporation of solvent. The excess solvent was removed at 0.3 atm in a stream of dry nitrogen. The nitrogen was used to suppress loss of deuterium from the solvent by exchange with atmospheric water. Samples were stored at 0 °C.

Solids NMR Spectrometer. Magic-angle spinning ^{1}H, ^{13}C, and ^{2}H NMR spectra were obtained using three channels of a four-channel spectrometer built around an 89 mm, vertical-bore superconducting solenoid operating at 7.05 T. Multifrequency tuning was accomplished by the use of a coaxial transmission line connecting tuning components outside the magnet[10] to a single, four-turn, 9 mm diameter solenoidal coil wound from 14-gauge, tinned bus wire. Chemagnetics pencil-shaped zirconia rotors were spun at 5 kHz with ± 2 Hz active control. An ENI 1 kW, LPI-10 transmitter was used for the deuterium channel. Kalmus 1 kW, LP-1000 and 600 W, 166-UP transmitters were used for the carbon and proton channels, respectively. The spectrometer was controlled by a four-channel Chemagnetics CMX-300 console.

REDOR. Two versions of the pulse sequence for two-dimensional, ^{13}C-observe, ^{2}H-dephase REDOR NMR[11] were used: symmetric and asymmetric (see Figure 2). Half of the π
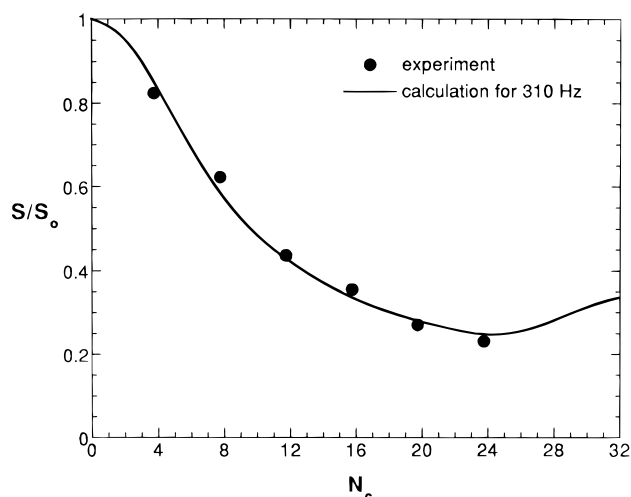
Figure 3. REDOR dephasing for one part of zinc bis([1-^{13}C]methyl acetate-d_3) recrystallized with nine pairs of natural-abundance zinc acetate. The pulse sequence of Figure 2 was used with $t_1 = T_r/4$ and variable N_c. The solid line was calculated for an isolated CD$_3$ group with a ^{13}C$-^2$H dipolar coupling of 310 Hz.

pulses were placed on the ^{13}C channel at the completion of the rotor periods. The other half were placed either symmetrically or asymmetrically at t_1 on the ^{2}H channel. The symmetric placement of these pulses results in the refocusing of the *J* coupling, while the asymmetric placement does not.[7b] A two-rotor cycle Hahn echo in the middle of the pulse sequence refocused ^{13}C isotropic shifts. Simple *XY* phase cycling[12,13] was used for both the 10 μs ^{13}C pulses and the 7.3 μs ^{2}H pulses. All three radio-frequency field amplitudes were monitored by a capacitive pickup along the transmission line and were adjusted after each scan. The initial carbon magnetization was generated from a 50 kHz matched spin-lock transfer from the protons. Proton decoupling was at 90 kHz. In one version of the two-dimensional REDOR experiment, N_c was fixed at 8, and the t_1 parameter was varied from zero (which defines S_0) to $T_r/2$ with $T_r = 200$ μs. In another version, t_1 was fixed at $T_r/4$ (rather than the usual $T_r/2$), and N_c was varied from 4 to 24. The latter protocol, which is optimized for the 4-nitrophenoxide system, was calibrated by observation of S/S_0 (Figure 3) for a double-labeled zinc acetate diluted to 10% by recrystallization with natural-abundance zinc acetate. REDOR dephasing for zinc acetate with $t_1 = T_r/2$ has been reported earlier.[11] For measurements with fixed $N_c = 8$, a 200 mg sample of dihydrated sodium hydrogen bis(4-nitrophenoxide) with natural isotopic abundances was used, and 3000 scans were accumulated at a sequence repetition rate of 25 s for each ^{13}C NMR full-echo or dephased spectrum. For measurements with variable N_c and fixed t_1, 397 mg of sodium hydrogen [10%-^{13}C-1]bis(4-nitrophenoxide) sample crystallized from 100% D_2O was used, and 128 scans were accumulated using a sequence repetition period of 25 s for each ^{13}C NMR full-echo or dephased spectrum.

Measurement of *J* Coupling. The direct measurement of the isotropic *J* coupling was obtained following the approach developed by Terao and co-workers.[14] In the first part of this two-part experiment, a fully refocused reference signal (S_0) was obtained from a ^{13}C Hahn echo with a total evolution time of NT_r and continuous high-power proton decoupling. The second part of this experiment was the same as the first except for the addition of continuous ^{2}H decoupling during the first half of the evolution period, i.e., prior to the refocusing π pulse. This resulted in a reduced signal, *S*. The magnitude of the isotropic *J* coupling was determined from plots of S/S_0 as a function of total evolution time.
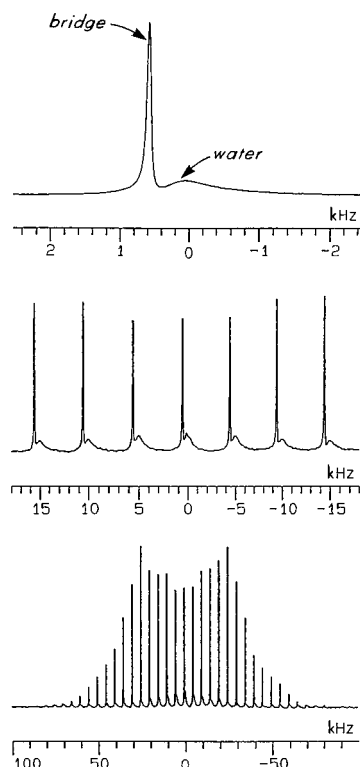
Figure 4. (bottom) The 46 MHz ^{2}H NMR spectrum of sodium hydrogen bis(4-nitrophenoxide) crystallized from 100% D$_2$O. The spectrum as the result of a Fourier transform of a complete Hahn rotational echo train following a single ^{2}H $\pi/2$ inspection pulse. Magic-angle spinning was at 5 kHz. (middle) Expansion of a part of the bottom spectrum revealing the presence of two isotropic chemical shifts. (top) Fourier transform of only the Hahn rotational-echo maxima.

TABLE 1: D/H Fractionation and Apparent Fractionation Factor (α') for Sodium Hydrogen Bis(4-nitrophenoxide) Crystallized from D$_2$O/H$_2$O Mixtures

mole fraction deuterium in solvent water	mole fraction bridge deuterium in crystal		α'
	^{2}H NMR	^{13}C−^{2}H REDOR	
1.00	1.00	0.95	
0.90	0.85		0.63
0.70	0.58	0.60	0.59
0.60	0.50		0.67

Results

Deuterium NMR. The ^{2}H NMR spectrum of the sodium hydrogen bis(4-nitrophenoxide) crystallized from D$_2$O is a Pake pattern broken into sidebands arising from the magic-angle sample spinning (Figure 4, bottom). The separation of the maxima in the Pake pattern is about 50 kHz. Expansion of the center of the pattern reveals the presence of two lines, one sharp and one broad (Figure 4, middle). The sharp line, which is shifted about 600 Hz (13 ppm) to low field from the broad line, is 5 times more intense and has the wider spinning-sideband pattern. The relative intensities of the two lines are determined accurately by the Fourier transform of the time-domain, rotational-echo maxima. This process folds all sideband intensities into the centerbands (Figure 4, top). The intensity of the sharp, low-field line depended systematically on the fraction of ^{2}H in the D$_2$O−H$_2$O solvent from which the 4-nitrophenoxide crystallized (Table 1).

The apparent isotopic fractionation factor, α', is defined as ([DX]/[HX])/(H/D)$_{H_2O}$, where [DX] and [HX] represent the fractions of D and H, respectively, bound in the bridge position of the 4-nitrophenoxide crystal, and (H/D)$_{H_2O}$ represents the ratio of atom fractions H and D in the aqueous solvents from which
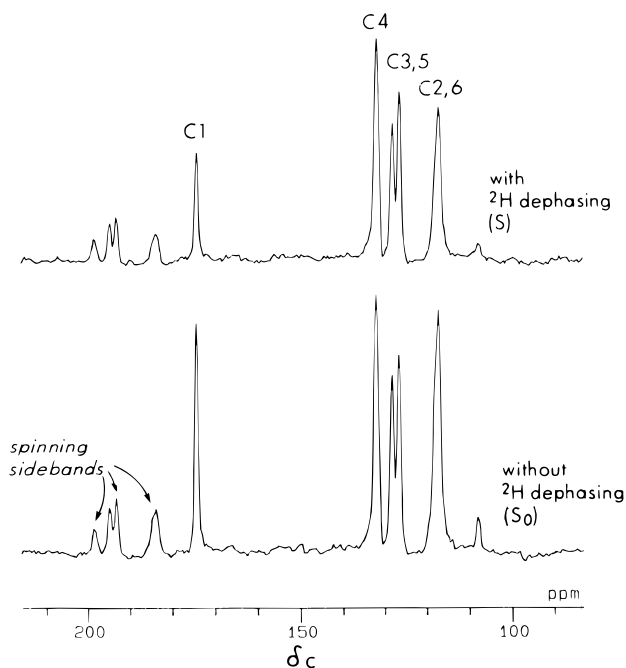
the crystals were precipitated. The value of ([DX]/[HX])/(H/D)$_{H_2O}$ for a crystal that was fully equilibrated with an aqueous solvent would be the equilibrium fractionation factor, α.[15,16] (A fully rigorous definition of α also requires the stipulation that the measurements be made for (H/D)$_{H_2O}$ = 1.0, but this fine point need not concern us here.) The average value of α' determined by ^{2}H NMR (Table 1) is 0.63, substantially less than one. We assume that the bridge hydrogen has not exchanged with atmospheric water, even though the structural water clearly has. This assumption is supported by the observation that the sample prepared from nominally pure D$_2$O is completely deuterated in the bridge position. If the uncertainty in [DX] is 0.02 (a reasonable estimate), then the uncertainty in α' is 0.08. This is consistent with the experimental scatter for α' shown in Table 1.

Experiments to study the dependence of α' on rates of crystallization were also performed on a series of samples precipitated from a mixture of 53% H$_2$O and 47% D$_2$O with variations in evaporation rates and sonication times. Significant variations in α' were observed despite the fact that isotopic fractionation of water during evaporation is slight. A diminution in α' of 20% was observed for samples prepared with slowed crystallization rates.

REDOR. The full-echo natural abundance ^{13}C REDOR spectrum of 4-nitrophenoxide has five of the six aromatic carbons resolved (Figure 5, bottom). The assignment of the C-1 carbon line is obvious from its low-field chemical shift. The other assignments are based on the extent of ^{2}H dephasing (Figure 5, top). In an eight-cycle, two-dimensional REDOR experiment with variable t_1 (Figure 2), S/S_0 decreases from 1 to about 0.5 (Figure 6) for the C-1 carbon of dihydrated sodium hydrogen bis(4-nitrophenoxide) crystallized from 100% D$_2$O. This dephasing is better simulated by a sum of strong and weak couplings (Figure 6, solid line) rather than one intermediate coupling (Figure 6, dotted line). In all of our fits, long-range coupling to distant ^{2}H in D$_2$O can be ignored. (Note: another approach to fitting these data is to introduce an anisotropic **J** tensor. This approach is discussed below.) The couplings are
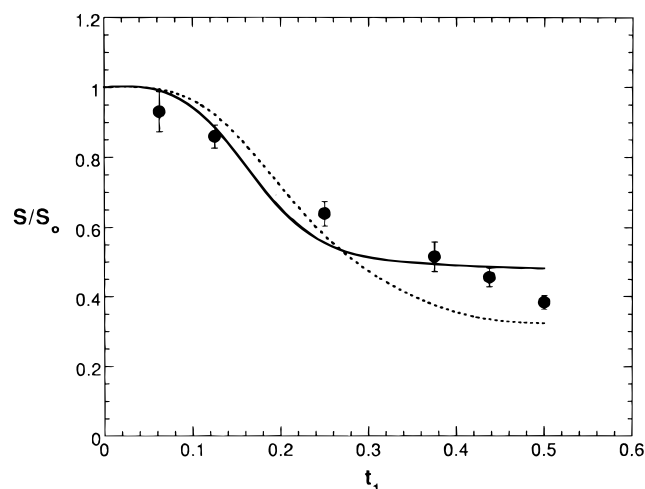

Figure 5. Full-echo (bottom) and ^{2}H-dephased (top) 75 MHz ^{13}C REDOR NMR spectra of sodium hydrogen bis(4-nitrophenoxide) crystallized from 100% D$_2$O. The pulse sequence of Figure 2 was used with $t_1 = T_r/2$ and $N_c = 8$.
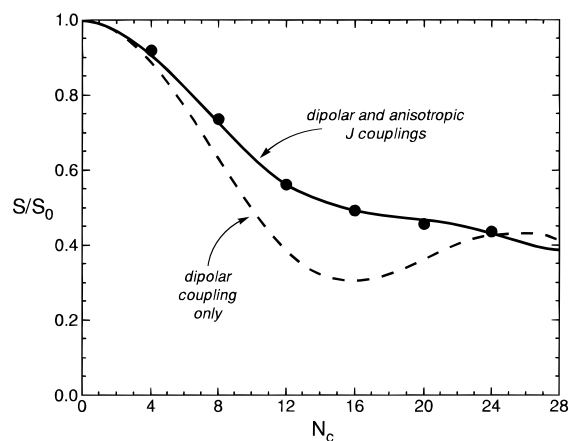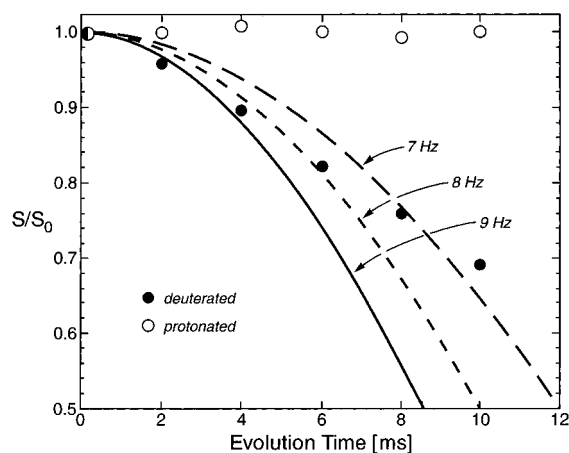
Figure 6. REDOR dephasing for the C-1 carbon of sodium hydrogen bis(4-nitrophenoxide) crystallized from 100% D_2O. The pulse sequence of Figure 2 was used with variable t_1 $N_c = 8$. The solid line is the arithmetic average of the dephasing calculated for one isolated $^{13}C-$ ^2H pair with an internuclear separation of 1.83 Å and a second with a separation of 2.50 Å. The dotted line is the dephasing calculated assuming a single dipolar coupling corresponding to a $^{13}C-^2H$ pair with an internuclear separation of 2.2 Å.
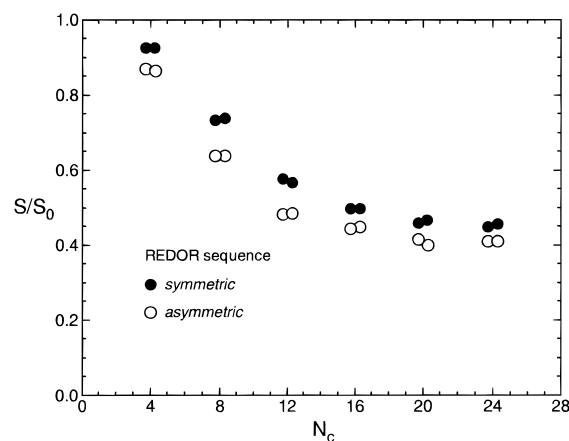

Figure 7. REDOR dephasing for the C-1 carbon of sodium hydrogen [10% ^{13}C-1]bis(4-nitrophenoxide) recrystallized from 100% D_2O. The pulse sequence of Figure 2 was used with variable $N_c = t_1 = T_r/4$. The dashed line is the dephasing calculated assuming a single dipolar coupling corresponding to a single $^{13}C-^2H$ pair with an internuclear separation of 2.2 Å. The solid line is the dephasing calculated for a single dipolar coupling of 360 Hz and an anisotropic J of 160 Hz with $\theta = 20 \pm 10°$, where θ is the relative orientation of the axially symmetric **J** and **D** tensors.

based on the crystal coordinates[1] assuming either one-half deuteron 0.95 Å from each phenoxy oxygen (as shown in Figure 1) to produce the strong and weak couplings or one deuteron at an average position to produce a single intermediate coupling.

Data for the sodium hydrogen [10%-^{13}C-1]bis(4-nitrophe-noxide) crystallized from 100% D_2O with fixed $t_1 = T_r/4$ and variable N_c are shown in Figure 7. Even more clearly than for the variable-t_1 dephasing of Figure 6, the variable-N_c dephasing behavior is poorly simulated assuming a single intermediate coupling ($D = 411$ Hz) corresponding to one deuteron at an average position midway between the two oxygen atoms (Figure 7, dashed line). A somewhat worse single-coupling fit ($D = 498$ Hz) was obtained if each site is assumed to have half deuterons 1.83 and 2.50 Å from each aromatic C-1 resulting from rapid oscillation of the deuteron between the two basic oxygen sites. However, the REDOR dephasing for the sum of

Figure 8. J coupling dephasing for the C-1 carbon of sodium hydrogen [10% ^{13}C-1]bis(4-nitrophenoxide) crystallized from 100% D_2O (closed circles) or 100% H_2O (open circles).


Figure 9. Symmetric and asymmetric REDOR dephasing for the C-1 carbon of sodium hydrogen [10% ^{13}C-1]bis(4-nitrophenoxide) crystallized from 100% D_2O. The pulse sequences of Figure 2 were used with variable $N_c = t_1 = T_r/4$.

two couplings gives an improved fit. A source for the second coupling is the anisotropic **J** tensor. In optimizing this simulation, a fixed dipolar coupling of 360 Hz was used and the size of the anisotropic J was allowed to vary. This resulted in an excellent fit to the data (Figure 7, solid line) for an anisotropic J of 160 Hz with $\theta = 20 \pm 10°$, where θ is the relative orientation of the **J** and **D** tensors.

Isotropic J Coupling. Fits to dephasing data obtained using a version of the pulse sequence of Terao et al. suggest an isotropic J coupling of 8 ± 1 Hz (Figure 8). This translates to a J(HOC) of 52 Hz, which can be compared to J(HCC) = 27 Hz for the aldehyde proton of CH_3CHO.[17] Results from REDOR experiments comparing symmetric and asymmetric placements of the dephasing pulses are shown in Figure 9. The observed differences are indicative of the existence of a substantial isotropic J coupling between the C-1 carbon and the bridge deuterium.

Temperature Dependence. The natural abundance ^{13}C NMR spectra of the dihydrated sodium hydrogen bis(4-nitrophenoxide) are essentially independent of temperature between 200 and 300 K (Figure 10). In addition, no significant change in the isotropic line shape for the C-1 carbon was observed in measurements made at 300 and 12 K on a sodium hydrogen [10% ^{13}C-1]bis(4-nitrophenoxide) sample prepared from 100% H_2O (data not shown). That is, no sign of splitting was seen at 12 K.
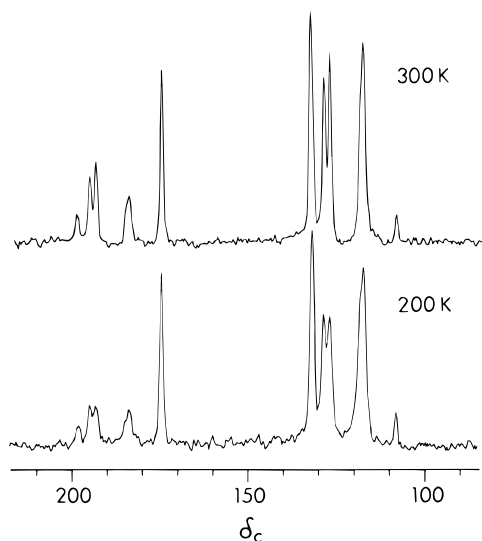
Figure 10. The 75 MHz CPMAS ^{13}C NMR spectra of sodium hydrogen bis(4-nitrophenoxide) crystallized from 100% D_2O at 300 K (top) and 200 K (bottom).

Discussion

Fractionation Factor. The 13 ppm low-field ^2H chemical shift identifies the sharp-line component of Figure 4 (top) as due to the bridging deuteron. The 50 kHz separation of maxima in the bridge-deuteron Pake pattern is about half that observed for more conventional deuterons, consistent with a bridge deuteron between two oxygens separated by 2.5 Å.[18] The broad-line component arises from structural water. We attribute the low intensity of the structural-water ^2H peak to exchange with atmospheric water and the reduction in the width of the structural-water sideband pattern to local motion. The apparent fractionation factor (α'), calculated from the concentration and intensity data of Table 1 is 0.63. Even though adventitious exchange of D by H can only lower, not raise, the fractionation factor, no adventitious exchange was observed in the bridging position of the sample prepared from 100% D_2O (Table 1, Figure 7). We conclude that α' is between 0.6 and 0.7.

However, the true value of the fully equilibrated fractionation factor, α, is probably smaller than α'. The overestimation of the true α may be traced to details of the crystallization process. The bridged anion that adds to the growing crystal has the isotopic composition appropriate for it in aqueous solution. The appropriate equilibrium composition probably changes as the anion is incorporated in the bulk solid phase, but local crystal growth appears to be faster than isotopic equilibration. Once the anion is imbedded in the bulk solid, it does not exchange. Thus, the anion in the solid must have close to the isotopic composition that it had in aqueous solution, which is probably not the equilibrium composition for the solid. This explains the sensitivity of the observed apparent fractionation factor to the method of crystallization The observed value of α' is substantially lower than values around 1.0, which are typical for hydroxylic compounds[19] but higher than the value of 0.31 $\pm$ 0.03, which has been reported for bis(4-nitrophenoxide) in acetonitrile solution.[20] The value of α for a fully equilibrated crystal is probably close to the value in acetonitrile solution, as the IR spectrum of the anion is essentially the same in the solid and in acetonitrile solution, and α is determined by the vibrational frequencies of the anion and liquid water.[21]

Fractionation factors for strongly hydrogen bonding hydrogens are often lower in nonhydroxylic solvents than in aqueous solution.[20,22] However, this effect is not expected in the aquated

crystal, as it is thought to depend on the unlimited abundance and random orientation of water in the liquid.[1,22] If α were really higher in the hydrated crystal than in acetonitrile solution, one might also expect a weaker hydrogen bond.[20] But there is no experimental indication that the hydrogen bond in the hydrated crystal is weaker than that in unhydrated salts of the same anion with other cations.[1] We conclude that α' is not an equilibrated fractionation factor for the bridging hydrogen in the dihydrated, crystalline salt. It may be close to the value of α for the bridging hydrogen in an aqueous solution of the anion. The isotopic fractionation factor of the aqueous bifluoride ion is 0.6.[23]

REDOR Dephasing. The total observed dephasing of Figures 6 and 7 is matched by either the calculated, arithmetic sum of the two dephasing curves or the combination of one dipolar coupling plus a second coupling described by an axially symmetric anisotropic **J** tensor. The experimental dephasing cannot be described using a single coupling of any value. However, the 4-nitrophenoxide C-1 carbon has only *one* chemical shift. No classical hopping rate, fast or slow, is consistent with the combination of *two* dipolar couplings and *one* chemical shift, and a quantum mechanical description with two dipolar couplings requires that the bridging proton (or deuteron) is in a *stationary* tunneling state. (We seriously considered a tunneling explanation involving stationary states but could find no supporting experimental evidence.) Therefore, the second approach, the combination of one dipolar coupling plus an anisotropic *J* interaction, is adopted. The effects of two-bond anisotropic *J* couplings have been observed in REDOR experiments on glycine[24] and cadmium phosphide.[25] An anisotropic *J* coupling in the 4-nitrophenoxide system seems plausible in view of the large isotropic *J* coupling (Figures 8 and 9).

The conclusion that a combination of dipolar and **J** tensors is present means that the bridging hydrogen of sodium hydrogen bis(4-nitrophenoxide) is in a low-barrier, double-well potential. Even though the dipolar coupling used to fit the data of Figure 7 (solid line) is consistent with either a single deuteron approximately midway between the two phenoxide oxygens or half-deuterons 1 Å from each phenoxide oxygen, there is no ambiguity about the nature of the potential. The former picture corresponds to a tight single-well potential, a possibility which can be discarded from a consideration of the X-ray and neutron scattering results. We adopt the latter picture which corresponds to a low-barrier, double-well potential and an inverse-r^3-weighted average dipolar coupling resulting from rapid oscillation of the deuteron between the two basic oxygen sites. We reject the possibility of a broad single-well potential that would allow the deuteron to move continuously between oxygen sites. In this sort of motional model, the deuteron to C-1 distance would vary from approximately 1.5 to 2.8 Å, which would result in an average dipolar coupling of about 700 Hz. Matching the experimental REDOR dephasing would therefore require an anisotropic **J** tensor twice as large as that of Figure 7, which seems implausible.

Double-Well Barrier Height. The two C-1 resonances of two solid hydrogen bis(4-nitrophenoxide) salts, in which the hydrogen is localized by the asymmetry of the crystal, are split by 7 and 10 ppm, respectively.[1] The observation of a single, unbroadened C-1 resonance at 12 K in the present salt would lead to a classical barrier hopping rate $> 10^4$ s^{-1}, even at that temperature.[26] That, in turn, gives a free energy of activation of approximately 0.4 kcal mol^{-1} assuming conventional rate theory.[27] A simple, low-barrier classical model is undoubtedly oversimplified and quantitatively unreliable, as tunneling and coupling of the hydrogenic motion to the O-O breathing motion

probably both have a strong influence on the rate.[28,29] However, as discussed above, the REDOR results are best fitted by a low-barrier double-well potential, which is consistent with what is known about similar compounds.[1-3,6] We believe the model is qualitatively correct.

A barrier of around 1 kcal mol^{-1} or less would be consistent with a fully equilibrated fractionation factor of about 0.3 ($\alpha \ll \alpha'$), as observed for the anion in acetonitrile solution.[20] A fractionation factor between 0.6 and 0.7 would suggest a barrier rising about 5 kcal mol^{-1} above the lowest allowed vibrational level,[30] and a barrier that large appears to be excluded by the low-temperature ^{13}C chemical-shift results. A low barrier is also consistent with the observation of the large chemical shift of 16.8 ppm for the bridge deuterium in the solid dihydrated sodium salt. In a low-barrier double-well potential there is a significant proton population at and near the midpoint, where the proton is furthest removed from the dense clouds of shielding electrons associated with the oxygens. Such low-field chemical shifts are a distinguishing characteristic of Speakman-Hadži ions,[1,31] of which the present compound is an example. Presumably these unusual chemical shifts all have the same origin.

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