Carbon-13 Nuclear Magnetic Resonance Studies of a Solid Inclusion Complex

Thomas A. Early,[†] James F. Haw, Ad Bax, Gary E. Maciel,*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

and Mohindar S. Puar

Schering-Plough Corporation, Bloomfield, New Jersey 07003 (Received: January 27, 1983; In Final Form: June 20, 1983)

A solid inclusion complex containing *n*-hexane as the mobile guest component was studied via cross polarization nuclear magnetic resonance techniques. The hexane is found to yield a cross polarization spectrum, demonstrating that its motion in the lattice is anisotropic. The hexane also yields a relatively sharp spectrum with the proton decoupler off, showing reduced ^1H–^{13}C scalar splittings. A theory developed by Sack and Pople to account for the effect of ^{14}N relaxation on the appearance of the ^1H spectrum of NH_3 is applied here to account for the reduced splitting in terms of a proton–proton flip-flop mechanism. A flip-flop rate of 110–135 s^{-1} is determined for the methylene groups. The ^{13}C spin–spin relaxation time is used in a rough characterization of rotational motion of the hexane. The qualitative correlation time obtained is intermediate between that for a liquid and that for a rigid solid.

Introduction

The existence of a class of solid complexes, known as inclusion complexes, with bonding weaker than covalent between the components, has been known for some time.[1] Inclusion complexes are formed when a host compound crystallizes in the presence of a suitable guest compound. The host molecules are arranged in such a fashion to form "channels" in which the guest molecules reside. van der Waals and steric interactions trap the guest within the crystalline matrix. X-ray diffraction permits the diameter of the channel to be determined, but the guest molecules are generally too mobile to yield a definitive diffraction pattern.[2]

Although interesting in their own right, inclusion complexes are also potentially important model systems for mobile components adsorbed in zeolites, certain intercalation compounds, and other systems with channel structures. Elucidation of the structure and dynamics of an inclusion complex constitutes an important and interesting chemical problem, and is especially interesting from the standpoint of nuclear magnetic resonance. Standard solution-state NMR techniques could yield a spectrum of the guest molecules if their motion is sufficient to average dipolar interactions and chemical shift anisotropy. Solution-state techniques would not be expected to yield any information about the host, which is in a rigid environment. Dipolar cross-polarization (CP) approaches would be expected to yield a ^{13}C spectrum of the host, but the generation of a CP spectrum of the guest molecules will depend on details of their motion in the host. A rapid isotropic motion of the guest would preclude generating ^{13}C signals of the guest in a CP spectrum. The present study addresses the nature of a CP spectrum obtained in an interesting inclusion complex, and its implications regarding the nature of the spin physics and dynamics of the system.

Experimental Section

The inclusion complex used in this study has as the host compound, beclomethasone dipropionate, the structure of which is as follows:
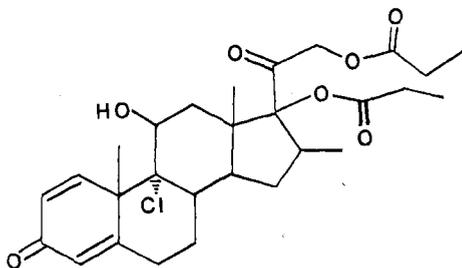
†Present address: Nicolet Magnetics Corp., 255 Fourier Ave., Fremont, CA 94539.

The guest compound is *n*-hexane. The preparation of this inclusion complex has been described in the patent literature.[3] Attempts to obtain useful X-ray diffraction data for beclomethasone dipropionate inclusion complexes have, for the most part, yielded disappointing results. This is due in part to the progressive loss of the guest molecule components under the conditions used to obtain diffraction data[4] and to the high mobility of the guest component (vide infra).

^{13}C CP/MAS spectra were obtained at 50.3 MHz on a modified Nicolet NT-200 spectrometer. Cross polarization was carried out at proton and carbon rf field strengths corresponding to 40 kHz, while the carbon signal was obtained under proton decoupling corresponding to 50 kHz. Typically, a 2-ms cross polarization period and a 3-s repetition time were used. The sample was spun at 1700 Hz, using a bullet spinner.[5] The Dixon side-band-suppression technique was employed[6] for spectra with signals from the rigid host. Relaxation rates were calculated with standard Nicolet software.

Interrupted-decoupling experiments were carried out in the usual way, inserting a delay between the cross polarization period and the start of data acquisition.[7] During this delay dephasing occurs as a result of ^{13}C–^1H dipolar interactions. A modification was made to this experiment by adding a 180° ^{13}C pulse in the center of the acquisition delay in order to refocus inhomogeneous line-broadening mechanisms. Figure 1 shows a schematic diagram of this modified interrupted-decoupling pulse sequence. In order to prevent anomalous spectral distortions, one should place the refocussing pulse at an integer number of spinner revolutions after the cross polarization period. Therefore, spinning speeds were accurately measured by the KBr method.[8]

Results and Discussion

Shown in Figure 2 is the high-resolution ^{13}C CP/MAS spectrum of the inclusion complex formed by hexane and beclomethasone dipropionate. The resonances of the complex are straightforward to assign on the basis of the solution-state spectra of the two components (data not shown). The three resonances of hexane are labeled with asterisks in Figure 2. Those three resonances are seen to be very sharp, implying that the hexane molecules are either (1) highly ordered and immobile in the complex (hence, yielding the sharp lines characteristic of a crystalline solid, rather than the broader lines of an amorphous solid), or (2) highly mobile,

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(2) Smith, A. E. *J. Chem. Phys.* **1950**, *18*, 150.
(3) U.S. Patent No. 4 225 597, issued to Schering Corp., Kenilworth, NJ.
(4) Puar, M. S., unpublished results.
(5) Bartuska, V. J.; Maciel, G. E. *J. Magn. Reson.* **1981**, *42*, 312.
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(7) Opella, S. J.; Frey, M. H. *J. Am. Chem. Soc.* **1979**, *101*, 5854.
(8) Frye, J. S.; Maciel, G. E. *J. Magn. Reson.* **1982**, *48*, 125.
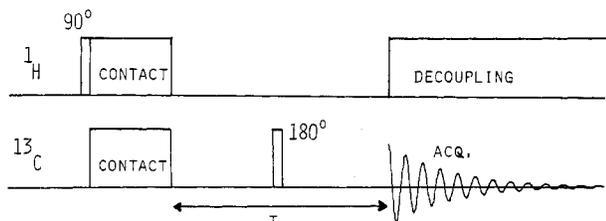
Figure 1. Diagram of the pulse sequence used to measure T_2 in the presence of proton coupling. The 180° pulse should be applied an integral number of spinner revolutions after the end of the contact.
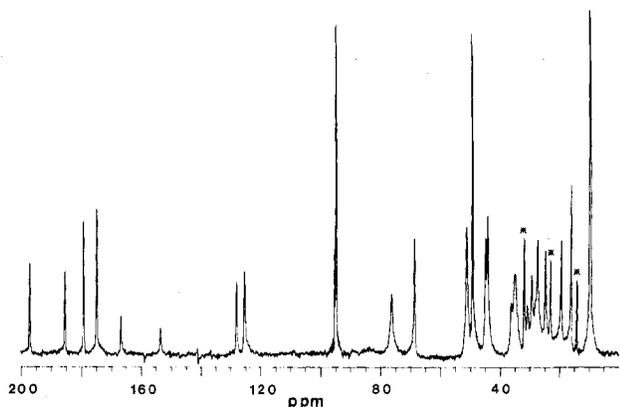
Figure 2. The 50.3-MHz ^{13}C spectrum of beclomethasone dipropionate–*n*-hexane inclusion complex. Signals due to *n*-hexane are indicated with asterisks.

Figure 3. The 50.3-MHz ^{13}C spectrum of *n*-hexane in beclomethasone dipropionate obtained with the decoupler off. Resolution enhancement has been used to improve the clarity of scalar coupling.

Figure 4. Results of the modified interrupted-decoupling experiment (Figure 1) for the inclusion compound. All signals are due to *n*-hexane.

yielding motionally averaged chemical shifts. The first possibility is unlikely on the basis of the X-ray studies.[4] The fact that the hexane signals are generated by cross polarization would therefore require an anisotropic character to the rapid averaging central to the second possibility. Such anisotropic averaging would not be expected to alter the average chemical shift dramatically from the isotropic, liquid-state average, because chemical shift anisotropies of aliphatic carbons are small.[9]

In order to obtain a measure of the intramolecular ^{13}C–^{1}H dipole–dipole interaction strengths in this system, a standard interrupted-decoupling experiment was carried out (data not shown). The results of this experiment were unexpected in that, although the resonances due to the host molecule decayed with the usual relaxation times of 10–150 μs, the resonances of the guest molecule, hexane, decayed with time constants of 1.4 $\pm$ 0.5 ms, unusually long for typical solid-state samples.

The observed transverse relaxation rates for the hexane resonances are so slow that dephasing effects other than static ^{13}C–^{1}H dipolar interactions may be contributing significantly to the observed relaxation rate during the decoupling-interrupt period. In order to examine this point, we carried out additional experiments. In one set of experiments the CP/MAS technique was used to generate the ^{13}C magnetization, but after the cross polarization period the decoupler was gated off and the free induction decay acquired without ^{1}H decoupling (with MAS). The resulting spectrum is shown in Figure 3. (In generating this spectrum a 200-μs acquisition delay without decoupling was also used in order to suppress further the signals due to the host molecule.) A 20-Hz resolution enhancement was used in the processing of this spectrum. Very surprising is the observation of broad multiplets due to indirect ^{13}C–^{1}H coupling, with the three ^{13}C resonances split into two triplets and a quartet, as expected for CH_2 and CH_3 groups. The fact that ^{13}C–^{1}H splittings are observed in the spectrum obtained without ^{1}H decoupling during acquisition shows that proton–proton flip-flops in the hexane are slow compared to (or comparable to) the reciprocal of the scalar coupling constant (about 8 ms), otherwise proton–proton spin flip-flops would ef-

fectively decouple the ^{1}H scalar interaction from the ^{13}C spins. Standard Nicolet deconvolution software was used to obtain a decomposition of the broad methylene signals into individual components. The best fit (obtained with a Lorentzian line shape) showed a separation of 100 Hz between the components of each triplet. This observed splitting is significantly less than the value, 124 Hz, expected from solution-state data. The source of the attenuation in the observed splitting is the aforesaid proton–proton flip-flops, which would be extremely efficient in a rigid solid and very slow in a true liquid. A priori another possible reason for an attenuated J_{CH} value would be anisotropic averaging of an anisotropic indirect ^{13}C–^{1}H interaction; however, the anisotropies of ^{13}C–^{1}H indirect coupling tensors are too small to account for the observed effect.[10,11]
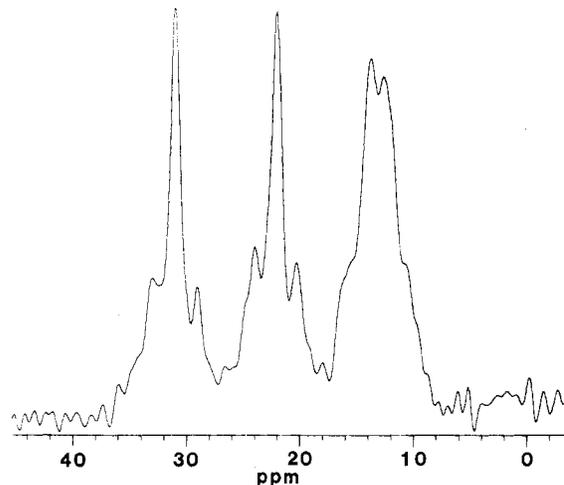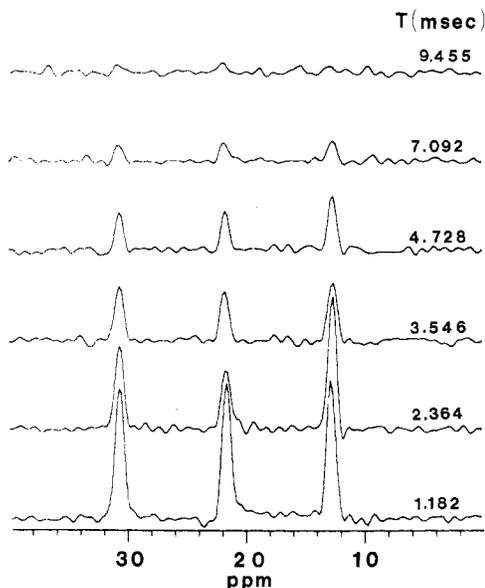
The observation of spin–spin splittings in the absence of ^{1}H decoupling has important implications for the interrupted-decoupling experiment. ^{13}C magnetization components dephase during the interrupted-decoupling period because of ^{13}C–^{1}H scalar coupling. This dephasing is in principle reversible by a refocussing pulse, if ^{1}H–^{1}H flip-flops have not rendered this interaction ho-

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(10) Emsley, J. W.; Lindon, J. C. "NMR Spectroscopy Using Liquid Crystal Solvents"; Pergamon Press: New York, 1975; p 276.
(11) Ditchfield, R.; Snyder, L. C. *J. Chem. Phys.* **1972**, *56*, 5823.
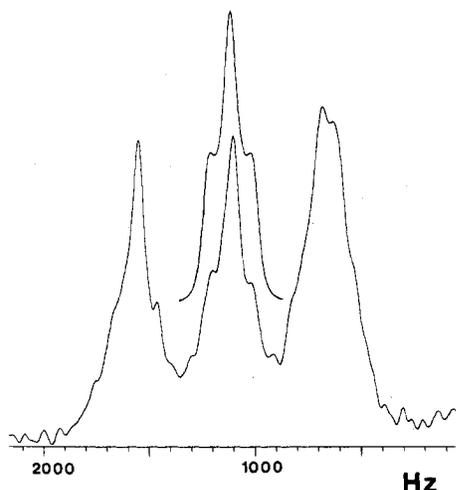
Figure 5. Comparison of the spectrum of n-hexane in beclomethasone dipropionate (spectrum is the same as in Figure 3 except for resolution enhancement) with a simulation for a methylene group undergoing ^{1}H–^{1}H flip-flops with a rate constant k of 127 s^{-1}.

mogeneous. The observation of a J_{CH} splitting means that such flip-flops have a limited rate in the hexane component of this complex. The modified interrupted-decoupling experiment (Figure 1) suppresses dephasing by reversible pathways, providing a more direct measure of transverse relaxation via irreversible pathways. The results of using this modified interrupted-decoupling experiment on the beclomethasone dipropionate–hexane complex are shown in Figure 4. The relaxation constant for the hexane ^{13}C resonances calculated from these data is larger by almost a factor of two (2.5 ± 0.5 ms) than the value obtained without the refocussing pulse. Clearly at least some of the transverse relaxation pathway(s) were suppressed by the inclusion of the refocussing pulse.

The ^{13}C–^{1}H J multiplets shown in Figure 3 were obtained with a 20-Hz exponential resolution enhancement. The multiplets obtained without such data treatment are presented in Figure 5, and are seen to be considerably broadened, with slightly attenuated splittings.

In order to explore the self-decoupling phenomenon further we have carried out spectral simulations for various trial values of the proton spin–spin flip-flop rate. The theoretical basis of these simulations were treatments by Sack[12] and Pople,[13] who considered the effects of ^{14}N spin–lattice relaxation on the manifestation of ^{14}N–^{1}H scalar coupling in proton spectra. The theoretical model employed here considers the methylene proton spin multiplet pair represented in Figure 6. The rate of proton spin–spin flip-flops that cause interconversion between state 1 and 2 is characterized by the rate constant, k. Spin–spin flip-flops are assumed to involve one proton of a specific methylene group and one proton outside that methylene group. Mutual flip-flops of the two methylene protons will also occur, but will not affect the observed splitting. The multiplet patterns shown in Figure 7 were obtained for various values of k. Comparison with Figure 5 shows that the ^{1}H–^{1}H flip-flop rate for the CH$_2$ protons of hexane in this complex can be best characterized by a rate constant of 127 s^{-1}. A good fit of the observed line shape is also achieved for a slightly lower rate constant if the simulated line shape is convoluted with a Lorentzian line of modest width (e.g., a Lorentzian line width of 10 Hz yields a best fit with a 115-s^{-1} rate constant. These simulations indicate a flip-flop rate of 110–135 s^{-1}. Additional spectral simulations, which did not include the ^{1}H–^{1}H flip-flop model, showed that the observed CH$_2$ line shape could not be fit by either a superposition of Lorentzian lines or Gaussian lines centered at $-J$, 0, and J Hz; i.e., a close fit to the observed methylene line shape required the flip-flop model. Further evidence for ^{1}H

(12) Sack, R. A. *Mol. Phys.* **1958**, *1*, 163.
(13) Pople, J. A. *Mol. Phys.* **1958**, *1*, 168.
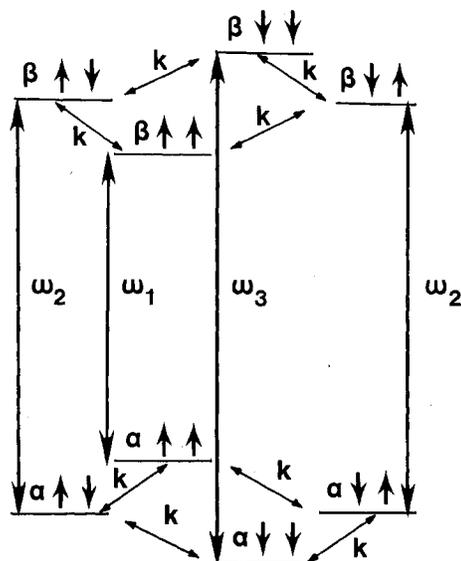
Figure 6. ^{13}C energy-level/transition diagram of CH$_2$ spin system. (Proton Zeeman energies are neglected.) α, β represent ^{13}C spin states; $\uparrow$, $\downarrow$ represent ^{1}H spin states. ω's represent ^{13}C transition frequencies; k represents the rate constant for flip-flops between two protons in different CH$_2$ groups.
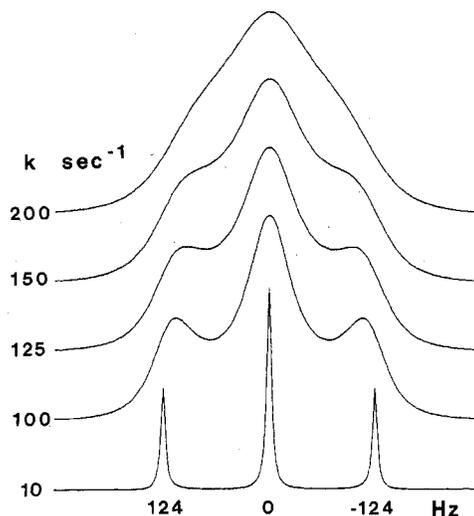
Figure 7. Simulations of methylene ^{13}C line shapes for several values of the proton–proton flip-flop rate (k).

spin–spin flip-flops is the observation that all three carbon types in hexane are cross polarized via protons with identical T_1 values (590 ms). This determination was made with the cross-polarization variation of the proton inversion-recovery experiment.[14]

Proton spin–spin flip-flops have important consequences with regard to the T_2 experiment described in Figure 1. The 180° pulse refocusses inhomogeneous interactions. But if flip-flops are not much slower than the time scale of the experiment, then scalar ^{13}C–^{1}H coupling is not fully refocussable. If a flip-flop occurs during the period between the end of the spin lock period and the 180° pulse, then incomplete refocusing of dephasing due to scalar coupling will occur. The relaxation rate measured with the modified interrupted–decoupling experiment (420 s^{-1} for the methylene groups) is only three times faster than the spin diffusion rate determined from the simulations in Figure 6. Hence, proton flip-flops must account for a significant amount of the observed nonrefocussable carbon transverse relaxation.

In order to estimate the mobility of hexane in the inclusion complex, one can in principle analyze the observed ^{13}C–^{1}H spin–spin relaxation rate in terms of a suitable model which

(14) Sullivan, M. J.; Maciel, G. E. *Anal. Chem.* **1982**, *54*, 1615.

includes anisotropic overall motion, internal motion, and multispin correlations. However, such an analysis involves more degrees of freedom than could be addressed meaningfully with the available data. Therefore, a well-known relaxation expression[15] for a simple isotropic rotor was used to estimate an approximate rotational correlation time for the hexane methylene groups. A value of 20 ns was obtained. The transverse ^{13}C relaxation rate obtained with the refocussing pulse modification of the interrupted decoupling experiment was used in this calculation. This estimated correlation time is intermediate between those commonly found for liquids and for rigid solids, a result consistent with the overall NMR behavior of this system.

(15) Abragam, A. "The Principles of Nuclear Magnetism"; Oxford University Press: London, 1973; p 296.

The work reported in this contribution has inspired further NMR studies of inclusion complexes in this laboratory. Prospects of using inclusion complexes as models of organics in zeolites, for adsorbed species, and for studied of cross-polarization dynamics of mobile components of heterogeneous solids in general are currently being assessed.

Registry No. Hexane, 110-54-3; beclomethasone dipropionate, 5534-09-8.

COMMENTS

Comparison of Electron Magnetic Resonance and X-ray Studies of the Structure of $VO(H_2O)_5^{2+}$

Sir: Van Willigen[1] has called attention to differences between some structural parameters of $VO(H_2O)_5^{2+}$ determined by electron spin echo modulation (ESEM) in frozen solutions[2] and by electron nuclear double resonance (ENDOR) in single crystals of the $Mg(NH_4)_2(SO_4)_2 \cdot 6H_2O$ Tutton salt.[3] It is also concluded that the single-crystal ENDOR results are consistent with powder ENDOR results[4,5] although the powder ENDOR results have not been analyzed to give specific structural parameters. A more complete comparison of the extant structural data is shown in Table I which includes results of separate ESEM studies from two different laboratories[2,6] as well as single-crystal X-ray crystallographic results on $VOSO_4 \cdot 5H_2O$.[7] It should be noted that the X-ray diffraction results showed that the VO^{2+} species in the sulfate crystal is coordinated to one axial water at 0.222 nm and to three slightly inequivalent equatorial waters at 0.204 nm and one equatorial sulfate at 0.198 nm where the distances are to the oxygens. Thus the X-ray results do not strictly correspond to the structure of $VO(H_2O)_5^{2+}$ but may be considered a close approximation. The structure of $VO(H_2O)_5^{2+}$ is interpreted by all techniques as four equatorial waters in a plane perpendicular to the V=O bond and one axial water in the plane of the V=O bond with the axial water being more distant than the equatorial waters from V. V–O distances are determined directly in the X-ray studies, while V–H distances are determined from the dipolar hyperfine splittings in the ESEM and ENDOR measurements. In Table I the V–H distances have been converted to V–O distances by assuming that the water molecule dipole is oriented toward V. There is some ambiguity in this conversion since the orientation of the H_2O planes relative to the V–O bond axes is not known, but the actual ambiguity in the distances is small.

From Table I the overall average V–O distances determined by all the techniques are 0.24 ± 0.02 nm for the axial waters and

(1) Van Willigen, H. *J. Phys. Chem.* 1983, *87*, 3366.
(2) Suryanarayana, D.; Narayana, P. A.; Kevan, L. *J. Phys. Chem.* 1982, *86*, 4579.
(3) Atherton, N. M.; Shackelton, J. F. *Mol. Phys.* 1980, *39*, 1471.
(4) Van Willigen, H. *J. Magn. Reson.* 1980, *39*, 37.
(5) Van Willigen, H.; Mulks, C. F.; Atherton, N. M. *Inorg. Chem.* 1982, *21*, 1708.
(6) Dikanov, S. A.; Yudanov, V. F.; Tsvetkov, Yu. D. *J. Magn. Reson.* 1979, *34*, 631.
(7) Ballhausen, C. J.; Djurinskij, B. F.; Watson, K. J. *J. Am. Chem. Soc.* 1968, *90*, 3305.

0.21 ± 0.01 nm for the equatorial waters. Both of these average values agree to less than 0.02 nm with the X-ray values. However, as mentioned above, the X-ray results may be slightly different for the actual pentahydrate structure. For the equatorial protons the agreement between the V–O or V–H distances determined by all the techniques seems to be adequate. For the axial protons the ESEM result from ref 2 seems significantly high. This is because different interpretations of the data analysis were made between ref 2 and 6. The axial proton distance from ESEM in ref 2 was determined from the interpulse time at which the modulation changed phase in a three-pulse echo experiment.[2] This analysis is felt to be valid for a point dipole approximation at distances beyond ~0.3 nm,[8] but the possible effects of a small isotropic hyperfine coupling or quadrupole coupling on this analysis have not been explored in much detail. Then a two-shell simulation analysis involving axially coordinated water and equatorially coordinated water of two-pulse echo data was performed to determine the number and distances of the equatorial protons. In the other ESEM study[6] the three-pulse echo data also gave a distance of 0.35 nm for 8–10 deuterons, *but* this distance was interpreted as due to uncoordinated waters. Then a three-shell simulation analysis involving noncoordinated waters, axially coordinated water, and equatorially coordinated water of two-pulse echo data was done. Generally, the uniqueness and the validity of the ESEM parameters for disordered systems becomes worse when multishell simulations are required. However, in this case the ESEM parameters from the three-shell simulation in ref 6 agree better with the ENDOR and X-ray parameters than do the parameters from the two-shell simulation in ref 2. Hence, the three-shell simulation seems superior in this case. It is noteworthy that the powder ESEM analysis gives results comparable to single-crystal ENDOR analysis for the ligand distances.

Comparison of the isotropic hyerfine coupling determined by *single-crystal* ENDOR with that determined by *powder* ESEM is also given in Table I. The single-crystal ENDOR study[5] gives a wide range of isotropic couplings from –0.05 to +8.67 MHz for the eight protons in the equatorial waters around vanadyl; this range of values can only be qualitatively compared with average values determined in powder systems. Powder ENDOR data of Van Willigen and co-workers was originally interpreted to give an average isotropic coupling of ~5 MHz,[4] but their subsequent work[5] has shown that a relevant part of the original powder ENDOR data was wrongly interpreted and no revised average

(8) Narayana, P. A.; Kevan, L. *J. Magn. Reson.* 1976, *23*, 385.