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Cobalt-59 NMR as a Sensitive Probe into Hydrophobic Effects

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Abstract: The cobalt-59 chemical shift is measured for cobalt hexacyanide, in the presence of various quaternary ammonium cations, in water, in methanol, and in propylene carbonate solution. A detailed study is made of the concentration dependence of the ^{59}Co shift for $K_3Co(CN)_6$, $K_2QCo(CN)_6$, $KQ_2Co(CN)_6$, and $Q_3Co(CN)_6$, where $Q^+ = {}^+N(n\text{-Bu})_4$, in water solution. The temperature and concentration dependence are investigated for $Q_3Co(CN)_6$ in H_2O, in order to provide the attendant thermodynamic parameters, for the four equilibria which are found to be sufficient to describe these systems: ion pairing, triple ion formation, quadrupole formation, and clustering of the least charged of the $[Q_XCo(CN)_6]^{3-X}$ species. All these equilibria are entropy driven, as a consequence of the hydrophobic interactions associated with the $N(n\text{-Bu})_4{}^+$ cation. As could be expected, the tendency to form polymolecular aggregates is less important in methanol than in water, and becomes negligible in propylene carbonate, an unassociated solvent.

High-resolution cobalt-59 NMR has two stumbling blocks: many cobalt complexes—in fact, all cobalt(II) and many cobalt(III) compounds—are paramagnetic; and even with low-spin cobalt(III) complexes, the ^{59}Co nucleus has such a large electric quadrupole moment ($Q = 0.404$ barn)[1] that line widths can become prohibitively large. To bypass these two difficulties, we restrict our consideration to hexacoordinated low-spin cobalt(III) complexes of O_h symmetry (CoL_6).

The stunning sensitivity of the ^{59}Co chemical shift, with a total range greater than 18 000 ppm, reflects the presence of low-lying excited states for the cobalt atom. This second-order paramagnetism, upon application of the magnetic field, corresponds for the O_h cobalt(III) complexes studied here to the mixing of the $^1A_{1g}$ ground state with the $^1T_{1g}$ excited state.

We have already shown in a preliminary communication[2] how the ^{59}Co chemical shifts for the hexacyanide triple anion $Co(CN)_6{}^{3-}$ are extremely sensitive to solvent polarity and to solvent hydrogen-bond donor strength. In this earlier work[2] the solvent was the variable, while the counterion—most often an alkali metal or a tetrabutylammonium cation—remained constant. In the present work, keeping the solvent constant (H_2O), we investigate the dependence of ^{59}Co observables, chemical shifts, and line widths upon the nature of a tetraalkyl quaternary ammonium cation Q^+.

This is a novel method for studying ion pairing involving Q^+ ions. In addition to ion pairing, the method is so sensitive that it detects also the small amounts of triple ions and of quadrupoles formed in aqueous solution. The method is quantitative, and we analyze the data for the relevant equilibrium constants. We find that the various contributing equilibria are entropy driven, as a consequence of the hydrophobic interactions displayed by the Q^+ ions. This leads to a novel view of ion pairing and hydrophobic interactions in aqueous solution.

Hence, the present work is greatly relevant to the extensive use made of such Q^+ ions in diverse applications such as phase-transfer catalysis[3-6] and studies of the hydrophobic interaction.[7] It also serves as a test for the extrathermodynamic assumption frequently made in studies of ion pairing and sovation;[8-12] it consists of the hypothesis that use of sterically hindered anions (e.g., $BPh_4{}^-$) or cations (e.g., Q^+), by blocking the approach of the counterion, renders ion pairing negligible, even in organic solvents.

Experimental Section

Potassium hexacyanocobaltate was purchased from Alfa-Ventron. Hexacyanocobaltic acid[13] was prepared by elution of $K_3Co(CN_6)$ on a strongly acidic cation exchange resin (Dowex 50 W-X8). The free acid obtained in this way was neutralized with water solutions of the suitable hydroxides to yield the hexacyanocobaltates of lithium, sodium, rubidium,

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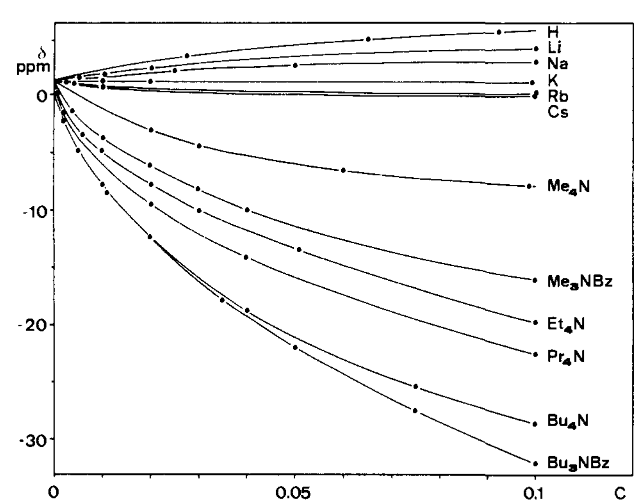

Figure 1. Plot of the ^{59}Co chemical shift for $M_3Co(CN)_6$ salts in H_2O solution, at 33.05 ± 0.02 °C, as a function of total salt concentration (M) and of the nature of the univalent cation M.

cesium, and tetraalkylammonium. The higher members of this series were extracted in dichloromethane and purified according to the procedure of Burmeister.[14] All the salts used in this study were recrystallized from water or water/methanol and dried under vacuum at 90 °C overnight. All solvents were of the purest grade available commercially (<0.02% H_2O typical), and were further passed over activated 4 Å molecular sieves.[15] Solutions were quickly transferred to 10 mm NMR tubes and fitted with a 5 mm coaxial tube containing the reference solution ($K_3Co(CN)_6$ 0.1 M in D_2O).

^{59}Co spectra were obtained on a Bruker WP-80 spectrometer at a frequency of 18.97 MHz. ^{59}Co free induction decays were accumulated by using alternating single-phase crystal filter detection, a spectral width of between 5 and 10 KHz, and 4K to 8K data points. The FIDs were exponentially multiplied (2 Hz typical), zero filled to 16K data points, and Fourier transformed. Due to the great variation of ^{59}Co chemical shifts with temperature,[16,17] all samples were thermally equilibrated in the probe during at least 30 min prior to recording the spectra. Temperature variations in the thermostating gas stream were continuously monitored with a thermistor. A second thermistor placed in a spinning NMR tube of the same weight as those used for our measurements revealed that the temperature inside the samples remained typically constant at 33.05 ± 0.02 °C for several hours. This factor sets a precision limit of less than ±0.04 ppm on the chemical shifts.

Folding of bands is a frequent occurrence in the recording of ^{59}Co FT NMR spectra, because of the big spread in chemical shift. For each absorption, the frequency was measured with respect to the external reference by enclosing both signal and reference within the spectral window, and after having ascertained that the reference line was unfolded. This was easy to check: in water solution (as in some other solvents which give little line broadening) the ^{59}Co resonance of cobalt hexacyanide is accompanied by two ^{13}C satellites, each with a relative intensity of 3% at natural abundance, whose mean frequency is offset with respect to the central line by a small positive increment (low-field shift). Hence, a folded spectrum will appear with the central resonance down field from the center of the doublet due to scalar coupling with the ^{13}C nuclei.

Viscosities, of the pure solvents and of the solutions (Figure 7a, ±2%), were measured[18] at 30 ± 0.1 °C, using a Desreux-Bischoff viscosimeter calibrated with tetrahydrofuran and water.

Qualitative Description

In our earlier work,[2] we had found small downfield shifts of the cobalt-59 resonance upon attachment of electrophilic small metallic cations to the nitrogen lone pairs of the $Co(CN)_6^{3-}$ anion. In pronounced contrast, quaternary ammonium cations Q^+ appear to cause *large upfield* shifts (Figure 1); this was the initial observation which led to the present study.

Comparison between the effects of six different tetraalkylammonium cations, ranging in size from tetramethyl to tri(*n*-butyl)benzyl indicates that the effect grows in proportion to the size of the alkyl chains in the Q^+ ion (Figure 1).

Qualitatively, the *upfield* shifts observed upon increasing the concentration in the presence of a Q^+ counterion (Figure 1) are similar to those undergone by the same $Co(CN)_6^{3-}$ anion in organic solvents as compared to water.

Ion pairing by potassium counterions has a negligible influence, as seen from Figure 1. Hence, additional and complementary information can be obtained from measurement of the ^{59}Co NMR for the two salts $KQ_2Co(CN)_6$ and $K_2QCo(CN)_6$. With all three salts, increasing the concentration produces a high-field shift of the ^{59}Co resonance.

Hence, a simple interpretation of the influence of the Q^+ cations upon the cobalt-59 resonance frequency recognizes two factors: First, by contrast to H^+ and to the alkali metal ions, the Q^+ ions are sterically prohibited from binding to the terminal nitrogens in $Co(CN)_6^{3-}$, and thus are unable to withdraw electronic charge from the lone pair—as seen from Figure 1, this is a relatively minor contribution. Second, the Q^+ cations could expel water molecules from the $Co(CN)_6^{3-}$ solvation sphere; since deshielding occurs in proportion to the strength of hydrogen bonding between $Co(CN)_6^{3-}$ and a protic solvent,[2] this partial removal would correspond to an upfield chemical shift, such as is observed. This second and predominant factor would be due to nearest-neighbor interactions. Hence, to first approximation, we consider that the observed upfield shifts result from replacement of $(NC)_5Co^{-3}—C{\equiv}N{:}H_2O$ by $Co(CN)_6^{3-},Q^+$ interactions.

Turned around, the question then becomes: what can be learned about the $Co(CN)_6^{3-},Q^+$ ion pairing interactions from observation of the ^{59}Co chemical shifts and line widths? Do these two classes of observables reflect a titration of the triple anion, as it becomes neutralized, in stepwise manner, by one, two, or three molecules of the Q^+ counterion? Furthermore, since the end result of such titrations is salt precipitation at high concentrations, should one also take into account self-association of the ion pairs, triplets, etc. to form *n*-mers? We outline below the mathematical analysis which we have applied to the data in order to answer these various queries.

The Mathematical Model

We consider the following equilibria, in which Co denotes the cobalt hexacyanide trianion and Q a substituted quaternary ammonium cation:

$$\mathrm{Co} + \mathrm{Q} \underset{}{\overset{K_1}{\rightleftharpoons}} \mathrm{CoQ} \qquad \text{(ion-pair formation)}$$

$$\mathrm{CoQ} + \mathrm{Q} \overset{K_2}{\rightleftharpoons} \mathrm{CoQ_2} \qquad \text{(triple ion formation)}$$

$$\mathrm{CoQ_2} + \mathrm{Q} \overset{K_3}{\rightleftharpoons} \mathrm{CoQ_3} \qquad \text{(neutralized salt formation)}$$

Denoting the neutralized salt CoQ_3 by C_1, we further consider the clustering equilibria:

$$C_1 + C_1 \overset{K}{\rightleftharpoons} C_2$$

$$C_2 + C_1 \overset{K}{\rightleftharpoons} C_3$$

$$C_3 + C_1 \overset{K}{\rightleftharpoons} C_4$$

etc.

This model makes the two simplifying assumptions: (i) only the least charged entities (in this case, CoQ_3) form clusters; (ii) a *single* cluster formation constant *K* is sufficient to describe the aggregation process. These assumptions are necessary for the number of parameters to be determined to remain small. Since ion pairs and triple ions are charged entities, with two and one negative charge(s), respectively, they should be less liable to self-associate than the fully neutralized CoQ_3 entities. As to the

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second assumption (ii), it also appears to be reasonable as long as all of the species present remain in solution.

Hence, the following equations can easily be derived:

$$[\mathrm{CoQ}] = K_1[\mathrm{Co}][\mathrm{Q}] \tag{1}$$

$$[\mathrm{CoQ_2}] = K_1K_2[\mathrm{Co}][\mathrm{Q}]^2 \tag{2}$$

$$[\mathrm{CoQ_3}] = K_1K_2K_3[\mathrm{Co}][\mathrm{Q}]^3 \tag{3}$$

$$[\mathrm{C_2}] = K[\mathrm{C_1}]^2 \tag{4}$$

$$[\mathrm{C}_i] = K^{i-1}[\mathrm{C_1}]^i \tag{4a}$$

Another two obtain because of the conservation of mass and of electroneutrality:

$$[\mathrm{Co}]_\mathrm{t} = [\mathrm{Co}] + [\mathrm{CoQ}] + [\mathrm{CoQ_2}] + \sum_{i=1}^{\infty} i[\mathrm{C}_i] \tag{5}$$

$$[\mathrm{Q}]_\mathrm{t} \equiv 3[\mathrm{Co}]_\mathrm{t} = [\mathrm{Q}] + [\mathrm{CoQ}] + 2[\mathrm{CoQ_2}] + 3\sum_{i=1}^{\infty} i[\mathrm{C}_i] \tag{6}$$

Equations 5 and 6 can be combined to yield:

$$[\mathrm{Q}] - 3[\mathrm{Co}] - 2[\mathrm{CoQ}] - [\mathrm{CoQ_2}] = 0 \tag{7}$$

which, in conjunction with eq 1 and 2, leads to:

$$[\mathrm{Q}] - 3[\mathrm{Co}] - 2K_1[\mathrm{Co}][\mathrm{Q}] - K_1K_2[\mathrm{Co}][\mathrm{Q}]^2 = 0 \tag{8}$$

Equation 8 rearranges into:

$$[\mathrm{Co}] = \frac{[\mathrm{Q}]}{3 + 2K_1[\mathrm{Q}] + K_1K_2[\mathrm{Q}]^2} \equiv \frac{[\mathrm{Q}]}{D} \tag{9}$$

Replacing [Co] by its values $[\mathrm{Q}]/D$ in eq 1-3 gives likewise:

$$[\mathrm{CoQ}] = K_1[\mathrm{Q}]^2/D \tag{10}$$

$$[\mathrm{CoQ_2}] = K_1K_2[\mathrm{Q}]^3/D \tag{11}$$

$$X = \mathrm{K}[\mathrm{CoQ_3}] \equiv K[\mathrm{C_1}] = KK_1K_2K_3[\mathrm{Q}]^4/D \tag{12}$$

Cluster concentrations are obtained by combining eq 4a and 12.

We now build up an equation $G(\mathrm{Q})$,[19] in the following manner: by replacing C_i (eq 4a) into (6),

$$[\mathrm{Q}] + [\mathrm{CoQ}] + 2[\mathrm{CoQ_2}] - 3[\mathrm{Co}]_\mathrm{t} + 3\sum_{i=1}^{\infty} iK^{i-1}[\mathrm{C_1}]^i = 0$$

or

$$K[\mathrm{Q}] + K[\mathrm{CoQ}] + 2K[\mathrm{CoQ_2}] - 3K[\mathrm{Co}]_\mathrm{t} + 3X\sum_{i=1}^{\infty} iX^{i-1} = 0$$

so that

$$G(\mathrm{Q}) = K[\mathrm{Q}] + K[\mathrm{CoQ}] + 2K[\mathrm{CoQ_2}] - 3K[\mathrm{Co}]_\mathrm{t} + \frac{3X}{(1-X)^2} = 0 \tag{13}$$

In order to solve the equation $G(\mathrm{Q}) = 0$, the first derivatives of eq 9-13 with respect to [Q] are computed in a straightforward manner. The solution, by a Newton-Gauss procedure, provides the value of [Q], the concentration in free cation.

Finally, we introduce the ^{59}Co chemical shifts with respect to the reference δ_0:

$$\Delta = \delta_\mathrm{sample} - \delta_0$$

$$\Delta_1 = \delta(\mathrm{CoQ}) - \delta_0$$

$$\Delta_2 = \delta(\mathrm{CoQ_2}) - \delta_0$$

$$\Delta_3 = \delta(\mathrm{CoQ_3}) - \delta_0$$

where Δ_1, Δ_2, and Δ_3 are the *limiting* chemical shifts for the pure ion pair, triple ion, and fully neutralized species, respectively. Again in order to maintain the number of adjustable parameters to a manageable level, we further impose the following constraints: (iii) additivity of chemical shifts, i.e., $\Delta_2 = 2\Delta_1$ and $\Delta_3 = 3\Delta_1$; (iv) likewise with clusters, $\Delta_i = i\Delta_3 = 3i\Delta_1$; and (v) the temperature dependence of the cobalt-59 chemical shift[16,17] is the same for all species in solution as that for the coaxial reference ($\mathrm{K_3Co(CN)_6}$ 0.1 M in $\mathrm{D_2O}$). Accordingly, Δ_1, Δ_2, Δ_3, and Δ_i are considered to be temperature invariant.

Since cobalt concentration in the ith cluster is equal to i times the cluster concentration $[\mathrm{C}_i]$:

$$\Delta = \frac{\Delta_1K[\mathrm{CoQ}] + 2\Delta_1K[\mathrm{CoQ_2}] + 3\Delta_1K\sum_{i=1}^{\infty} i^2[\mathrm{C}_i]}{K[\mathrm{Co}]_\mathrm{t}} \tag{14}$$

or:

$$\Delta = \frac{\Delta_1}{K[\mathrm{Co}]_\mathrm{t}}\left\{K[\mathrm{CoQ}] + 2K[\mathrm{CoQ_2}] + 3\frac{X(1+X)}{(1-X)^3}\right\} \tag{15}$$

Entirely similar equations can be written for the $\mathrm{KQ_2Co(CN)_6}$ and for the $\mathrm{K_2QCo(CN)_6}$ systems. For the former:

$$\mathrm{Co} + \mathrm{Q} \xrightleftharpoons{K_1'} \mathrm{CoQ}$$

$$\mathrm{CoQ} + \mathrm{Q} \xrightleftharpoons{K_2'} \mathrm{CoQ_2} \equiv \mathrm{C_1}'$$

$$\mathrm{C_1}' + \mathrm{C_1}' \xrightleftharpoons{K'} \mathrm{C_2}'$$

$$\mathrm{C_2}' + \mathrm{C_1}' \xrightleftharpoons{K'} \mathrm{C_3}'$$

For the latter:

$$\mathrm{Co} + \mathrm{Q} \xrightleftharpoons{K_1''} \mathrm{CoQ} \equiv \mathrm{C_1}''$$

$$\mathrm{C_1}'' + \mathrm{C_1}'' \xrightleftharpoons{K''} \mathrm{C_2}''$$

$$\mathrm{C_1}'' + \mathrm{C_2}'' \xrightleftharpoons{K''} \mathrm{C_3}''$$

etc.

The resulting three sets of equations are then linked in a computer program to a SIMPLEX minimization[20] subroutine. The three water systems, viz., $\mathrm{Q_3Co}$, $\mathrm{KQ_2Co}$, and $\mathrm{K_2QCo}$, are analyzed separately. In water solution, δ_0 has the fixed value +23.1 Hz relative to infinite dilution.

We have checked that *simultaneous* fitting of the three systems in water solution did not lead to significantly different answers: the resulting equilibrium constants and limiting chemical shifts do not differ much (less than 20%) from those obtained in the *independent* fitting procedure. We have also confirmed, by least-squares multiple regression, the accuracy of the derived parameters: it is better than ±10%, provided that a prior estimate of δ_1 is made by Simplex adjustment. The δ_1 value suffers from a ±20% maximum uncertainty.

Results

The best computer fit to the experimental points is shown in Figure 2 for $\mathrm{Q_3Co}$, $\mathrm{KQ_2Co}$, and $\mathrm{K_2QCo}$ in water solution.

We have also applied a similar treatment to measurements in methanol and in propylene carbonate solution, where the $\mathrm{Co(CN)_6}^{3-}$ chemical shift δ_0 is an additional unknown. Methanol is a solvent somewhat less self-associated than water,[2] but with a much smaller dielectric constant (32.6), while propylene carbonate strictly is a nonprotic solvent and has a dielectric constant close to that for water ($\epsilon = 65.1$). The results for $\mathrm{Q_3Co}$ in these two solvents are shown graphically in Figures 3 and 4.

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Table I. Final Computed Parameters, ±10%

sample	N^a	S, %	K_1	K_2	K_3	K	δ_0, Hz	Δ_1, Hz	$\langle N\rangle_{0.4}{}^b$
K_2QCo in H_2O^c	11	1.5	55			2.9	+23.1^e	203	1.5
KQ_2Co in H_2O^c	16	0.5	50	37		4.8	+23.1^e	186	1.55
Q_3Co in H_2O^c	17	2.7	51	31	19	5.4	+23.1^e	182	1.98
Q_3Co in PPC^d	19	0.002	462	163	126	0.01	−4692	212	1.01^f
Q_3Co in CH_3OH	23	0.11	516	152	105	4.3	−1276	119	1.86

[a] Number of experimental points. [b] Average cluster size at $[Co]_t = 0.4$ M. [c] Independent fitting of each system. [d] PPC = 1,2-propanediol carbonate. [e] Fixed value. [f] Extrapolated value.

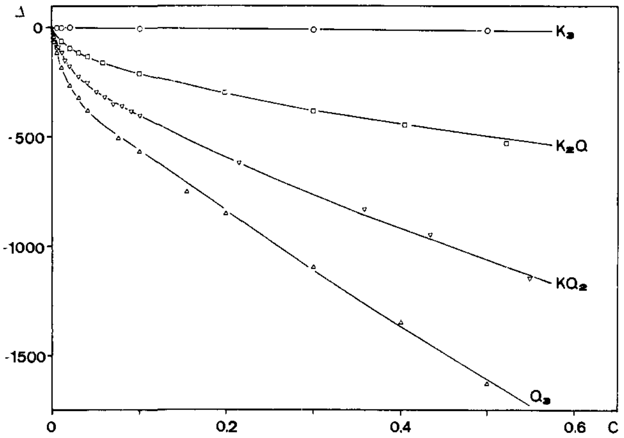

Figure 2. Curves resulting from the fitting procedure (see text), shown as plots of Δ vs. $[Co]_t$, for all three systems $K_2QCo(CN)_6$, $KQ_2Co(CN)_6$, and $Q_3Co(CN)_6$ (Q = n-Bu_4N^+), in H_2O solution, at 33.05 ± 0.02 °C. The points are experimental values. $K_3Co(CN)_6$ points are added for comparison.

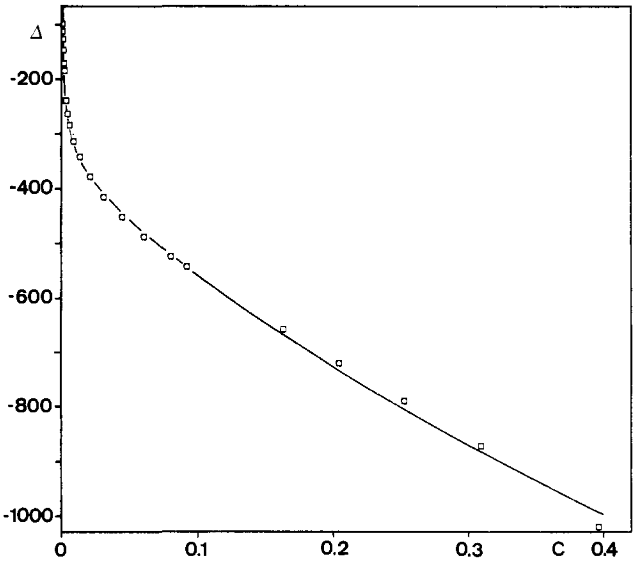

Figure 3. Comparison for $Q_3Co(CN)_6$ in MeOH, solution at 33.05 ± 0.02 °C, of the calculated curve of Δ vs. $[Co]_t$, with the experimental points.

The final values for the various quantities are given in Table I, where the goodness of fit parameter S is defined as:

$$S = \frac{100}{N}\sqrt{\sum_{i=1}^{N}\left(\frac{\Delta_{\text{obsd}} - \Delta_{\text{calcd}}}{\Delta_{\text{calcd}}}\right)^2}$$

Notice that the CoQ_3 salt forms clusters *only in the protic solvents*, and not in the aprotic propylene carbonate solution.

A useful visualization of the computed cluster sizes is from their distribution as a function of size. Defining the probability of observing an n-mer as $P_n = [C_n]/\sum_{i=1}^{\infty}[C_i]$, the average cluster size $\langle N\rangle$ at a given total cobalt concentration $[Co]_t$ is given by:

$$\langle N\rangle = \sum\nolimits^{\infty}_{i=1} iP_i = \frac{\sum^{\infty}_{i=1} i[C_i]}{\sum^{\infty}_{i=1}[C_i]} = \frac{1}{1 - X} \qquad (16)$$

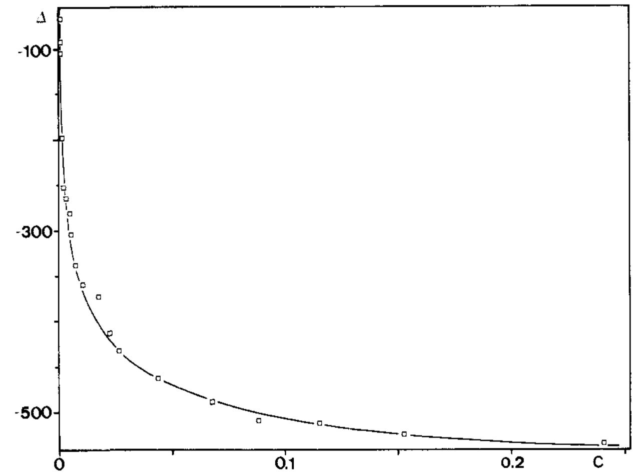

Figure 4. Comparison for $Q_3Co(CN)_6$ in 1,2-propanediol carbonate (PPC) solution, at 33.05 ± 0.02 °C, of the calculated curve of Δ vs. $[Co]_t$, with the experimental points.

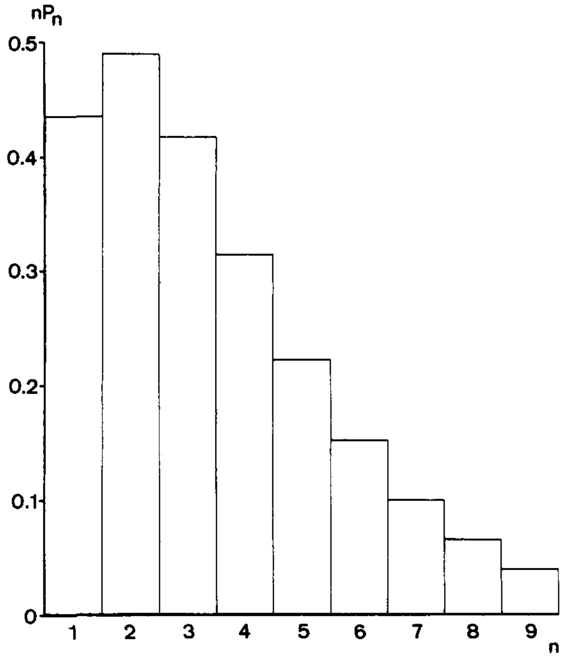

Figure 5. Calculated partition function for the n-mers formed by self-association of $Q_3Co(CN)_6$ (Q = n-Bu_4N^+) in H_2O solution at 33.05 ± 0.02 °C, with $[Co]_t$ = 0.603 M. The computed average cluster size is $\langle N\rangle$ = 2.303 under these conditions.

It should be noted here that the very simple form taken by eq 16 has its origin in our using a *single* cluster formation constant K, irrespective of cluster size (assumption ii). The calculated distribution for the clusters formed by $(n\text{-}Bu_4N)_3Co(CN)_6$ at 0.603 M concentration in water is shown in Figure 5. The partition function iP_i is not normalized, its sum over i being equal to $\langle N\rangle$ (eq 16). Interestingly, this Poisson-like distribution does not decay too abruptly: appreciable concentrations of nonamers are present in the sample, although the *average* cluster size is slightly greater than 2. We have also plotted the relative cobalt concentration

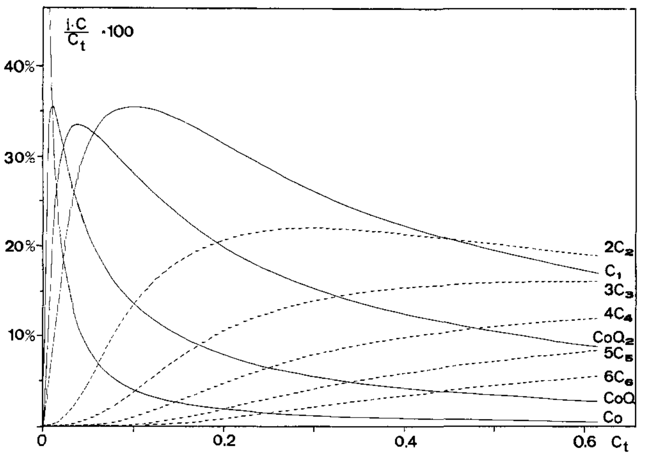

Figure 6. Normalized distribution of the species coexisting in solution as a function of total concentration (continuous lines for monomers, dotted lines for *n*-mers).

Table II. Thermodynamic Parameters for the Various Ion Pairing and Clustering Equilibria

equilibrium	ΔH, cal·mol^{-1}, ±20%	ΔS, cal·mol^{-1}·K^{-1}, ±10%
$Co + Q \rightleftarrows CoQ$ (K_1)	+87	+8.3
$CoQ + Q \rightleftarrows CoQ_2$ (K_2)	−50	+5.7
$CoQ_2 + Q \rightleftarrows CoQ_3$ (K_3)	−48	+6.1
$C_i + C_1 \rightleftarrows C_{i+1}$ (K)	+63	+3.7

of each species, $100iC/[Co]_t$, where i is the number of $Co(CN)_6^{3-}$ units in the species whose concentration is C, vs. the total concentration $[Co]_t$. This normalized graph, shown on Figure 6, gives a better overview of the overall solution composition at any given concentration. Independent confirmation for these trends, with clusters appearing at concentrations greater than ca. 0.05 M (Figure 6), is afforded by the line widths.

Rather than a monotonic increase with concentration, the plot of the line width vs. concentration for $Q_3Co(CN)_6$ in water (Figure 7a) shows an inflexion point at $[Co]_t \sim 0.04$ M, where clusters start forming (the value of $\langle N \rangle$ at this concentration is 1.07), while the viscosity of the solution does not show such an anomaly. The reduced line width (Figure 7b) increases markedly, at low concentrations, as a consequence of ion pairing which both induces an electrostatic field gradient and increases the reorientational correlation times. When the total concentration is $\simeq 0.05$ M, clusters start forming, and the line width increases again because of the greater hydrodynamic volume of the particles.

In order to gain better insight into the origin of the phenomena investigated here, viz., ion-pair and triple-ion formation and appearance and clustering of the fully neutralized and *un*dissociated salts, we have examined the temperature dependence of the cobalt-59 chemical shift on the example of $Q_3Co(CN)_6$ (Q = NBu_4), in H_2O solution.

For the corresponding enthalpy and entropy changes to be significant, an enormous data base was required: we measured the cobalt-59 chemical shifts at 22 different concentrations ranging from 0.5 M down to 10^{-4} M, and at eight temperatures, from 33.05 ± 0.02 °C up to 72.5 ± 0.3 °C. Simultaneous computer fitting of all eight sets of data points yielded the enthalpies and entropies listed in Table II. The enthalpy terms are vanishingly small—all four association phenomena are entropy determined.

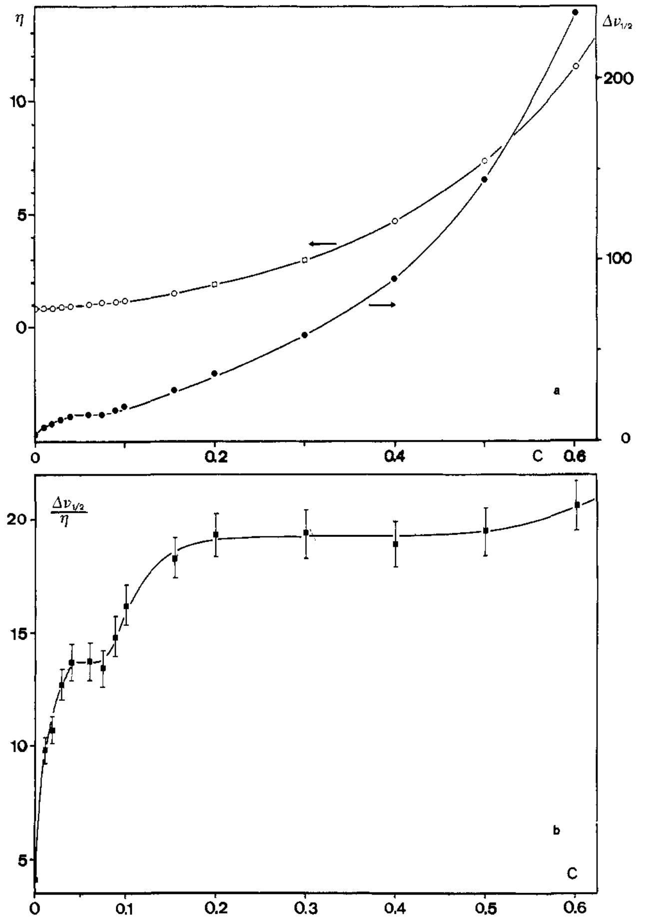

Figure 7. (a) Comparison of the plots for the line width $\Delta\nu_{1/2}$ (Hz) and for the observed bulk viscosity η (cP), as a function of total concentration. (b) Plot of the line width reduced to unit viscosity as a function of total concentration.

Discussion

Is our model pertinent to the data: could we be dealing in fact with a purely physical interaction, for which a treatment in terms of chemical equilibria would be utterly artificial and misleading? One could argue for instance that, as a result of the concentration increase, the cobalt(III) anion would come under the growing influence of the electrostatic field gradient from the presence of the cationic charges at reduced distances. The electrostatic field gradient would vary as the reciprocal of some power of distance, $1/r^n$ ($n > 2$), i.e., as the concentration elevated to power p ($p > 6$): indeed the plot of the line width vs. concentration (Figure 7) displays rapid increase of this sort. One might also expect the chemical shift to reflect an increased electrostatic field gradient at the nucleus, mediated by d electron polarization as expressed in the Sternheimer antishielding factor: Deverell's theory,[21] for instance, would predict a change in the paramagnetic part of the shielding constant linear with the increase of the quadrupolar coupling constant. This first objection is dispelled easily: it is apparent from Figure 1 that no change of the chemical shift occurs when the concentration varies between 10^{-3} and 0.6 M, with alkali metal counterions (likewise, the cobalt-59 line width remains fairly constant in that case). Also, cobalt complexes whose chemical shifts differ by ca. 100 ppm have been assumed to have equivalent quadrupolar couplings.[22]

Or one could argue that we are monitoring merely a local water depletion around the cobalt hexacyanide, as a necessary consequence of the concentration increase. Again, comparison with the rather invariant alkali metal ion salts (Figure 1) rules out such an explanation. Furthermore, there are on the average more than 100 water molecules for solvation of either the anion or the cation at 0.1 M concentration; even at 0.6 M, i.e., at the highest concentrations reached in our experiments, there are on the average 20 water molecules available to solvate each ion, more than enough to provide a first solvation sphere.

In addition, while the values of the equilibrium quotients K_1/K_3 for the Q_3Co salt (Table I) vary *qualitatively* in inverse relation

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Table III. Effective Ionic Strength (I_{eff}, mM) Debye-Hückel Activity Coefficient Factors (f_i) for Various Values of the Total Salt Concentration (C_t, mM) and of the Total Ionic Strength (I_t, mM)[a]

		hyp$_1$				hyp$_2$			
C_t	I_t	I_{eff}	f_1	f_2	f_3	I_{eff}	f_1	f_2	f_3
0	0	0	1.00	1.00	1.00	0	1.00	1.00	1.00
1	6	5.77	1.44	1.28	1.13	5.78	1.51	1.31	1.15
10	60	47.1	1.94	1.56	1.25	48.4	2.28	1.73	1.32
50	300	147	2.26	1.72	1.31	161	2.95	2.06	1.43
100	600	213	2.37	1.78	1.33	238	3.20	2.17	1.47
200	1200	280	2.44	1.81	1.35	320	3.38	2.25	1.50
500	3000	349	2.49	1.84	1.36	403	3.53	2.32	1.52

[a] These are calculated for solvent-separated pairs (hyp$_1$) and for intimate pairs (hyp$_2$) (see text).

to the dielectric constant ϵ of the solvent, when compared for methanol, propylene carbonate, and water, we do not find a linear dependence of ln K on ϵ^{-1} as would be expected on the basis of a Denison–Ramsey treatment. Hence, the electrostatic terms (charge–charge and charge-induced dipole, between the ions; charge–dipole and charge–induced dipole, between the ions and the solvents) are accompanied by another, dominant, and more specific component.

Thus, the conclusion of a *chemical* interaction, specific to the Q^+ salts, seems unescapable. Considering the thermodynamic parameters of Table II, they are surprisingly similar for all four equilibria: ion pairing, triple ion formation, full anion neutralization, and dimerization (or each individual step in cluster formation). In all these cases, the enthalpy change is minuscule; most of the negative ΔG comes from the entropy increase in the process.

Consider the first step, that of ion pairing between $(Co(CN)_6)^{3-}$ and Q^+. It implies desolvation of both ionic partners, with the resulting ion pair being solvated less than they were initially. There is a need to form a cavity within the solvent to accommodate the ion pair larger than the combined volumes for the individual cavities around the anion and the cation, due to electrostriction of water molecules around these ions. The partial loss of solvation energies upon ion pairing is offset by the electrostatic anion–cation Coulombic attraction. There is also an electrostatic repulsion term involved: when the anionic charge approaches the low dielectric environment of the *n*-butyl chains, an image charge of like sign is set up in this low dielectric slab.[23] However, all these various energy terms, viz., Coulombic attraction, electrostatic repulsion by the image charge, desolvation of the ions, solvation of the ion pair, and change in the energy of cavity formation, turn out to have a near-zero sum. The situation is somewhat reminiscent of the dissociation of haloacetic acids $XCH_2COOH \rightleftarrows XCH_2COO^- + H^+$ (X = F, Cl, Br, I), in water solution, where the acidity changes are also mostly entropy driven.[24] Here, the entropy gain must originate in the reduced solvation of the ion pair as compared to the free ions, with an attendant gain of translational degrees of freedom for water molecules.

The following two steps in the stepwise full neutralization of the triple anion by the Q^+ counterions admit a similar description. In them as in the self-association of the fully neutralized CoQ_3 particles enters the hydrophobic effect of bringing the *n*-butyl chains of the Q^+ ion in close proximity. Indeed, comparison at the qualitative or semiquantitative level (the tangents to the curves at the origin are proportional to $K_1\Delta_1$) of the curves in Figure 1 for various Q^+ ions of variable size shows, even for the first ion-pairing step, that ΔG grows the more negative as the Q^+ ions become more voluminous, just as is regularly observed for the hydrophobic effect itself.[7,25] In order to provide confirming evidence for intervention of the hydrophobic effect in all steps subsequent to ion pairing, we did a control experiment in propylene carbonate solution. In this dipolar aprotic solvent, with a dielectric constant close to that for water (ϵ = 65.1), no hydrophobic effect can occur. Indeed, the plot of $\delta(^{59}Co)$ vs. concentration of $(Bu_4N)_3Co(CN)_6$ is invariant with concentration above $[Co]_t \sim 9.10^{-2}$ M (Figure 4), which we interpret by ion pair formation in the 10^{-4}–10^{-1} M range, which is *not* followed by further association at higher concentrations.

But is one really dealing with entropy effects (Table II) associated with desolvation of the hydrophobic Q^+ ions upon ionic neutralization? The phenomenon could occur conceivably through the temperature dependence of the dielectric constant for the water solvent,[26] so that the apparent *entropy* change would be really a temperature-dependent *energy* change. But the partial derivatives $\partial\epsilon/\partial T$ appear of insufficient magnitude to account quantitatively for our observations.

A noticeable fact, which can be gleaned from Table I, is the small variation of the constant K for self-association for the cobalt salts in the two protic solvents. This is rather good evidence in support of one of the assumptions made in our mathematical model, when we decided to lump together all of the clustering steps under a *single* equilibrium constant K (assumption ii).

As for assumption i, viz., that only the fully neutralized entities CoQ_3 form clusters, it appears both as intuitively justified and as of no drastic influence on the results, considering that the self-association constant K is significantly smaller, by a factor of 4–10, than the neutralization constants K_1–K_3 (Table I). Assumptions iii and iv derive support from observation of additive chemical shift increments for solvates of a number of cations,[27,28] including direct observation of individual solvates, such as those of Al^{3+}.[29] Assumption v is really based on the observed temperature gradients of the ^{59}Co chemical shifts which vary by a mere factor of 2 between $K_3Co(CN)_6$ and $Co(acac)_3$;[17] here, the structural change is much less, since we are measuring the ^{59}Co chemical shift in the hexacyanide anion, merely changing the nature of its counterion, or anion-cation distance.

Another assumption implicit in our treatment is that the only triplets to be taken into account are the CoQ_2^- species. Indeed, even though they might suffer from less steric hindrance, formation of the Co_2Q^{5-} triplet appears less probable because of the strong repulsion between the triply charged anions.

In order for the parameters K_1–K_3 and K (Table I) to be true equilibrium constants, activities rather than concentrations should be used. In order to evaluate activity coefficients, we resort to a Debye–Hückel treatment. However, given the large magnitudes of the equilibrium constants in Table I, obviously ion pairing, triple ion formation, etc. will decrease ionic concentrations much below the total concentration of the salt C_t. Hence, it will not be sufficient to make a crude estimate of the activities based on the ionic strength calculated on the basis of C_t only. Rather, activities have to be determined from the concentrations of ions *effectively* present in the solutions. Defining "true" equilibrium constants $K_{i,t} = K_i f_i$, where f_i is the appropriate product and quotient of activity coefficients, the problem is to determine the f_is. For this purpose, we use the equations of Scatchard, Rush, and Johnson.[30]

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In order not to prejudge the tight or loose structure of the ions pairs formed by the Q^+ cations and the cobalt hexacyanide anion, we do the calculations for *both* assumptions: we take a parameter $a' \simeq 6$ for the system in which the distance between centers is 11.6 Å, as representative of a solvent-separated pair,[31,32] while a parameter $a' \simeq 4$ is appropriate to anion–cation distances of 7–7.5 Å, corresponding to intimate pairs, as found in organic solvents.[33] The results are shown in Table III for $Co(CN)_6^{3-},3^+N(n\text{-}Bu)_4$ in aqueous solution as an illustration. They are obtained from an iterative self-consistent procedure, starting with the *apparent* equilibrium constants of Table I as input for determining the concentrations of each of the ionic species from eq 1–13 according to the cyclic scheme:

$$K_{\mathrm{i,1N}} \xrightarrow{(1\text{–}13)} [\mathrm{Co,CoQ,CoQ_2,C}_i] \xrightarrow[\text{et al.}^{30}]{\text{Scatchard}} \{f_1,f_2,f_3\} \rightarrow K_{i,\mathrm{OUT}}$$

using the method of Scatchard, Rush, and Johnson.[30] In general convergence is obtained in less than 10 iterations, i.e., I_{eff} is obtained and remains invariant within $\pm 10^{-5}$ M (Table III).

These results show that neglect of activities, as in Table I, leads to a maximum variation by a factor of 3.5 at most for the whole of the concentration range studied. We notice also that the activity coefficient factors f_i vary relatively little, from ca. 1.5 to 3, as the total concentration C_t goes from 1–200 mM; most of our experimental points in Figure 2, which lead to the parameters in Table I, are determined in this concentration range.

The two hypotheses (hyp_1 and hyp_2) considered in the calculations of Table III should be considered as limiting assumptions: the interionic separation of $^+NBu_4$ and $Co(CN)_6^{3-}$ should be in the range of 7–12 Å indeed.

In short, neglect of activity coefficients does not affect significantly the conclusions: the "true" thermodynamic equilibrium constants $K_{1,t}$–$K_{3,t}$ do not differ much from the apparent values K_1–K_3 of Table I. As for K, which describes the self-association of the uncharged species, Table I gives the "true" values within the Debye–Hückel approximation.

Considering now the mean aggregation numbers (Table I, and Figure 5), *dimers* are the predominant species to form in the protic solvents. This is probably due to steric reasons, i.e., to the difficulty of packing into a single solvent cavity up to six (or more) voluminous NBu_4^+ cations together with a pair of cobalt hexacyanide anions which are also bulky. The distribution of *n*-mers (Figure 6) also shows that, rather than a micelle-like microemulsion, one deals with a normal aggregation phenomenon. But this could be an artefact from our model, since obviously assumption ii will impose the calculated distribution.

A much more significant conclusion, because it was much less expected, is the considerable amount of ion pairing, triple ion formation, etc. in these systems. As seen from the quite large values of the equilibrium constants K_1–K_3, in water solution, there are significant amounts of undissociated species. There are a number of studies showing appreciable amounts of ion pairs involving quaternary ammonium salts Q^+ in low dielectric solvents such as THF, chloroform, methylene chloride, acetonitrile, acetone, chlorobenzene, ..., at interionic distances of 5–10 Å from a halide, tetraphenyl borate, perchlorate, or picrate counterion.[33-39]

Interionic separations have also been derived, for systems closely similar to those studied here, from isotropic paramagnetic shifts of the proton resonances of a Q^+ ion paired to a magnetically anisotropic anion,[40] such as $[Co(Ph_3P)Br_3]^-$. They often range between 5 and 8 Å for water solutions.[40] However, these values were obtained assuming a predominantly dipolar mechanism for the observed isotropic shifts. They are semiquantitative at best, because of the competing contact mechanism, which has been shown to dominate in certain cases.[41-43] Such studies are also limited to 1:1 electrolytes, because nonaxial symmetry can be present in 2:1 and 3:1 electrolytes.[40]

The important aspect of our finding is tied to the nature of the solvent: even in water solution, because of the *triply* charged cobalt anion, ion pairing is extensive. This result ought to be kept in mind, in view of the frequent recourse to an extra-thermodynamic assumption[8-12] of the absence of ion pairing when bulky ions such as BPh_4^- or $N(n\text{-}Bu)_4^+$ are used.

This novel use of ^{59}Co NMR to investigate ion pairing has the merits of sensitivity and of being a quantitative method, from which equilibrium constants can be extracted in a reliable and self-consistent manner (see Table I). Other methods, such as conductivity, colligative property measurements, and vibrational spectroscopy,[33-39] which also "see" pairing between Q^+ and their counterions, provide complementary information about the *structure* of the ion pairs: interionic sepation; loose or tight character. As for isotropic NMR shifts induced by a paramagnetic complex,[40-43] only 1:1 electrolytes are amenable strictly to the approximate treatment, which has to assume axial symmetry of the ion pair together with a dipolar mechanism for the observed shifts.

Conclusions

Our results appear to be consistent with the assumption by Zana "that an electrically charged group can bring about a rearrangement of the water molecules around neighboring alkyl groups, in conjunction with the reduction of electrostriction of the charged group owing to the stering hindrance of the alkyl group".[44]

We view the hydrophobic interaction with the alkyl groups in the accepted manner, as occurring from a partial loss of degrees of freedom by the water or methanol molecules in the first hydration layer of the hydrophobic solute. Indeed NMR and dielectric relaxation measurements have found restricted rotational and translational motions of water molecules in the first hydration sphere around Q^+ ions[45-47] and aliphatic alcohols and carboxylic acids.[48]

Moreover they appear as relevant to a variety of applications, ranging from the stereochemistry of elimination from quaternary ammonium salts, which depends upon ion-pair formation;[49] to the pronounced influence of aggregation phenomena upon product distribution in the $K_3[Co(CN)_5H]$-catalyzed hydrogenation of conjugated dienes to monoenes;[50] to the resemblance between the Q^+ ions investigated here and acetylcholine, for which hydrophobic forces are known to play a role in its binding to acetylcholinesterase;[51] and, lastly, to the possibility of probing the hydrophobic

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regions at the active site of enzymes with a cobalt(III) complex, as an extension of the present study, which is also encouraged by the success of optical spectra in the identification of the ligands bound to cobalt(III) in the active sites of enzymes.[52]

There are many other applications to which the considerable sensitivity of the cobalt-59 chemical shift to its environment can be put; we hope to report on some of these in the near future.

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NMR Relaxation Parameters in Molecules with Internal Motion: Exact Langevin Trajectory Results Compared with Simplified Relaxation Models†

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Abstract: The interpretation of NMR relaxation experiments on flexible molecules is explored by use of stochastic dynamics trajectories. The effect of internal motion on the relaxation parameters (T_1, T_2, and NOE) of simple alkanes and of aliphatic side chains of proteins is determined. The correlation functions and spectral densities required for the evaluation of ^{13}C NMR relaxation times are evaluated from trajectories lasting up to 100 ns and the results are compared with the predictions of simplified analytical models for the motion. It is shown that for small molecules tumbling in the motional narrowing limit it is possible to approximately separate the NMR relaxation into contributions from tumbling and internal motions. For butane and heptane in aqueous solution, the spin-lattice relaxation times (T_1) are predicted and the gradient in relaxation times along the heptane chain is found to be close to that observed in the pure liquid. Detailed trajectory results are presented for ^{13}C relaxation of an alkane side chain on macromolecules. Wigner functions are used to express the side chain relaxation with respect to the coordinate frame embedded in the macromolecule. Uncoupling the motions about the individual side chain internal rotation axes or introduction of the independent lattice jump model for the motion is shown to describe incorrectly the short-time and long-time relaxation behavior. Nevertheless, for short side chains with barriers to rotation on the order of 3 kcal/mol, both models provide a good approximation for the ^{13}C NMR relaxation. This suggests that the models can be used for the interpretation of NMR experiments on lipids and aliphatic amino acid side chains protruding into solution, although errors are expected when the motion of the chain under consideration is constrained by the rest of the system.

I. Introduction

Nuclear magnetic resonance relaxation measurements provide an important probe of the dynamics of molecules since the spin-lattice (T_1) and spin-spin (T_2) relaxation times and the NOE enhancement factor (η) are all functions of the thermal motions. Carbon-13 NMR of protonated carbons is particularly well-suited for the study of dynamics because the relaxation is dominated by the fluctuating dipolar interactions between ^{13}C nuclei and directly bonded protons. Applications of ^{13}C NMR have been made to the dynamics of small molecules in solution,[1-6] polymers,[7-13] and molecules of biological interest including lipids[14-16] and proteins.[17-23] Since the motions of molecules with many internal degrees of freedom (e.g., macromolecules) are complicated, the interpretation of NMR measurements for such systems is often not unique. Empirical rules have been developed to fit the relaxation data to the molecular tumbling time combined with internal segmental motions.[6-8] Alternatively, the experimental results have been interpreted in terms of analytically tractable descriptions of the dynamics based on continuous diffusion,[9,24] restricted diffusion,[25-28] and lattice jump models.[24,26,29,30] While it is usually possible to fit the experimental results in this way, the data in themselves generally are not sufficient to determine whether a model gives the correct description of the dynamics.

A powerful method for testing relaxation models is provided

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