Deuterium Nuclear Magnetic Resonance Study of Solid Deoxycholic Acid Adducts: Structure, Dynamics, and Photochemical Reactivity

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We report cn an ²H NMR study of polycrystalline powders of several deoxycholic acid (DOCA) inclusion compounds between 150 and 350 K. The information obtained relates primarily to the conformation, flexibility, and mobility of the guest molecules, their intrachannel orientation and site multiplicity, and the effect of a photochemical guest-host reaction on these characteristics. With acetopheonone, fluoroacetophenone, acetic acid, p- and o-xylene, and acetone rapid internal methyl rotation persists at all temperatures investigated. The C-CD₃ bonds were found to fluctuate about a mean orientation within the channel. The amplitude of these fluctuations was found to be site specific, temperature dependent, and suppressible upon cooling and following occurrence of the guest-host reaction. Ring inversion was observed with tetrahydrofuran (THF), cyclohexane, and cyclohexanone. Discrete jumps about symmetry axes of the guest molecule or the host lattice were detected with acetone and o-xylene, the flip motion taking place between unequally populated sites. In some cases, such as the cyclohexane and acetic acid adducts, there are sites in the host lattice where, on the average, the guest molecules reorient isotropically.

I. Introduction

Solid deoxycholic acid inclusion compounds are built of a steroid channel-type framework wherein the guest molecules reside.¹ Some of these solid adducts are photochemically reactive, with the guest becoming bound chemically to the channel wall following UV irradiation with $\lambda > 300 \text{ nm.}^2$ The selectivity of these chemical events, involving both regio- and stereospecificity, turns them into models for enzymatic reactions, as well as chemical events taking place in ordered systems such as liquid crystals and model and biological membranes. Various physical methods such as X-ray crystallography, neutron diffraction, ESR, etc. have been used to elucidate mechanistic details.¹⁻³ The information obtained with these techniques related mainly to structural characteristics. However, dynamic properties of the guest molecules, such as conformational flexibility and overall mobility, are also necessarily related to their ability to interact chemically. Most previous physical measurements informed little on dynamics; it is these aspects we propose to study with solid-state NMR, a technique ideally suited for this purpose and thereby of an informatively complementary value. This is so as a variety of dynamic processes of unexplored nature do often take place in inclusion crystals at rates of the order of 1-10⁶ Hz, i.e. are just of the right order of magnitude to affect solid-state NMR spectra. However, the conventional NMR techniques-broad-line NMR and relaxation measurements-are not very informative, the former due to the complexity of the spectrum and the latter because they are only applicable in the limit of rapid motions, whereas spectral sensitivity to intricate details of structure and dynamics is fully borne out by, and therefore only obtainable with, slow-motional spectra, wherein features belonging to individual molecular orientations had not yet been averaged out completely.⁴

The recent development of experimental solid-state NMR methodologies,⁵ advances in theoretical formulations of dynamic effects in NMR line shapes,⁶ and progress in the chemistry of selective isotope labeling have led to a third approach, namely careful line-shape analysis of high-resolution dynamic NMR spectra,⁷ incorporating all the indispensable aspects the techniques discussed above are deprived of.

We have recorded and analyzed ²H NMR spectra from polycrystalline powders of several DOCA and apocholic acid (APA) adducts using deuterated guest molecules, both as a function of temperature and UV irradiation.

The acetophenone- d_3 and fluoroacetophenone- d_3 methyls reorient rapidly at all temperatures. We find that the axes of internal methyl rotation do not orient uniquely within the channels; rather, they wobble rapidly about a mean orientation, and we detect two types of methyl groups differing in the extent of these fluctuations. By decreasing the temperature or by triggering the photochemical reaction, one can practically suppress the amplitude of these fluctuations. The acetone- d_6 methyls both reorient internally and interchange, the latter process occurring rapidly at high temperatures and slowly at low temperatures. Moreover, the two methyl sites are not equally populated. A similar phenomenon is detected with o-xylene, with one of the two sites becoming energetically favored in a gradual fashion upon cooling. The methyl spectrum is averaged both by methyl rotation and by ring flips whereas the aromatic deuteron spectrum is affected by the latter process alone. On the other hand, the p-xylene ring does not hop at any of the temperatures examined.

With acetic acid methyl spinning is the only dynamic process operating at low temperatures. Above 230 K a second spectral component, indicative of a globally isotropic reorientation, was detected. The nature of this site, which dominates the cyclo-

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hexane- d_{12} -DOCA spectrum, is not clear.

Throughout the temperature range investigated, cyclohexanone- d_{10} and tetrahydrofuran- d_8 (THF- d_8) execute simultaneoulsy rapid ring inversion and biased reorientation about the molecular symmetry axis, with the rate of the latter process slowing down gradually upon cooling. We detect two types of THF- d_8 molecules, differing in the extent of nonuniformity of the anisotropic molecular reorientation.

Experimental details are summarized in section II. The theoretical background required to follow our interpretation of the NMR spectra is given in section III. Results are presented and discussed in section IV, and our conclusions appear in section V.

II. Experimental Section

Acetophenone- d_3 , acetone- d_6 , cyclohexane- d_{12} , acetic- d_3 acid, cyclodexanone- d_{10} , tetrahydrofuran- d_8 , and o- and p-xylene- d_{10} were purchased from Merck Sharpe and Dohme, Canada.

Deuteration at the α -position of acetophenone, fluoroacetophenone, methyl ethyl ketone, and methyl pentyl ketone was performed by refluxing with D₂O and sodium bicarbonate for 24 h and repeating the procedure until the desired percentage of deuteration (commonly 95%) was achieved.

The DOCA and APA adducts were prepared as described in ref 1-3.

The polycrystalline powders were packed tightly in 5-mm-o.d. NMR tubes 2 cm in length.

The ²H NMR experiments were performed on a Brucker CXP-300 spectrometer. The deuterium Larmor frequency was 46.07 MHz, and a horizontal solenoid coil high-power probe was used. All ²H NMR spectra were obtained with the quadrupole echo (90_{±x}, τ_e , 90_y, t) experiment with a delay time of 20-30 μ s (in cases wherein we wished to assess qualitatively whether a given line shape is of a slow-motional type, τ_e was varied between 20 and 100 μ s—see below for details) and a 90° pulse length of 3.3 μ s and by Fourier transformation of the quadrature detected echo signal after $t = 2 \tau_e$, following the first pulse. Repetition times were chosen so as to preclude spectral distortions due to T₁ anisotropy. Instrumental artifacts due to finite pulse length one is likely to encounter (see ref 7b) did not alter our conclusions. Spectra were obtained with 1000-5000 accumulations with a repetition time of 1-2 s. The temperature of the sample was controlled with a flow of N2 gas and stabilized with a temperature control unit with a precision of roughly ± 1 °C.

III. Theoretical Background

The main anisotropic term in the spin Hamiltonian of a deuterium nucleus in a solid is the quadrupole interaction.⁸⁻¹⁰ If one assumes, for the sake of simplicity, axial symmetry, the NMR spectrum of a carbon-bonded deuterium atom with the C-D bond oriented at a unique angle θ with respect to the external field H_0 is a doublet with a splitting^{9,10}

$$\Delta = (3e^2qQ/2h)(1/2)(3\cos^2\theta - 1)$$
(1)

in frequency units. $e^2 qQ/h$ is the quadrupole constant Q_0 of the axial tensor Q_0 . For a polycrystalline morphology the spectrum will be given by properly weighted superimposed doublets, resulting in a typical pattern such as that illustrated in Figure 1a, obtained with $Q_0 = 165$ kHz and a natural line width $T_2^{*-1} = 0.21$ kHz. The spectrum is symmetric about the Larmor frequency ν_0 , and the dominant features of this line shape are two strong peaks disposed symmetrically about ν_0 and separated by $\delta_0 = (3/4)Q_0$ and two extreme shoulders separated by $2\delta_0$, the former corresponding to $\theta = 90^\circ$ orientations (we shall refer to these as the



Figure 1. (a) Axial rigid-limit powder spectrum obtained with a quadrupole constant $Q_0 = 165$ kHz and a natural line width $T_2^{*-1} = 0.21$ kHz. (b) Partially averaged powder spectrum obtained by allowing the C-D bond associated with trace a to spin rapidly about a diffusion axis orthogonal to the C-D bond (i.e., $|(1/2)(3 \cos^2 \alpha - 1)| = 0.5$). (c) Asymmetric rigid-limit powder spectrum obtained with $Q_0 = 165$ kHz, $\eta =$ 0.205, $T_2^{*-1}(x) = T_2^{*-1}(y) = 2.4$ kHz, and $T_2^{*-1}(z) = 4.7$ kHz (x, y, and z denote the principal axes of the quadrupole tensor).

"perpendicular peaks") and the latter to $\theta = 0^{\circ}$ orientations (to be called the "parallel peaks").

The spectrum we just described is a rigid-limit axial powder spectrum. With onset of motion, the molecules will span the various orientations in space in a fashion determined by the nature of the dynamic process and the line shape will alter accordingly. In principle, the type of motion, the symmetry and magnitude of local orienting potentials, as well as geometric features such as tilt angles between diffusion and magnetic axes can be derived from the spectral analysis.⁶ A simple case, relevant to the forthcoming discussion, is rapid reorientation about a diffusion axis tilted at an arbitrary angle α relative to the C-D bond. Should this motion be uniformly diffusive or should the molecule execute discrete jumps between equivalent sites of symmetry equal to, or higher than, C_{3v} , partial averaging of the original tensor Q_0 to an effective axially symmetric tensor \mathbf{Q} , with its principal axis z' along the diffusion axis, will occur.⁶ The principal value Q can be calculated straightforwardly from those of Q_0 and the orientation of the diffusion axis in the local frame of the latter and vice versa: given Q, one can derive geometric parameters. With a polycrystalline powder one would therefore expect a pattern analogous to a true rigid-limit powder spectrum "scaled down " by the factor $(1/2)(3\cos^2\alpha - 1)$ (i.e., $Q = Q_0(1/2)(3\cos^2\alpha - 1)$, as illustrated in Figure 1b for $\alpha = 90^{\circ}$).

Since the quadrupole tensor is traceless, isotropic motion will lead to complete collapse of the quadrupole structure to give, in the motional narrowing regime, a single line centered at v_0 . Note, however, that a similar spectrum will result with $\alpha = 54.7^{\circ}$, the so-called "magic angle", for which $3 \cos^2 \alpha - 1 = 0$.

We shall refer repeatedly in the following presentation to partially averaged axial powder spectra obtained as a result of fast reorientation about internal diffusion axes. In many cases, Q will be determined directly from the experimental spectrum by measuring the distance δ between the perpendicular peaks.

Should the molecule investigated contain several inequivalent C–D bonds, in the sense of identical quadrupole constants Q_0 but different orientations α_i relative to the internal diffusion axis, the ²H NMR spectrum will consist of a superposition of *i* powder spectra. The potential of obtaining conformational characteristics is straightforward and will be illustrated below.

A relevant extension of the simple considerations outlined above relates to nonuniform reorientation about a unique diffusion axis. In general, in the fast-motional limit such a process will lead to an asymmetric, rather than axially symmetric, partially averaged quadrupole tensor, associated with the powder pattern shown in Figure 1c. If one can specify the nature of this nonuniformity (for example, adopting the model of flips between two sites), the line shape can be predicted. The o-xylene rings and the acetone methyls are engaged in such 180° jumps. Taking this argumentation one step further, one can qualify the bias of the motion

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⁽¹⁰⁾ Reference 5a, p 30.





Figure 2. Experimental ²H NMR spectra obtained from a polycrystalline powder of acetophenone- d_3 -APA at (a) 297 K and (b) 140 K, and spectrum c was obtained from a polycrystalline powder of methyl parathione- d_6 at ambient temperature.



Figure 3. Experimental ²H NMR spectra obtained from a polycrystalline powder of acetophenone- d_3 -DOCA (a) at 297 K and (b) following exposure to a UV source with $\lambda > 300$ nm for about 30 days, and spectrum c was obtained from a polycrystalline powder of methyl parathione- d_6 at ambient temperature.

in terms of the population ratio of the two sites.

For slower motions, of the order of the anisotropy in the quadrupole interaction, a time regime wherein spectral features particular to given orientations in space have not yet been averaged out completely, the line shape is model dependent.⁶

Finally, should the diffusion axis itself experience additional motions, the spectrum will be further averaged. We consider a simple extension of spatially fixed diffusion axes, namely wobbling rapidly within a cone centered at a given orientation in space. It is easy to see that the axial powder pattern obtained in the absence of wobbling will be further averaged to another axial powder pattern of reduced width, and an order parameter, similar to the parameter used to estimate ordering in anisotropic fluids,^{11a} can be defined as the ratio of the perpendicualr peak separation in the presence and in the absence of wobbling.

IV. Results and Discussion

a. Acetophenone- d_3 and Fluoroacetophenone- d_3 Complexes with DOCA and APA. We show in Figures 2-4 ²H NMR spectra from polycrystalline powders of acetophenone- d_3 -APA, acetophenone- d_3 -DOCA, and fluoroacetophenone- d_3 -DOCA complexes, respectively, recorded under various conditions, as detailed below.

The spectrum labeled a in Figure 2 was obtained at room temperature and b at 140 K, and spectrum c was generated by a polycrystalline powder of an inorganic compound, namely methyl parathione- d_6 . Note that spectra b and c are practically indentical with $\delta = (3/4)Q$ of the order of 40 kHz, as expected for rapidly spinning methyl groups (if we assume a value of 165 kHz for the rigid-limit quadrupole constant and a tetrahedral angle of $\alpha = 109^{\circ}$, the predicted value of δ is 42 kHz). On the other hand, the splitting between the intense peaks of spectrum a is reduced to $Q_{\rm I} = 33$ kHz, outside the range of any sensible variation in Q_0 and α . Besides, a second spectral component, apparently an axial powder pattern with a further reduced quadrupole constant $Q_{\rm II} = 22.5$ kHz, becomes visible in the spectrum, as implied by the



Figure 4. (a) Experimental ²H NMR spectra obtained from a polycrystalline powder of fluoroacetophenone- d_3 -DOCA at room temperature. (b) Experimental ²H NMR spectra obtained from a collection of cylindrical single crystals aligned with their symmetry axis perpendicular to the external magnetic field at room temperature. (c) As in (b), with the spectrum recorded at 140 K.

minor pair of peaks (corresponding to the "perpendicular" orientations) and by the stepwise decrease to zero of the intensity in the wings, suggestive of two pairs of "parallel" shoulders.

We interpret the temperature-induced changes with a wobbling motion of the C-CD₃ axes about a mean orientation within the channels, with the wobbling amplitude decreasing, hence the value of the effective quadrupole constant increasing, upon cooling. The two spectral components combining into spectrum a, with $Q_1 =$ 33 kHz and $Q_{II} = 22.5$ kHz, are interpreted to be generated by two types of acetophenone guest molecules which, due to inequivalence in their spatial disposition within the inclusion channels, experience more or less motional freedom. The difference in local mobility then becomes negligible at 140 K (cf. spectrum b), where we observe an axial powder pattern, nearly identical with spectrum c, generated by an inorganic material with methyl grups reorienting rapidly about rigid symmetry axes.

Spectrum a in Figure 3 was obtained from a polycrystalline powder of acetophenone- d_3 -DOCA adduct at room temperature; spectrum b was generated by the same sample following exposure to UV irradiation, whereby nearly 40% of the guest molecules react with the channel walls (to which they become attached following hydrogen abstraction^{1,2}), and Figure 3c is identical with Figure 2c.

It is suggested that the undue breadth of the perpendicular peaks of spectrum a is indicative of a composite line shape generated by the superposition of two axial powder spectra with unresolved pairs of perpendicular peaks.

We have carefully considered the possibility of a single-component spectrum with the particular features mentioned above stemming from slow-motional effects. Yet, slow-motional spectra should be both temperature and τ_e dependent, and we found that the spectrum under consideration is practically invariant over nearly 50 °C and upon varying τ_e between 20 and 100 μ s. Then, spectra 3a and 2a are essentially of the same type, with the 2a components better resoled than the 3a ones, implying that the DOCA channels are housing, similar to the APA tunnels, two types of acetophenone molecules differing in local mobility in the sense outlined previously.

Alterations in dominant spectral features brought about by irradiating the sample can be understood, if one assumes that the wobbling of the C-CD₃ axes is totally suppressed in those molecules that reacted. Thus, we interpret the outer shoulders of spectrum 3b to be generated by the reactive acetophenone molecules with C-CD₃ bonds immobilized as a result of chemical attachment to the channel walls and, hence, with spectra identical with line-shape 3c. This component, when superimposed on the spectrum of the unreacted acetophenone molecules, shown in

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Figure 3a, is very likely to give the composite spectrum labeled 3b. This interpretation is based on assuming that the positions of the parallel peak pertaining to the individual components (Figure 3a,c) are not shifted considerably following spectral superposition. Indeed, calculations such as those shown in Figure 3 of ref 11b support this premise.

Finally, we conceive the Figure 4 fluoroacetophenone- d_3 spectra in the same spirit. Spectra a and b were obtained respectively from a polycrystalline powder and from roughly 20 elongated single crystals aligned with their symmetry axis perpendicular to the external magnetic field H_0 . Since the C-CD₃ bonds lie, with this geometry, within the plane containing H_0 , we expect to observe a typical two-dimensional (2D) powder pattern. With the supperior resolution of the 2D spectrum as compared with the 3D line shape, the inner peaks in spectrum b, corresponding to the perpendicular components of the more mobile component II, with $Q_{\rm H} \approx 24$ kHz are clearly distinguishable besides the dominant component with $Q_I = 35.5$ kHz. Similar to acetophenone-DOCA and -APA complexes, we interpret this doubling to indicate prevalence of two types of fluoroacetophenone- d_3 guest molecules, differing in the extent of wobbling of the C-CD₃ axes. Upon cooling the sample that generated spectrum 4b, we obtained spectrum 4c: while the spectra of the low-temperature acetophenone complexes indicate that all C-CD₃ fluctuations stopped and the two guest species become, therefore, indistinguishable, the 140 K fluoroacetophenone- d_3 spectrum appears to be a composite line shape. Thus, the central portion of the 140 K spectrum is similar to that of the 297 K spectrum, contrary to the typical axially symmetric powder spectrum recorded at 140 K with the acetophenone-APA complex (cf. spectra 2b). Moreover, the monotonous decrease to zero of the intensity in the wings of spectrum 4c is also suggestive of two (rather than a single) axial powder components. We conclude that cooling down to 140 K suppresses the C–CD₃ wobbling of species I only, with Q increasing from 35.5 kHz at room temperature to roughly 40 kHz at 140 K, whereas those fluoroacetophenone molecules labeled as species II preserve the mobility experienced at higher temperatures.

b. Acetone- d_6 -APA and -DOCA Complexes. ²H NMR spectra of polycrystalline powders of the two above-mentioned complexes obtained as a function of temperature are shown in Figure 5a and 6a, respectively. The notable temperature dependence of these spectra and their invariance upon heating above room temperature are indicative of a dynamic effect. Explicitly, the acetone- d_6 guest molecules experience a dynamic process with rates of the order of the deuterium quadrupole constant, having reached completion at approximately 297 K. Unfortunately, our equipment precluded lowering the temperature below 150 K, and we could not, therefore, reach the rigid limit.

The straightforward motion one would associate with a methyl group is internal reorientation about its symmetry axis. The activation energy for this process is usually a few kcal/mol; at 150 K, methyl groups usually still spin rapidly on the NMR time scale. The expected ²H NMR spectrum is an axial powder pattern with an associated quadrupole constant of roughly 42 kHz. The overall spread in frequency units of the spectra in Figures 5a and 6a is of the order of 35–40 kHz; however, the line shapes are categorically different from an axial (or even a slightly nonaxial) powder pattern and they are obviously temperature dependent.

It is, therefore, likely that the spinning methyl groups experience an additional dynamic process with rates of the order of 40 kHz, besides internal reorientation. In fact, the main features of the room-temperature spectra in Figures 5a and 6a are typical of 180° jumps about an axis tilted at $\alpha = 54.7^{\circ}$ with the APA adduct and $\alpha = 66$ or 51° with the DOCA complex, relative to the C-CD₃ bond, as shown by the corresponding calculated spectra in Figures 5b and 6b (spectral sensitivity places an error limit of ±1° on α). Furthermore, spectra calculated with slower jump rates do also reproduce quite satisfactorily their experimental counterparts (cf. Figures 5a,b and 6a,b). The spectra in Figure 5b,c and 6b,c were computed by using the formalism of Spiess and Sillescu,¹² which



Figure 5. (a) Experimental ²H NMR spectra obtained from a polycrystalline powder of acetone- d_6 -APA recorded at temperatures denoted in the figure. (b) Spectra calculated for discrete jumps between two equivalent sites by using the analytical expression given by Spiess and Sillescu¹² for jump rates denoted in the figure, the time between the two 90° pulses in the quadrupole echo experiment $\tau_e = 30 \ \mu$ s, a natural line width about 15% of the quadrupole constant, and the tilt angle between the diffusion axis and the principal axis of the quadrupole tensor $\theta =$ 54.7°. (c) Same as (b), with the relative population of the two sites R = 2 (rather than 1 as in (b)) and $\theta = 45^\circ$ (or 66°).

accounts for the effect of τ_e , the time between the two pulses, on the NMR line shapes. In an attempt to further improve the fit, we allowed for 180° jumps between *unequally populated* sites. With R defined as the relative population, we calculated the series of line shapes shown in Figures 5c and 6c, obtained with $\alpha = 66^{\circ}$ (or 45°) for APA and 55° for DOCA and rates as denoted in the figures (again, the estimated error in α is ±1°). Although the series in Figure 5c and 6c are, to our mind, better fits to the

⁽¹²⁾ Spiess, H. W.; Sillescu, H. J. Magn. Reson. 1981, 42, 381.



Figure 6. (a) Experimental ²H NMR spectra obtained from a polycrystalline powder of acetone- d_6 -DOCA recorded at temperatures denoted in the figure. Insert: Experimental spectra obtained from a polycrystalline powder of acetone- d_6 -DOCA (a) at 300 K, (b) following exposure to a UV source with $\lambda > 300$ nm for about 30 days, and (c) at 160°, prior to irradiating the sample. (b) Same as in Figure 5b but θ = 51° (or 58.6°). (c) Same as in Figure 5c but $\theta = 55°$.

respective experimental series, the match is still subject to further improvement.

In particular, systematic discrepancies, such as those illustrated in Figure 7, where room-temperature spectra (solid lines) are shown together with their R = 2 calculated counterparts (dashed lines), were of concern to us. It can be seen that there is con-



Figure 7. (a) Superposition of top spectra from Figure 5, a (-) and c (--). (b) Superposition of top spectra from Figure 6, a (-) and c (--).

sistently a deficiency in intensity in the "shoulders" of the experimental traces.

Let us reconsider at this point the physical model: we are dealing here with interchanging methyl groups, *either* with respect to the C=O bond *or* with respect to the channel axis. From purely geometric considerations based on spectral equivalence of the two methyl groups of a given acetone molecule, the tilt angle α between the channel axis *d* and the C-CD₃ axes must lie between 60° (for pure sp² hybridization) and 90° (for *d* orthogonal to the C-CD₃ bonds). With the premise that the hopping takes place with respect to the C=O bond, α is expected to be equal to 60°, and any deviation from that value will necessarily imply distortions from a purely sp² hybrid.

We believe that the residual discrepancy between theory and experiment illustrated in Figure 7 is due to the simplicity of the dynamic model employed. For example, it would be very plausible to visualize methyl hopping to occur between two energy minima of a depth determined by the crystal fields set up by the host lattice. The proper approach would require theoretical formulations incorporating various functional forms of potentials to be then tested through line-shape simulation. With the present state of the art we feel we cannot pinpoint the value of the angle α which is contingent upon R and thereby identify the jump axis. Note that with both R = 1 and R = 2 the best-fit values of α are in the vicinity of 60° (in view of the ambiguity inherent in obtaining two sets of principal values of the partially average quadrupole tensor with (respectively) reversed signs, each spectrum in Figures 5b,c and 6b,c is associated with two solutions for α ; out of the two, one is close to 60°).

The sound and unambiguous findings emerging from our analysis are the detection of a second motion, besides internal methyl reorientation, a qualitative statement as to the intricate nature of this process to be a discrete jump type (rather than diffusive), and estimates of the jump rates. Also, realizing that ²H NMR line shapes are potentially useful to study the nature of the ordering potentials exerted on intrachannelly residing molecules is promising. Deeper insight into the physics of these systems must await more general theoretical developments and further experiments.

In spite of the uncertainties regarding the mechanistic details of the jump process, we can qualify the effect of the photochemical guest-host reaction in terms of the methyl exchange being suppressed in those acetone molecules that had reacted. This is shown in the insert of Figure 6a, where we display the spectrum obtained from a polycrystalline powder of acetone- d_6 -DOCA at room



Figure 8. Experimental ²H NMR spectra obtained from a polycrystalline powder of *p*-xylene- d_{10} -DOCA at room temperature (---) and at 140 K (--).

temperature (spectrum a), at 140 K (spectrum c), and at room temperature, following irradiation with a UV source with $\lambda > 300$ nm for approximately 30 days (spectrum b). Similar to the acetophenone- d_3 -DOCA spectra shown in Figure 3, it is easy to see that trace b is a composite spectrum consisting of a spectrum a type component (from the unreacted molecules) and a spectrum c type component, as both cooling and the chemical event apparently suppress the methyl hopping. Note that at first glance the line shape labeled b in the Figure 6a insert is reminiscent of some of the slow-motional line shapes shown in Figure 6a-c. Yet, its overall spread along the frequency axis exceeds considerably that of the spectrum labeled a in the same insert, contrary to theoretical expectations (see Theoretical Background section). The crucial argument, however, ruling out the possibility of this spectral pattern being a slow-motional spectrum is based on its τ_e and temperature independence, which were both explored prior to suggesting the interpretation of a composite spectrum, made of two superimposed components.

c. p-Xylene- d_{10} and o-Xylene- d_{10} Complexes. The respective ²H NMR spectra are shown in Figure 8 and 9. All line shapes were found to be invariant for $20 < \tau_e < 100 \ \mu s$. We interpret the room-temperature p-xylene- d_{10} spectra in terms of two superimposed powder spectra, with the central one, corresponding to $Q_{\rm I}$ = 36.6 kHz, associated with the methyl deuterons and the peaks at low and high frequencies, separated by $Q_{\rm II} \approx 115$ kHz, associated with the ring deuterons (note that the parallel shoulders of spectrum II are apparently below the noise level). The 140 K spectrum is similar to the room-temperature one, except for a slight overall expansion and a concomitant line broadening of both spectral components. We estimate $Q_{\rm I} \approx 38$ kHz and $Q_{\rm II} \approx$ 132 at 140 K, close to what one would expect for rapidly spinning methyl deuterons (42 kHz) and static ring deuterons (142 kHz, with $Q_0 = 190$ Hz).^{5a,b} The temperature dependence of Q_1 and $Q_{\rm II}$ is compatible with fluctuatiaons of the entire molecule about a unique symmetry axis, of notable amplitude at room temperature and of reduced amplitude at 150 K.

The o-xylene- d_{10} spectra shown in Figure 9 are, on the other hand, not quite as simple as the p-xylene- d_{10} ones. In general, the Figure 9 line shapes consist of an inner component with a temperature-dependent shape and outer broad peaks disposed symmetrically relative to the center. Both the overall breadth of the inner component (I) and the separation of the outer absorbance (component II) increase substantially upon cooling. Thus, we measure approximately 60 kHz for the latter parameter at 330 K and roughly 95 at 188 K. The line shapes corresponding to spectrum I are essentially asymmetric powder patterns with a temperature-dependent asymmetry parameter η .

We interpret the o-xylene- d_{10} spectra assuming that, besides internal methyl reorientation, the entire molecule is executing rapid twofold jumps about a tilted symmetry axis. This dynamic process was shown to generate an asymmetric powder pattern in the motional narrowing limit.¹² The temperature-induced changes in spectrum I were reproduced by assuming that the population ratio of the two energy minima increases gradually from 1 at room temperature to 2 at 170 K, as shown in Figure 10. The overall "scaling" mentioned previously is assigned to fluctuation of the entire, molecule about the C_{2v} axis, with amplitudes decreasing



Figure 9. Experimental ²H NMR spectra obtained from a polycyrstalline powder of o-xylene- d_{10} -DOCA at temperatures denoted in the figure.

upon lowering the temperature.

The excessive breadth of the outer peaks in Figure 9 is compatible with this picture as the pairs of aromatic deuterons, ortho and metha to the methyl groups, are expected to generate different spectra. Thus, doubling of these absorbances is indeed conspicuous in the 265 and 245 K spectra.

It would be of interest to correlate these NMR results with free energy calculations, and we plan to proceed along these lines in the foreseeable future.

d. Cyclohexane- d_{12} and Acetic- d_3 Acid Complexes with DOCA. The ²H NMR spectrum obtained from a cyclohexane- d_{12} -DOCA sample is shown in Figure 11. This is essentially a structureless line centered at the Larmor frequency, suggestive of (on the average) slow isotropic motion or a distribution of motional rates. This is definitely a solid-state spectrum, as judged from its overall width.

All we can say is that cyclohexane reorients on the average isotropically. On the basis of stoichiometric estimates and X-ray powder diffraction measurements, we believe that the cyclohexane molecules reside within the inclusion channels. Any further statement as to the physics of the system is, however, not justified.

The ²H NMR spectra obtained from a polycrystalline powder of acetic- d_3 acid-DOCA at various temperatures are shown in Figure 12. The 160 K spectrum is a typical axial powder spectrum with Q = 42.3 kHz, compatible with rapidly spinning methyl groups about uniquely oriented C-CD₃ bonds. Upon heating the powder the spectrum narrows up slightly, indicating onset of C-CD₃ wobbling, and a second isotropic component shows up, similar to the isotropic spectrum shown in Figure 11. This is, apparently, a second acetic- d_3 acid species with characteristics Solid Deoxycholic Acid Adducts



Figure 10. Experimental ²H NMR spectra obtained from a polycrystalline powder of *o*-xylene- d_{10} -DOCA at temperatures denoted in the figure (—). Spectra are calculated for discrete jumps between two sites with relative populations *R* denoted in the figure, a natural line width T_2^{*-1} about 1.5% of the quadrupole constant, the mean time between jumps $\tau = 10^{-8}$ s, and the time between the two 90° pulses in the quadrupole echo experiment $\tau_e = 30 \ \mu s \ (--)$.



Figure 11. Experimental ²H NMR spectrum obtained from a polycrystalline powder of cyclohexane- d_{12} -DOCA at ambient temperature.



Figure 12. Experimental ²H NMR spectra obtained from a polycrystalline powder of acetic- d_3 acid-DOCA at temperatures denoted in the figure.



Figure 13. Experimental ²H NMR spectra obtained from a polycrystalline powder of cyclohexanone- d_{10} -DOCA at temperatures denoted in the figure. Insert: Superposition of the top spectrum in the figure and the spectrum calculated with $Q_0 = 43.2$ kHz, $T_2^{-1} = 4$ kHz, and $\eta = 0.17$.

similar to the cyclohexane- d_{12} -DOCA spectrum (cf. Figure 11 and relevant discussion). Experiments performed on acetic-d acid support this picture.

The Figure 11 spectrum and the two upper traces in Figure 12 were found to be invariant upon varying τ_e between 20 and 100 μ s.

e. Cyclohexanone- d_{10} and THF- d_8 Adducts with DOCA. The respective ²H NMR spectra obtained from polycrystalline powders of these complexes are shown in Figures 13 and 14.

 $Cyclohexanone-d_{10}$. The top spectrum in Figure 13 is an asymmetric powder spectrum. We have to account for the overall



Figure 14. Experimental ²H NMR spectra obtained from a polycrystalline powder of tetrahydrofuran- d_8 -DOCA at temperatures denoted in the figure.

spectral breadth and shape and for the observed temperature dependence.

Note that the spectrum is structured, implying that the dynamic processes responsible for the partial averaging are anisotropic in nature. Then, a single spectral component is contingent upon rapid ring interconversion which would render all 10 deuterons equivalent. The overall breadth of the Figure 13 spectra can be reconciled by assuming rapid ring inversion and reorientation about the symmetry axis of the average conformer. Ring inversion can be viewed as a twofold jump process about an axis bisecting the D-C-D angle whereby the axial and equatorial deuterons are being interchanged. In the limit where the rate of this motion is of the order of 10^7 s or higher, an asymmetric tensor **O** obtains, with the following values for the quadrupole constants along the principal axes x, y, and z (with y defined along the jump axis, z perpendicular to y within the plane containing the two C-D bonds, and x orthogonal to both y and z): $\delta_{xx} = -D$, $\delta_{yy} = D(3$ $\cos^2 \alpha - 1$) and $\delta_{zz} = D(2 - 3\cos^2 \alpha)$, where $D = 3eqQ_0/4h$ and α is the tilt angle between the jump axis and the two C-D bonds.¹² For typical values of $Q_0 = 165$ kHz and $2\alpha = 109^\circ$, one obtains $\delta_{xx} = 123.8$ kHz, $\delta_{yy} = -1.44$ kHz, and $\delta_{zz} = 125.2$ kHz.

The tensor Q is further averaged to Q' by rapid reorientation about the symmetry axis of the average conformer. The orientation of the latter in the x,y,z frame is defined by the polar angle $\beta = 33.8^{\circ}$ and the azimuthal angle $\varphi = 90^{\circ}$, and Q' was shown previously^{6b} to be axially symmetric, provided the motion is uniform. Then, $\delta_{z'} = (3/4)Q'$ is given by the expression^{6b}

$$\delta_{z'} = (1/3)(1/2)(3\cos^2\beta - 1)\delta_{zz} - (1/2)(\delta_{xx} + \delta_{yy}) + (3/4)(\delta_{xx} - \delta_{yy})\sin^2\beta\cos 2\varphi$$

(the factor 1/3 comes from the fact that $\delta_{ii} = 2\sigma_{ii}$ and $\delta_{z'} = (2/3)\overline{\Delta\sigma}$, with the expression for $\overline{\Delta\sigma}$ in the terms of the σ_{ii} 's given in ref 6b.

By inserting the proper figures, we obtain $\delta_{z'} = 43$ kHz, subject to possible variations in the value of Q_0 and 2α .

The top spectrum in Figure 13 (or the experimental trace in the insert) is an asymmetric, rather than axially symmetric, powder spectrum, with the arithmetic mean of the two inner discontinuities of the order of 40 kHz. The simplest interpretation is to assume that reorientation of the entire molecule about its symmetry axis is a nonuniform process, rapid at high temperatures and slowing down gradually upon cooling. Again, detailed simulations would require assumptions as to the nature of the dynamic bias; we do not venture into speculations and restrict ourselves to the statements made above, with a qualitative estimate of $10^{6}-10^{5}$ s for the motional rates at lower temperatures. Technically the top spectrum would be simulated satisfactorily with $\eta = 0.17$, as shown in the Figure 13 insert.

The THF- d_8 -DOCA spectra are shown in Figure 14. Following the rationale outlined above for cyclohexanone- d_{10} , we interpret the THF-D₈ spectra in a similar fashion, except for the doubling observed in the 297 and 220 K spectra, which we assign to prevalence of two sites differing in the intricate nature of the biased molecular motion. We estimate the splitting between the inner



Figure 15. Experimental ²H NMR spectra obtained from a polycrystalline powder of α -deuterated methyl ethyl- d_5 ketone-DOCA adduct at temperatures denoted in the figure.



Figure 16. Experimental ²H NMR spectra obtained from a polycrystalline powder of α -deuterated methyl pentyl- d_5 ketone–DOCA adduct at temperatures denoted in the figure.

peaks to be roughly 44 kHz and between the outer ones, 53 kHz. The 161 K line shape in Figure 13 was found to be sensitive to varying τ_e between 20 and 100 μ s. The low-temperature spectra in Figure 14 could not be subjected to this test in view of poor signal-to-noise ratio.

f. DOCA Complexes with Deuterated Methyl Ethyl Ketone and Methyl Pentyl Ketone. ²H NMR spectra of α -deuterated methyl ethyl-d₅ ketone (MEK-d₅) and α -deuterated methyl pentyl-d₅ ketone (MPK-d₅) are shown in Figures 15 and 16, respectively. We observe a considerable temperature dependence and quite a few spectral features, indicating that these are dynamic spectra composed, apparently, of at least two spectral components.

Let us commence our discussion of the spectra in Figures 15 and 16 by outlining straightforward expectations. As we deal here with guest molecules trapped within restrictive inclusion channels, each containing deuterated methyl and methylene groups, it is logical to think of rapid internal methyl reorientation and immobile methylene deuterons. The ²H NMR spectrum is thus expected to contain an axial powder spectrum component with $\delta \approx 42$ kHz, associated with the spinning methyl groups, superimposed on a true rigid-limit spectrum, with $\delta \approx 125$ kHz, pertaining to the methylene deuterons.

These predictions are largely borne out by the 170 K MPK- d_5 spectrum in Figure 16, although the methyl component may still be affected by slow motions and the methylene spectrum is represented by the outer shoulders associated with the "perpendicular peaks" alone.

We measure at 170 K a splitting of 123.5 kHz between the extreme shoulders to be reduced gradually to 99 kHz at 320 K. Interestingly, the centrally located methyl spectrum is being squeezed by roughly the same factor with a dramatic alteration of its shape, as compared to the nearly invariant (in shape, but not in their splitting) of the "methylene shoulders". These global observations are suggestive of two dynamic processes, the former experienced by all the deuterium atoms of the MPK- d_5 molelcule and the latter affecting the methyl deuterons only.

We cannot specify the detailed nature of the first process beyond a general statement regarding internal bond flexibility or overall molecular fluctuations. On the other hand, one may hope to analyze the well-resolved methyl line shapes in terms of microscopic details of the averaging process. We will be discussing simultaneously the spectra in Figure 15 and 16. Note that broad outer peaks, disposed symmetrically with respect to the center, are visible in the Figure 15 spectra as well. Yet, due to extremely low resolution, we will not dwell on these features, except for associating them with the methylene deuterons, by following the rationale employed for the assignment of the outer shoulders in Figure 16.

Interestingly, the methyl spectra in Figure 15 and 16 evolve in a similar fashion up to about 200–210 K, whereas at higher temperatures the line shape develops into an axially symmetric powder spectrum, obtained with MEK- d_5 at 297 K, and an apparently asymmetric powder spectrum, recorded with MPK- d_5 at 320 K.

As mentioned previously, the dynamic averaging of the methyl spectra is due to the combined effect of several local motions. Due to this intrinsic complexity, we have not carried out a careful line-shape study, considering such an approach unjustified in this particular case. We wish, however, to comment on the 297 K MPK- d_5 line shape in Figure 16. This spectrum was basically invariant upon increasing the temperature up to 340 K and varying τ_e between 20 and 100 μ s, indicating that the fast-motional limit has been attained. A similar comment applies to the 297 K MEK- d_5 spectrum in Figure 15. The former spectrum is featuring three pairs of discontinuities, typical of an asymmetric powder spectrum obtained as a result of 180° jumps about a diffusion axis tilted at an arbitrary angle α relative to the principal axis of the quadrupole tensor.^{7g} By comparing the 320 K line shape in Figure 16 with published spectra, such as those shown in Figure 3 of ref 7g, we estimate α to be roughly 60–65°, suggesting that the jump axis may lie along the $CO-CD_3$ bond.

The fast-motional MEK- d_5 line shape, on the other hand, resembles closely an axial (rather than an asymmetric) powder spectrum (cf. upper trace in Figure 15).

As the rationale of the spectral interpretation presented in this work is basically qualitative in nature, a detailed line-shape analysis of the spectra in Figure 15 was not pursued. It is, however, conspicuous that the line shapes in the latter figure certainly do not reflect 180° jumps, examples of which are shown in Figures 5 and 6. As discussed previously, spectral modifications due to this type of motion would leave the perpendicular splittings of the rigid spectrum unaltered and lead, in the limit of fast hopping, to an asymmetric partially averaged spectrum. On the other hand, the evolution of the spectra in Figure 15 is typical of 120° jumps about a diffusion axis tilted at 90° relative to the CO-CD₃ bond. Line shapes calculated with this dynamic model have been published previously (for example, the reader is referred to ref 13) to find that the fit with experimental spectra of the kind shown in Figure 15 is good (the agreement could not be improved by including the effect of the time τ_e between the two pulses¹³). The 180° jumps observed with MPK- d_5 may reflect an isomerization process about the CO-CD3 bond whereas the 120° jumps observed with MEK-d₅ may reflect effective crystal field potentials set up by the host lattice.

We consider these thoughts to be tentative suggestions only. The main point to be emphasized is that, with both α -deuterated ketones examined, methyl as well as methylene deuterons reflect motional averaging due to internal isomerization processes. Besides, the end methyl groups are engaged in an additional motion controlled by internal isomerization with MEK- d_5 and by external crystal fields with MPK- d_5 , with the dominating effect determined, among other factors, by the temperature.

V. Conclusions

²H NMR spectra from polycrystalline powders of several DOCA and APA inclusion compounds were interpreted in terms of internal and overall dynamic process. We detected internal methyl group reorientation, ring inversion, reorientation about molecular symmetry axes and/or symmetry axis of the host lattice, and fluctuations of diffusion axes. Model dependence was explored, sites housing guest molecules were classified according to the motional freedom of the guest molecule or particular moieties, and the effect of a chemical reaction between guest molecules and the channel walls was substantiated in terms of structure and dynamics.

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