High-Resolution Solid-State Nuclear Magnetic Resonance and X-ray Structure Study of Choline Chloride, Bromide, and Iodide

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¹³C and ²H high-resolution solid-state NMR studies of choline chloride and bromide in their radiation-sensitive α phases indicate the onset of reorientational motions at temperatures preceding the transition to their radiation-stable (higher-temperature) β phases. These motions are effectively isotropic both below and above the α -to- β phase transitions. The early onset of the rotational motion and the accompanying drop in the radiation sensitivity strongly suggest that the extreme difference in radiation sensitivity between the α and β phases is principally due to processes affected by the rotational motions and not to crystallographic differences. Choline iodide, which is radiation normal at all temperatures so far studied, shows motions of the two methylene carbons even at room temperature. An X-ray study of the latter compound at ambient temperature indicates $P_{2,1}/m$ as the possible space group with appreciable disordering between the symmetric positions related by the reflection plane defined by the O, N, and one of the methyl carbons. The reorientational motion in choline iodide becomes completely isotropic only at temperatures close to its third phase transition (ca. 163 °C). An analysis of the low-temperature spectra shows that in choline chloride and bromide the chemical shift tensor of the N-¹³CH₂ carbon is directed with σ_{33} approximately parallel to the N-CH₂ bond. The ²H spectra (OH position) show that the electric field gradient tensors of all three compounds have similar principal values, are approximately axial, and show the same effects of motion as the ¹³C.

Introduction

The biologically important choline ion exhibits as a crystalline salt a number of interesting physical properties. Choline chloride, [(CH₃)₃NCH₂CH₂OH]⁺Cl⁻, and choline bromide, $[(CH_3)_3NCH_2CH_2OH]^+Br^-$, are the most ionizing radiation-sensitive compounds known. They decompose with $G_{(-M)}$ values of about 50 000 and 10 000 respectively.¹ Their final radiolysis products are acetaldehyde and trimethylamine, and the detailed mechanisms by which they are formed have been postulated.¹ In contrast to the extraordinary sensitivity of the choline chloride and bromide, choline iodide, [(CH₃)₃NCH₂CH₂OH]⁺I⁻, and a large number of other analogues are radiation normal (see ref 1 and references therein). In addition, the radiation sensitivity of choline chloride and bromide, which is very pronounced at ambient temperature, is limited at higher temperature by phase transitions occurring respectively at ca. 78 and 89 $^{\circ}C.^2$ In addition, the radiation sensitivity is lost at temperatures well below room temperature. Choline iodide, which is radiation normal, shows three crystallographic transitions, at ca. 87, 93, and 163 °C.^{2,3} Structural data have been available so far only for choline chloride in its α^4 and β^5 phases. The former is characterized by an unusually long N–CH₂ bond of 1.56 Å as well as an OH…Cl bond of 3.07 Å. Since these are the bonds that dissociate upon γ irradiation, it has been suggested that the above features are essential to the unique radiation sensitivity of choline chloride's α form. However, since choline chloride also decomposes upon X-ray irradiation, the above long bonds could be X-ray induced artifacts. Our crystallographic studies of the choline chloride's β form⁵ have indicated a highly disordered phase with overall cubic symmetry. As a result, accurate bond lengths could not be obtained from the data. It is not obvious, therefore, whether the large differences in radiation sensitivity between the choline chloride's (and choline bromide's) α and β forms, and those between the choline chloride and choline iodide, are due to simple crystallographic differences or to more complicated molecular mechanisms.

In proton magnetic resonance studies of the line width, second moment, and T_1 and $T_{1\rho}$ relaxation times, Graham and Hannon⁶ and McDowell et al.⁷ have reported a number of rotational motions in the choline chloride and bromide just below the α -to- β phase transition. In an effort to further characterize the thermally activated rotational motions and to understand their possible relations to the

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temperature dependence of the radiation sensitivity, we have undertaken high-resolution solid-state ¹³C and ²H NMR studies of selectively labeled samples of the choline halides. In these studies we have also been interested in the possibility of determining variations in the structural (e.g., bond lengths) and dynamic (e.g., rotational motions) features of the three salts at the sensitive positions N-CH₂ and OH that could be related to the large differences in radiation sensitivity at room temperature.

In parallel with the NMR studies we have also undertaken an X-ray study of the room temperature phase of the radiation stable choline iodide salt in an effort to locate simple crystallographic differences from the radiationsensitive α phase of choline chloride.

Experimental Section

Unlabeled compounds were purchased from Nutritional Biochemicals Corp. and Sigma Chemical Co. Compounds labeled with ¹³C and ¹⁵N were synthesized from (CH₃)₃¹⁵N·HCl (95% label; Stohler Isotope Chemicals) and Br¹³CH₂CH₂OH (90% label; KOR Isotopes). (CH₃)₃N vapor, generated by KOH addition to an ethanol solution of the hydrochloride, was slowly transferred into a tube with an equivalent amount of BrCH₂CH₂OH in EtOH at -78 °C. The tube was sealed, slowly warmed to 80 °C, and maintained at that temperature for 4 h. The choline bromide product was collected by evaporation of the solvent and purified by crystallization from $EtOH-Et_2O$; with this method little scrambling (ca. 5%) of the label into the CH_2OH position was observed. The chloride and iodide salts were generated by addition to the bromide of a slight excess of Ag₂O, followed by filtration, to form choline hydroxide, $[(CH_3)_3^{15}N^{13}CH_2CH_2OH]^+OH^-$. It was converted to the desired halide on the addition of equivalent amounts of HCl or HI. The final products were dried under vacuum at ca. 100 °C, and were transferred to, and sealed in, Pyrex sample tubes (glovebox operation, to avoid atmospheric moisture). Hydroxyl deuterated samples were generated by dissolving a small amount of each choline salt in excess D_2O , then evaporating the solution and drying the crystals.

Double resonance NMR experiments were performed on a spectrometer built in the Berkeley Chemistry Department;⁸ it operates at 46.5 MHz for ¹³C, 28.4 MHz for ²H, and 185 MHz for ¹H. The ¹³C spectra were taken by using either single-contact cross polarization⁹ or 90° pulses with pulsed proton decoupling. The temperatures of the samples were stabilized to ± 0.5 °C; measured temperatures deviated from the actual temperature by not more than 2 °C.

Single crystals of choline iodide for X-ray studies were grown by vapor diffusion of Et_2O into EtOH solutions at ambient temperature. A disk-shaped crystal of ca. 0.5 mm diameter and 0.2 mm thickness was used for the X-ray measurements. Data were obtained in the $2\theta-\theta$ mode on a P_{2_1} Syntex diffractometer with Mo radiation (graphite monochrometer). In all, 1143 independent reflections were measured, of which 1089 had amplitudes greater than 2 standard deviations from counting statistics.

NMR Results and Discussion

NMR Parameters. For our labeled molecules we must consider pairs of ¹³C and ¹⁵N spins. For observations of

TABLE I: Deuterium Quadrupole Splitting Parameters

	$e^2 q Q/h$, kHz	η
choline chloride	101 ± 2	0.11 ± 0.02
choline bromide	101 ± 2	0.05 ± 0.02
choline iodide	103 ± 2	0.11 ± 0.02
choline iodide	9.3 ± 0.2	0
(109 °C)		

the ¹³C we must consider the Hamiltonian with chemical shielding and dipolar terms:

$$\mathcal{H} = -\gamma_{\rm C} H_0 I_Z (1 - \sigma_{ZZ}) + \frac{\gamma_{\rm C} \gamma_{\rm N}}{R^3} (1 - 3 \cos^2 \theta) I_Z S_Z$$
(1)

where

$$\sigma_{ZZ} = \cos^2 \alpha \, \sin^2 \beta \sigma_{11} + \sin^2 \alpha \, \sin^2 \beta \sigma_{22} + \cos^2 \beta \sigma_{33}$$

and σ_{11} , σ_{22} , and σ_{33} are the principal values of the carbon shielding tensor, R is the distance between the C and N, and θ is the angle between the CN internuclear vector and the applied field. The Euler angles α and β describe the orientation of the shielding tensor in the laboratory frame. The indirect spin-spin coupling has been neglected because of its small size: $J_{\rm CN} \leq 7$ Hz from solution measurements. For powder samples this Hamiltonian gives rise to a complex pattern dependent on the values of σ_{11} , σ_{22} , σ_{33} , R, and the Euler angles relating the orientation of σ to the molecular frame.¹⁰

For the ²H NMR studies the chemical shielding and dipolar couplings are small relative to the quadrupole coupling and can be ignored, giving the Hamiltonian

$$\mathcal{H} = -\gamma_{\rm D} H_0 I_Z + \frac{eQ(3I_Z^2 - 1)V_{ZZ}}{4}$$
(2)

where

$$V_{zz} = \cos^2 \alpha' \sin^2 \beta' V_{11} + \sin^2 \alpha' \sin^2 \beta' V_{22} + \cos^2 \beta' V_{33}$$

and V_{11} , V_{22} , and V_{33} are the principal values of the electric field gradient tensor, and α' and β' define its orientation in the laboratory frame. For a powder sample this Hamiltonian gives a spectrum with easily recognizable discontinuity frequencies corresponding to V_{11} , V_{22} , and V_{33} .¹¹

The analysis of powder spectra for structural and chemical shielding parameters must be done with spectra taken at a temperature where the features are not averaged by molecular motion. For all of the choline halides, only methyl group rotation is still active at -50 °C.^{6,7} Since these proton motions will not affect the parameters of interest, spectra taken at this temperature are suitable for analysis. The unknown parameters in eq 1 were estimated by using a computer to generate powder spectra for various sets of parameters, which were then compared with experimental spectra. Since the dipolar coupling and chemical shift anisotropy are of similar size, there are no clear features from either one. The relatively severe broadening, probably due to intermolecular dipolar couplings, makes a very accurate refinement of the parameters impossible; however, spectra generated with R = 1.5 Å, σ_{11} $\simeq -25$, $\sigma_{22} \simeq -5$, and $\sigma_{33} \simeq 35$ ppm were consistent with observed spectra when the σ_{33} direction was near (within 30°) the CN bond direction. The deuterium quadrupole coupling parameters are shown in Table I. Since very little is known about coupling constants in hydrogen-halide bonds, these values cannot be interpreted in structural

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Figure 1. Temperature dependence of the ¹³C spectrum of $[(CH_3)_3^{15}N^{13}CH_2CH_2OH]^+C\Gamma$. The crystallographic phase transition is at ca. 78 °C. Chemical shifts are referenced to the labeled carbon at high temperature. The small high-field peak is due to a small amount of label at the CH₂OH position and natural abundance signals from the methyl carbons. The separation of the high temperature peaks is 14.0 ± 0.5 ppm.



Figure 2. As in Figure 1, but for the bromide salt. The crystallographic phase transition is at ca. 89 °C. The peak separation at high temperature is 13.8 ± 0.5 ppm.

terms. However, the very similar values of $e^2 q Q$ suggest that the deuteron has a very similar environment in each of these compounds.

Effects of Motion. The temperature dependencies of the ¹³C spectra of choline halides are shown in Figures 1–3. The onset of motional narrowing is observed in all of these compounds. The sharp lines observed for the choline chloride and bromide indicate rapid "isotropic" reorientation well below the phase transitions, as had been concluded from relaxation measurements.⁶ These motions clearly persist above the phase transition to the β form.

Line shapes for reorientation under a variety of models can be calculated once the static parameters are known. In general, the coexistence of a sharp central line with broader features indicates reorientation by jumps between symmetry related positions—in this case cubic or nearly cubic. Line shapes have been described for chemical shielding;¹² however, the inclusion of a dipolar coupling will not change the behavior qualitatively. For choline chloride we roughly estimate that reorientation reaches a frequency of 3 kHz at ~ 40 °C and exceeds 10 kHz at ~ 60 °C. For the bromide these temperatures are ca. 70 and 80 °C.

The deuterium spectra of the chloride and bromide also show the growth of a sharp line at the center of the quadrupole powder pattern, reflecting the same motion observed with ¹³C. The observation of a single sharp line indicates a motion of high symmetry.¹² Since the six halide neighbors of the choline ion in the choline chloride (and presumably bromide) structure do not form a regular polyhedron,⁴ jumps of the choline among the six possible hydrogen-bonded positions would lead to a greatly reduced, but nonzero, quadrupole splitting. Thus, the choline must either rotate freely or the halide positions must be changed upon rotation to yield an "average" cubic structure.

For choline iodide considerably different behavior with temperature is observed. The features in the powder pattern are even less distinct than in the chloride and

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Figure 3. As in Figure 1, but for the iodide salt. Crystallographic phase transitions occur at ca. 87, 93, and 163 °C, and 13.4 ± 0.5 ppm at 165 °C.



Figure 4. Deuterium NMR spectra of $[(CH_3)_3NCH_2CH_2OD]^+I^-$ at two temperatures. The line at \sim -10 kHz is an artifact at the spectrometer carrier frequency.

bromide. The spectrum also narrows slightly between -50 and 25 °C, well before the onset of tumbling. This suggests a small-amplitude motion, as is discussed in the next section in conjunction with the crystallographic measurements. With increasing temperature the line narrows further in a fashion similar to the chloride and bromide, again well below the first phase transition. Below this transition the chemical shift is different from that of the chloride and bromide. With further increase in temperature the line gradually shifts to the same position as for the other halides. Deuterium measurements at temperatures above the second, but well below the third, transition show that there is a residual quadrupole splitting (Figure 4), which indicates that the motion is of lower symmetry than in the chloride and bromide, until very high temperatures, where the line completely collapses.

X-ray Studies of Choline Iodide. The crystals of choline iodide are monoclinic, with cell constants a = 5.868 (1) Å, b = 8.178 (2) Å, c = 9.082 (2) Å, $\beta = 91.33$ (2) Å, and cell volume V = 435.7 (2) Å³. The space group, from systematic absences, is either P_{2_1} or P_{2_1}/m . The unit cell volume allows only two molecules, suggesting P_{2_1} as a possible space group, since in P_{2_1}/m the molecule, in an ordered structure, would have to lie in a mirror plane. The position of the I⁻ in the space group P_{2_1} was determined from a Patterson synthesis, and its y coordinate was fixed to y =



Figure 5. Projection of the two possible conformations of the choline ion in choline iodide on the *a*,*b* plane. The dotted line represents the mirror plane. Primed atoms represent the alternate configuration of the choline.

1/4. The difference synthesis, calculated with the phases of the Γ , showed two possible choices for the choline anion, each related to the other with a mirror plane at y = 1/4. The anions shared the N, O, and one CH₃(C(1)), all three lying on the y = 1/4 plane, as well as the two other CH₃ groups (C(2) and C(3)), which lay off the plane and were mirror images of each other. The two remaining carbons, C(4) and C(5), lay above and below the mirror plane, and their mirror images defined the two alternative choices for the choline, Figure 5.

One of the choline cations was chosen and was refined in the space group P_{2_1} , with an unconstrained least-squares refinement. Gradually, as the structure was being refined the bond distances and angles started to diverge appreciably from the expected values for the choline cation. Repeated attempts to refine an ordered model, in the P_{2_1} space group, failed to converge to a meaningful geometry. This was considered as an indication that the structure might be disordered, and an alternative refinement was attempted in the space group $P_{2,}/m$. The atoms, I, N, O, and C(1) were restricted to lie on the y = 1/4 mirror plane. The refinement converged to an $R_1 = 0.093$ and gave a reasonable geometry for the choline molecule. The bond distances were generally larger than those given in ref 3 for the choline cation in choline chloride. The three N- CH_3 distances were larger by 0.04 Å while the C(4)-C(5)and C(5)-O distances were larger by 0.2 and 0.1 Å.

The constraints imposed on the molecule by the P_{2_1}/m group introduce some distortions to the three angles of $C(4)-N-CH_3$ and the C(4)-C(5)-O angle, which is 95°. The

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C(4) and C(5) carbons show large thermal motions in the direction normal to the mirror plane with rms amplitudes of 2.9 and 3.2 Å, respectively. For these atoms, the distances for their mirror images are 0.98 and 1.46 Å. These distances and the large thermal amplitude suggest a disorder in which the molecule converts from the one configuration to its mirror image with large motions of the C(4) and C(5) atoms, and smaller motions of the rest of the atoms.

These results are in agreement and provide further insight into the rotational motions of choline iodide at room temperature indicated by the NMR parameters that were presented above.

Interpretation and Discussion

The observation of isotropic reorientation below the crystallographic phase transitions in both choline chloride and bromide prompted a more detailed reinvestigation of the temperature dependence of the radiation sensitivity,¹³ with the finding that there is a considerable drop in sensitivity well below the phase transition. Early research on choline halide radiation sensitivity led to the conclusion that the loss of that sensitivity at higher temperatures was due to the observed crystal phase transition¹⁴—the higher-temperature phase being radiation resistant, and the lower-temperature phase being very radiation sensitive. More recent studies, however, showed that the radiation sensitivity was lost at temperatures ten degrees or more below the phase transition.¹³ The observation of both motion and loss of radiation sensitivity below the phase transition greatly strengthens our earlier hypothesis¹³ that molecular motions and not crystallographic differences are

responsible for the change in radiation sensitivity. In particular, the onset of these motions would be expected to interfere with the processes of radical and hydrogen atom diffusions that appear to be involved in the radiolysis.¹

The molecular motions in choline iodide are significantly different from the chloride and bromide. There is apparently an exchange between two mirror image forms, activated at about the same temperature as the C_{3} rotation. A more general reorientation sets in at higher temperatures; however, it is not isotropic as for the other halides. The difference in chemical shifts and lower symmetry of the motion suggest that choline maintaines its low-temperature conformation and hydrogen bonding until near the highest-temperature phase transition. For choline chloride different conformations are observed by crystallography in high- and low-temperature forms. The observation of the same chemical shift above and below the phase transition suggests that the change in conformation occurs with the onset of motion for the chloride, but only at higher temperature for the iodide. The continuous shift of the line at high temperature indicates a rapid exchange of the two conformers at all temperatures with a change in population with increasing temperature. These high-resolution NMR studies provide a more detailed description of the molecular dynamics than is possible with relaxation measurements alone. Together they provide a detailed description of the motions and their activation energies.

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