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Supplementary Material Available. A partial listing of absorption features in high resolution spectrum of methylglyoxal will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-1667.

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Cadmium-113 Fourier Transform Nuclear Magnetic Resonance Spectroscopy

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Abstract: Cadmium-113 pulsed Fourier Transform nmr studies have been carried out on a variety of ^{113}Cd-metal-containing systems. It has been shown that millimolar concentrations of ^{113}Cd are readily adaptable for chemical shift and T_1 studies. Furthermore, the chemical shift range for ^{113}Cd exceeds 640 ppm which is consistent with large paramagnetic contributions to the shielding constant. As much as 300 ppm of this chemical shift range can be attributed to substituent effects, which occur in ^{113}Cd organometallic compounds. In addition to these findings, certain dialkylcadmium compounds have been shown unequivocally to undergo homoexchange with an upper limit to the rate constant of 4.5×10^2 sec^{-1} for the self-exchange process. Organic solvent interactions also play a major role in affecting the chemical shift range and the rates of exchange processes in dialkylcadmium compounds. A discussion of data concerning ^{113}Cd spin-lattice relaxation times is presented. It has been determined that spin-relaxation times in inorganic and organocadmium compounds arise from a variety of competing mechanisms.

Nuclear magnetic resonance studies of metals by methods of direct observation have not received the same level of scrutiny that nuclei such as ^{1}H, ^{19}F, and ^{13}C have received. There are a number of factors attributable, a few being (a) the inherent sensitivity associated with a particular metal isotope as compared to an equal number of protons, (b) the percentage of a naturally occurring metal isotope, (c) the associated quadrupolar moments of metal nuclides for which $I > \frac{1}{2}$ and, (d) commercial spectrometers which are unable to meet the stringent requirements necessary for metal observation.

In view of these problems, however, the literature contains a considerable amount of work involving metal systems. A significant fraction of early studies employed wide-line spectrometers and rapid passage techniques. The reader is referred to several reviews which deal, in brevity, with some of these earlier studies.[2-4] INDOR has proven to be a superior technique to CW methods previously employed and more recent studies[5-19] involving double resonance techniques are being utilized in order to gain more insight into metal-containing systems. INDOR, however, is limited at best in that its applicability requires indirect spin coupling to a nucleus having a large magnetic moment. Therefore, systems of solvated metal ions do not fall within the realm of investigation by this technique. Nor is it applicable when ^{1}H decoupling or studies involving time-dependent phenomena, such as dynamic nuclear polarization, reaction kinetics, and nuclear relaxation measurements, are to be employed.

Those metals, such as ^{113}Cd, ^{119}Sn, ^{199}Hg, ^{205}Tl, and ^{207}Pb, whose inherent nuclear properties are comparable to ^{13}C (i.e., $I = \frac{1}{2}$, sensitivity and natural abundance) could be investigated with the same experimental techniques presently employed for ^{13}C, i.e., pulsed Fourier Transform (FT) nmr. A number of researchers[20-29] have addressed themselves to just such an approach from both a variable field and a variable frequency standpoint. Variable frequency has the advantage of the employment of heteronuclear decoupling. A summary of some of these techniques can be found in recent reviews.[30,31]

The purpose of this investigation is to study the magnetic resonance parameters of cadmium-containing systems and to exemplify both the utility with which this study was carried out and the applicability of pulsed FT nmr techniques to other metal-containing systems. Because of its rich organometallic chemistry[32] solution properties,[33] biological relevance,[34] and receptiveness to an nmr experiment, ^{113}Cd is an excellent metal nuclide with which to test these new methods.

Waugh and Klein,[35] in 1959, made use of a double resonance technique to determine a precise value for the ^{111}Cd-^{113}Cd nuclear magnetic moment ratio and hyperfine anomaly. Maciel and Borzo[23] have carried out a series of preliminary measurements on inorganic and organometallic ^{113}Cd systems by pulsed FT nmr. Their data indicate that the chemical shift range for ^{113}Cd is relatively large. For the compounds reported, the range was over 538 ppm. In addition, these investigators noted that the ^{113}Cd chemical shifts of inorganic cadmium salts in aqueous medium were highly concentration dependent. Furthermore, it appears that for some of the cadmium compounds reported, the ^{113}Cd T_1's are similar (in time) to those observed for ^{13}C. More recently, Kostelnick and Bothner-By[36] have reported a ^{113}Cd CW nmr study on some representative cadmium salts. Their study was concerned mainly with the concentration dependence of the ^{113}Cd chemical shifts in aqueous solutions. In addition, ^{113}Cd chemical shifts of these salts were reported as a function of various concentrations of organic and amino acid ligands.

Owing to the paucity of detailed magnetic resonance parameters of the ^{113}Cd nucleus, it is necessary to establish a fundamental working knowledge of the following aspects, some of which will be presented in this study: (a) the lower limits of sensitivity as related to ^{113}Cd concentrations and the corresponding experimental time involvement required to obtain useful information for a given concentration; (b) the establishment of an overall ^{113}Cd chemical shift range for a variety of inorganic and organometallic cadmium species in solution; (c) the sensitivity of the ^{113}Cd chemical shift to both substituent and medium effects; (d) the application of ^{113}Cd nmr to the study of ligand exchange reactions of organocadmium species and the molecular dynamics involved in these reactions; and (e) T_1 (spin-lattice relaxation time) determinations for some representative inorganic and organometallic cadmium compounds and their corresponding relaxation mechanisms.

Experimental Section

Materials. The reagent grade cadmium salts $CdCl_2 \cdot xH_2O$, $CdBr_2 \cdot xH_2O$, $CdI_2 \cdot xH_2O$, $Cd(ClO_4)_2 \cdot xH_2O$, and $CdSO_4$ (anhydrous) were obtained from Matheson Coleman and Bell, and were used without further purification. These salts were dried to constant weight by heating under dynamic high vacuum and were assumed to be anhydrous. Samples of these inorganic salts were weighed under a dry nitrogen atmosphere and dissolved in deionized H_2O or in 99.77% deuterium oxide (Columbia Organic Chemical Co, Inc.) to form 1.0 *M* solutions. These 1.0 *M* solutions were freeze-thawed degassed five times in 12 mm nmr tubes by standard high vacuum techniques. The nmr tubes were then flame-sealed under dynamic vacuum.

In addition, several other inorganic cadmium compounds were prepared: (a) bis(manganese pentacarbonyl)cadmium(II), $Cd[Mn(CO)_5]_2$, was prepared by the method of Burlitch[37] and dissolved in CH_3OH to form a 0.8 *M* solution; (b) potassium tetracyanocadmate(II), $K_2Cd(CN)_4$, was prepared by the method of Biltz[38] and dissolved in D_2O to form a 1.0 *M* solution; (c) cadmium thiocyanate, $Cd(SCN)_2$, was prepared according to a literature method[39] and dissolved in D_2O to form a 0.2 *M* solution; (d) dichlorotetraamminecadmium(II) was prepared according to a known literature method[40] and dissolved in 50:50 v/v mixture of aqueous ammonia and deuterium oxide to form a 1.0 *M* solution. Tris(acetylacetonate)chromium(III), ($Cr(acac)_3$), was used as a paramagnetic doping agent[41] in some of the experiments.

The organocadmium compounds, dimethyl-, diethyl-, di-*n*-propyl-, and diphenylcadmium, were prepared by standard Grignard methods[42] in ether solution. The purification of dimethyl-, diethyl-, and di-*n*-propylcadmium was accomplished by high vacuum trap-to-trap fractionation[43] and variable-temperature cold column separation.[44] The purity of these organocadmium compounds was confirmed by either infrared, mass spectral, ^{1}H, ^{13}C, or ^{113}Cd nmr. Diphenylcadmium was sublimed at 125° (0.5 mm) and dissolved in *p*-dioxane to form a 1.0 *M* solution. The other organometallics were used as neat compounds for the determination of chemical shifts and T_1's. For the solvent-shift study, 1.0 *M* $Cd(CH_3)_2$ was dissolved in a variety of organic liquids.

Solvents. All solvents were either spectroquality or reagent grade solvents and were dried and distilled immediately prior to use under a dry nitrogen atmosphere. The drying agents used and their respective solvents are as follows: (a) sodium benzophenone ketal (benzene, bis(2-methoxyethyl) ether, cyclohexane, cyclopentane, dioxane, diethyl ether, tetrahydrofuran, and toluene); (b) activated molecular sieves (4Å) (acetone, dimethylformamide, and ethyl acetate); (c) phosphorus pentoxide (methylene chloride and methyl formate); (d) calcium hydride (acetonitrile and pyridine).

Preparation of 1.0 *M* $Cd(CH_3)_2$ Solutions. Each 1.0 *M* dimethylcadmium sample was prepared by distilling under high vacuum 3.00 ml of a particular solvent and 0.22 ml of $Cd(CH_3)_2$ into a 12 mm nmr tube. Each nmr sample was freeze-thawed degassed three times under dynamic vacuum before flame sealing.

Instrumental. Ir spectra were recorded on a Perkin-Elmer 257 Grating Infrared Spectrophotometer. Gas phase spectra were recorded in a 10-cm cell fitted with KBr windows. Other ir samples were prepared under a dry nitrogen atmosphere as Nujol mulls and were recorded between KBr disks sealed with transparent tape.

Mass spectra were obtained on a Perkin-Elmer RMU-6 mass spectrometer. Proton nmr spectra were obtained on a Varian-Associates A-60 spectrometer for the compounds dimethyl-, diethyl- and di-*n*-propylcadmium. Carbon-13 FT nmr spectra were obtained on a Varian XL-100-15 spectrometer operating at 25.16 MHz for the compounds potassium tetracyanocadmate(II) and dimethyl-, diethyl-, di-*n*-propyl-, and diphenylcadmium.

The ^{113}Cd FT spectra were obtained on a highly modified[24] Varian XL-100-15 nmr spectrometer operating at 22.18 MHz. A brief summary of the modification is presented in Figure 1. The Gyrocode[45] radiofrequency spin decoupler provides the necessary transmitter and local oscillator frequencies. The basic operating frequency is routed into the local oscillator frequency deriver module where it is divided into two parts: one part serving as the transmitter frequency and the other portion ultimately becoming the local oscillator frequency. The transmitter frequency is gated at which point it becomes the input to the low power amplifier stage of a standard ^{13}C transmitter. This final amplifier stage has sufficient band width to pass frequencies in the range 17-26 MHz. The amplified signal is then routed through the normal sequence of standard Varian components. Each of these components is sufficiently tunable to perform the experiment.

The portion becoming the local oscillator frequency is one input to a balanced mixer. The other input to the balanced mixer is the intermediate frequency (IF), 10.7 MHz. The output of the mixer is fed into a 10.7-MHz trap and high pass filter in order to remove both the unwanted 10.7 MHz and the difference frequency produced by the mixer. The remaining frequency is then amplified in a "home-made" wide band radiofrequency amplifier.[46] The resulting local oscillator frequency is the reference frequency for the first demodulator stage of the observe receiver.

The resulting demodulated frequency is then fed to an IF crystal filter (TYCO Filter Manufacturing, Inc., PN:001-24300) which has its low frequency 3dB point set at the IF, 10.700000 MHz. This arrangement prevents the noise aliasing about the carrier frequency and, therefore, gives rise to a signal-to-noise improvement by a factor of $\sqrt{2}$ over the conventional IF crystal-filter scheme.

The spin-lattice relaxation time (T_1) measurements were accomplished via two pulse sequences: either the Freeman-Hill[47] inversion-recovery method, $(PD\text{-}90°\text{-}AT\text{-}PD\text{-}180°\text{-}\tau\text{-}90°\text{-}AT)_n$, or by the MacDonald-Leigh[48] homospoil pulse sequence, $(90°\text{-}HS\text{-}\tau\text{-}90°\text{-}AT\text{-}HS)_n$. In these pulse sequences, PD and AT denote pulse delay and acquisition time, respectively. The other symbols

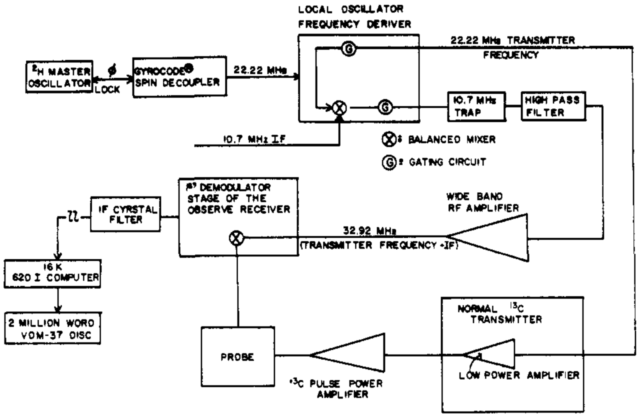


Figure 1. A block diagram of the experimental arrangement employed for the observation of ^{113}Cd at 22.2 MHz.

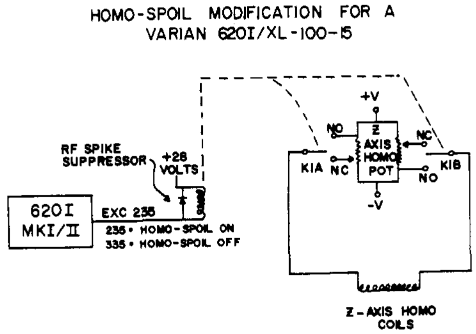


Figure 2. Schematic diagram of the necessary modifications to accomplish the homospoil sequence described in ref 48. Note that the EXC 235 and EXC 335 commands are computer dependent mnemonics. The length of the homospoil pulse may vary depending upon the particular spectrometer. With this arrangement we employ a 40-msec pulse.

have their usual meanings. Due to the recent introduction of the homospoil method, a schematic diagram illustrating the implementation of this sequence on a Varian XL-100-15 is shown in Figure 2. Details are provided in the figure captions.

Chemical shift measurements were made with respect to a variety of external references. By external we mean that the audio frequency of the standard was measured, then this sample was replaced with the compound of interest and its audio frequency was then determined. The chemical shift is then simply the difference frequency divided by 22.2 MHz. Resonances to lower frequencies are considered more shielded.

Results and Overall Trends

Tables I and II summarize the ^{113}Cd chemical shifts of some representative inorganic and organometallic cadmium compounds. These ^{113}Cd shifts were referenced to external 0.10 *M* $Cd(ClO_4)_2$ in D_2O. It should be noted that a negative value for a chemical shift denotes a resonance to lower shielding. The most shielded compound in Table I, 1.0 *M* $CdSO_4$, exhibits a 2.81 ppm chemical shift. The cadmium halides, CdI_2, $CdBr_2$, and $CdCl_2$, range in chemical shift from −55.13 to −108.60 ppm. The chemical shifts of the cadmium organometallics range from −489.11 to −642.23 ppm with respect to 0.1 *M* $Cd(ClO_4)_2$. The following deshielding trend with regard to the ^{113}Cd chemical shifts of the organocadmium compounds of Tables I and II can be noted: $Cd(CH_3)_2 > (CH_3)Cd(C_2H_5) > Cd(C_2H_5)_2 > Cd(n\text{-}C_3H_7)_2 > Cd(n\text{-}C_4H_9)_2 > Cd(C_6H_5)_2$. Also included in Table II is a list of ^{13}C chemical shift data for some of these organocadmium compounds. In each case the directly bonded carbons are deshielded with respect to the other carbons. A general shielding trend for a given organometallic compound can be surmised: $\delta C_\gamma > \delta C_\beta > \delta C_\alpha$.

Table I. Cadmium-113 Chemical Shifts for Some Representative Cadmium Compounds[a]

Compd	Solvent	Chemical shift
1.0 *M* $CdSO_4$	D_2O	2.81
1.0 *M* $Cd(ClO_4)_2$	D_2O	1.13
15 m*M* $CdSO_4$	D_2O + 3 mg $Cr(acac)_3$	−1.39
1.0 *M* CdI_2	D_2O	−55.13
0.2 *M* $Cd(SCN)_2$	D_2O	−60.14
1.0 *M* $CdCl_2$	D_2O	−97.84
1.0 *M* $CdBr_2$	D_2O	−108.60
15 m*M* $Cd(NH_3)_6Cl_2$	50:50 NH_3–D_2O	−274.35
1.0 *M* $Cd(NH_3)_6Cl_2$	50:50 NH_3–D_2O	−287.35
1.0 *M* $Cd(C_6H_5)_2$	*p*-Dioxane	−328.80
$Cd(C_4H_9)_2$[b]	Neat	−489.11
$Cd(C_3H_7)_2$	Neat	−504.28
1.0 *M* $Cd(CN)_4^{2-}$	D_2O	−509.80
$Cd(C_2H_5)_2$	Neat	−543.20
0.8 *M* $Cd[Mn(CO)_5]_2$	CH_3OH	−552.00
$(C_2H_5)Cd(CH_3)$	50:50 $Cd(C_2H_5)_2$–$Cd(CH_3)_2$	−593.06
$Cd(CH_3)_2$	Neat	−642.93

[a] Chemical shifts are reported in ppm with respect to external 0.10 *M* $Cd(ClO_4)_2$. A positive value for the chemical shifts denotes resonances to higher shielding. [b] See ref 23; assumed to be a neat liquid.

Presented in Table III are the values of $^nJ_{CdC}$ and $^nJ_{CdH}$ coupling constants (CdC refers to ^{113}Cd coupling to ^{13}C) for the organocadmium compounds reported. The directly bonded cadmium-carbon couplings, J_{CdC}, are the strongest, and range in magnitude from 498.0 Hz for $Cd(C_2H_5)_2$ to 537.3 Hz for $Cd(CH_3)_2$. The predominant J_{CdH} are 52-53 Hz and involve coupling between ^{113}Cd and the hydrogen on the terminal CH_3 groups.

Listed in Table IV are the ^{113}Cd chemical shifts for 1.0 *M* solutions of $Cd(CH_3)_2$ in 15 organic solvents. The overall solvent-shift range is 101.32 ppm.

Table V presents a summary of spin-lattice relaxation times for some representative inorganic and organocadmium compounds. For the inorganic cadmium halides, T_1

Table II. Organocadmium-113 and Carbon-13 Chemical Shifts

Compd	Solvent	^{113}Cd chemical shift,[a] ppm
$Cd(CH_3)_2$	Neat	00.00
$(C_2H_5)Cd(CH_3)$	*b*	49.87
$Cd(C_2H_5)_2$	Neat	99.73
$Cd(n\text{-}C_3H_7)_2$	Neat	138.65
$Cd(n\text{-}C_4H_9)_2$	Neat[c]	153.82
1.0 *M* $Cd(C_6H_5)_2$	*p*-Dioxane	314.13
		^{13}C chemical shift,[d] ppm
$Cd(CH_2\overset{*}{C}_\beta H_3)_2$	*p*-Dioxane	−12.97
$Cd(\overset{*}{C}_\alpha H_2CH_3)_2$	*p*-Dioxane	−16.27
$Cd(CH_3)_2$	*p*-Dioxane	−18.42
$Cd(CH_2CH_3\overset{*}{C}_\gamma H_3)_2$	Neat	−32.30
$Cd(CH_2\overset{*}{C}_\beta H_2CH_3)_2$	Neat	−32.65
$Cd(\overset{*}{C}_\alpha H_2CH_2CH_3)_2$	Neat	−36.61
1.0 *M* $Cd(CN)_4^{-2}$	D_2O	−75.93
1.0 *M* $Cd(C_6H_5)$	*p*-Dioxane	
Meta		−129.60
Para		−130.40
Ortho		−142.60
C_x[e]		−161.40

[a] ^{113}Cd chemical shifts are reported in ppm with respect to external neat $Cd(CH_3)_2$; δ(neat $(CH_3)_2Cd$) = δ(0.1 *M* $Cd(ClO_4)_2$) + 642.93. A positive chemical shift denotes resonances to higher shieldings. [b] $(C_2H_5)Cd(CH_3)$ resulting from an equimolar mixture of neat $Cd(CH_3)_2$ and $Cd(C_2H_5)_2$. [c] Assumed to be neat liquid; see ref 23. [d] ^{13}C chemical shifts reported in ppm with respect to external CH_4, δ(TMS) = $\delta(CH_4)$ − 2.3. [e] Ring carbon directly bonded to cadmium.

Table III. Cadmium–Carbon and Cadmium–Hydrogen Coupling Constants of Some Organocadmium Compounds

Compd	J_{CdC}[a]	$^2J_{CdC}$[a]	$^3J_{CdC}$[a]	J_{CdH}	$^2J_{CdH}$	$^3J_{CdH}$
$Cd(CH_3)_2$	−537.3[b]			52.0		
$Cd(C_2H_5)_2$	(−)498.0[c]				51.6	
$Cd(C_3H_7)_2$	(−)509.2[c]	19.0	44.8			53.5

[a] J_{CdC} denotes ^{113}Cd coupling to ^{13}C; all values given in Hz. [b] See ref 53. [c] Assumed to be negative from the sign determination reported in ref 53.

Table IV. Cadmium-113 Solvent Shifts For 1.0 *M* Solutions of $Cd(CH_3)_2$[a]

Solvent	^{113}Cd δ, ppm	Solvent	^{113}Cd δ, ppm
THF	66.65	Pyridine	28.26
Diglyme	65.93	Diethyl ether	5.32
N,N-DMF	55.18	Neat	0.00
Dioxane	50.77	Benzene	−2.03
Acetone	40.94	Toluene	−2.03
Acetonitrile	37.38	Methylene chloride	−3.13
Methyl formate	36.29	Cyclopentane	−33.08
Ethyl acetate	33.25	Cyclohexane	−34.67

[a] All solvent-solute systems referenced to external neat $Cd(CH_3)_2$; $\delta(\text{neat } Cd(CH_3)_2) = \delta(0.1\ M\ Cd(ClO_4)_2) + 642.93$. A positive sign denotes chemical shifts to higher shieldings.

Table V. Cadmium-113 Spin–Lattice Relaxation Time, T_1, for Some Representative Cadmium Compounds

Compd	Solvent	T_1, sec	NOE	% inter-molecular dipole–dipole
1.0 *M* $Cd(ClO_4)_2$[a]	$D_2O(H_2O)$	84.4 (30.7)	−1.2[c]	48
1.0 *M* $CdCl_2$[b]	$D_2O(H_2O)$	40.5 (20.0)	0.57[c]	20
1.0 *M* $CdBr_2$[b]	$D_2O(H_2O)$	7.1 (6.8)	0.10[c]	4
1.0 *M* CdI_2[b]	$D_2O(H_2O)$	6.5 (6.3)	0.11[c]	4
$Cd(CH_3)_2$[b]	Neat	3.5	0.0	
$Cd(C_2H_5)_2$[b]	Neat	1.2		
$Cd(n\text{-}C_3H_7)_2$[b]	Neat	0.6		
$Cd(n\text{-}C_4H_9)_2$[d]	Neat	0.2		

[a] T_1 value obtained by the MacDonald–Leigh homospoil method. [b] T_1 values obtained by the Freeman–Hill method. [c] Determined in H_2O solutions. [d] See ref 23.

increases in the order $^{113}CdI_2 < {}^{113}CdBr_2 < {}^{113}CdCl_2$. For the organometallic compounds, T_1 increases in the order $^{113}Cd(n\text{-}C_4H_9)_2 < {}^{113}Cd(n\text{-}C_3H_7)_2 < {}^{113}Cd(C_2H_5)_2 < {}^{113}Cd(CH_3)_2$.

Discussion

Sensitivity. Because of the importance of developing techniques to study heavy metals in the environment, one of the first questions to arise in a study of a heavy metal such as cadmium by FT nmr would be its sensitivity. The sensitivity of ^{113}Cd is 1.09 × 10^{-2} with respect to ^{1}H for an equal number of nuclei at constant field. Thus, it is about eight times as sensitive as the ^{13}C nucleus when natural abundances are considered. The relative ease in which a ^{113}Cd FT experiment is performed is demonstrated in Figure 3. Figure 3a depicts the result of one 90° pulse on a 1.0 *M* solution of $CdSO_4$. The resulting RMS signal-to-noise (S/N) ratio is 25:1.[49] This signal-to-noise ratio suggests that millimolar concentrations of cadmium compounds could be studied by FT methods. In order to confirm this point, the ^{113}Cd FT spectrum of a 15 m*M* solution of $CdSO_4$ was obtained. The results of this experiment are summarized in Figure 3b. The total time for this experiment was 4.5 hr and the resulting root mean square signal-to-noise ratio was 7:1. $Cr(acac)_3$ (1 mg/ml) was added to this solution to shorten the ^{113}Cd T_1.

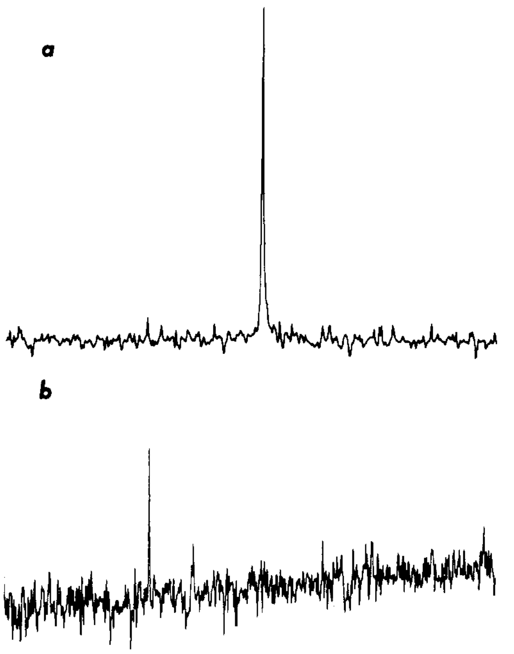


Figure 3. (a) This is a 500-Hz portion of an experiment on a 1.0 *M* solution of $CdSO_4$ in D_2O. In this experiment a single 90° pulse was applied to the sample. The resulting root mean square S/N ratio is 25:1. (b) This is a 500-Hz portion of an experiment on a 15 m*M* solution of $CdSO_4$ in D_2O with 1 mg/ml of $Cr(acac)_3$ added to shorten the ^{113}Cd T_1. The total time for this experiment was 4.5 hr, with a root mean square S/N ratio of 7:1.

Based upon these observations, it should be a routine process then to determine chemical shifts and spin-lattice relaxation time (T_1) values for moderately fast relaxing systems of dilute solutions of cadmium. Within a time scale of 12–24 hr, it is also evident that ^{113}Cd FT nmr could be used as a nondestructive analytical technique in environmental studies involving cadmium. However, such studies would be limited to systems in which the cadmium concentration was at least 3–4 m*M*.

Cadmium-113 Chemical Shifts and Coupling Constants. Table I summarizes the ^{113}Cd chemical shifts for the 14 inorganic and organometallic cadmium compounds studied. The range of ^{113}Cd chemical shifts is in excess of 640 ppm. The dissociated cadmium salts ($CdSO_4$ and $Cd(ClO_4)_2$) yield the most shielded resonances, whereas, the alkylorganocadmium compounds give rise to the most deshielded resonances. These data are consistent with the ^{113}Cd chemical shifts being dominated by paramagnetic contributions to the shielding constant. An isolated Cd^{2+} ion would have no paramagnetic contribution to its shielding constant. Symmetrically hydrating the Cd^{2+} ion will have the effect of introducing a small paramagnetic contribution to the observed shielding constant. Introduction of covalent bonds will, in turn, give rise to a large and negative paramagnetic contribution to the shielding constant. Therefore, the covalently bonded ^{113}Cd nucleus will yield resonances which are deshielded with respect to the corresponding solvated $^{113}Cd^{2+}$ salts. These observations are consistent with the experimental data.

It is apparent from Tables I and II that the ^{113}Cd chemical shifts are very sensitive to seemingly subtle substituent effects. To illustrate this, the ^{113}Cd chemical shifts for the organometallic cadmium compounds have been summarized in Table II. For further comparison Table II also contains the corresponding ^{13}C chemical shifts of these compounds. The replacement of the methyl groups in dimethylcadmium with ethyl groups produces a chemical shift of higher shielding of nearly 100 ppm! Changing the ethyl groups to *n*-propyl moieties yields a chemical shift with respect to diethylcadmium that is shielded by 40 ppm. The range of ^{113}Cd chemical shifts spanned by the organocadmium compounds reported here is in excess of 300 ppm, the order of which, in increasing shielding, is: $Cd(CH_3)_2 < (CH_3)Cd(C_2H_5) < Cd(C_2H_5)_2 < Cd(n\text{-}C_3H_7)_2 < Cd(n\text{-}C_4H_9)_2 < Cd(C_6H_5)_2$. This trend is not observed in dialkylmercury compounds where the *n*-propyl and ethyl shieldings are reversed.[50] Further, it should be noted that the scope of ^{113}Cd chemical shifts for this limited set of compounds is approximately 50% greater than the normal range of ^{13}C chemical shifts. What is not apparent from Tables I and II is the reason for this large chemical shift range and the apparent "hypersensitivity" of these shifts to substituent effects.

It is reasonable to assume that the valence orbitals available to a cadmium atom in organocadmium compounds are 5s and 5p orbitals. In this respect the bonding in organocadmium compounds is similar to that in carbon compounds, namely, s and p valence sets of atomic orbitals. Using this information as a starting point, one might expect that ^{113}Cd substituent chemical shifts might be similar in magnitude to those observed for ^{13}C shifts in the same compounds. Examination of Table II shows that the ^{113}Cd shifts are at least 15 times more sensitive to substituent effects than ^{13}C shifts.

Standard expressions for the paramagnetic contribution to the chemical shift can be reduced to a product of three terms, a set of atomic constants times the expectation value of r^{-3} for an *n*p orbital, $\langle r^{-3}\rangle_{np}$, times a collection of terms which relate the various amounts of induced current density in the atomic orbitals.[51] For a cadmium atom with the same coordination number as a carbon atom the terms relating current density will be approximately the same for the *valence orbitals*. However, the inner shell polarization contributions for cadmium may result in a scaling up for this term. Likewise, inner shell contributions to the value of $\langle r^{-3}\rangle_{5p}$ may lead to a significant scaling of this term. Hence, this hypersensitivity may be due in part to inner shell contributions to the shielding constant which are absent for the lighter atoms such as ^{13}C. Furthermore, higher order terms within the magnetic Hamiltonian may contribute to heavy atom chemical shifts which are unimportant for the lighter elements.[52] It is clear that more experimental work is needed with heavy atom systems before a more concise understanding of these chemical shifts is obtained.

Similar conclusions can be drawn about the cadmium-carbon and cadmium-hydrogen coupling constants reported in Table III. The signs of the directly bonded J_{CdC} coupling constants are taken to be negative.[53] If di-*n*-propylcadmium is a valid one point correlation, the value of $^{n}J_{CdC}$ may alternate with sign and magnitude. However, again, more experimental data are required before any firm conclusions can be drawn.

Exchange Reactions and Solvent Effects. Proton nuclear magnetic resonance techniques have been utilized extensively and almost exclusively in studies associated with alkyl group exchange[54-71] in various Group II and Group III organometallic systems. Such alkyl exchange reactions have been investigated in hopes of elucidating the overall intra- and intermolecular modes of interaction involved in molecular association and the characteristics of the homo- and hetero-exchange dynamics of these organometallic systems.

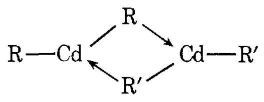
The question of "homo" or "self exchange" in some of these systems has been investigated. For example, proton nmr temperature studies of the known dimer, $[Al(CH_3)_3]_2$, in cyclopentane solution[72] have revealed two types of chemically nonequivalent protons. Such results are consistent with the occurrence of both bridge and terminal CH_3 moieties. Furthermore, multinuclear approaches by nmr have established evidence for rapid exchange between two species of mixed aluminum dialkyls.[73]

Investigations of Group IIB organometallic alkyl derivatives have been studied with the same interest. The question of rapid self-exchange or nonexchange has been subject to controversy.[63-65] From proton nmr studies of alkyl exchanges between Group II and Group III organometallics, and from solvent studies on these systems, an order for the exchange rates for the methyl derivatives has been established.[65] When the solvent is incapable of forming a "catalytic complex," the exchange rate decreases in the order Ga + Zn > Ga + Cd > Zn + Cd ≥ Cd + Cd.[65] In addition, systems containing a mixture of symmetrical zinc dialkyls, studied by ^{1}H nmr, have been unable to detect exchange and hence formation of an unsymmetrical dialkyl of the kind RZnR′.[66] The lack of this exchange phenomenon is attributable to the stability of the dialkylzinc compounds.[74] Studies involving the exchange between ZnR_2 and RZnX, where X is a halogen or electronegative group, have established rapid exchange and formation of a Schlenk equilibrium of the type

$$R_2Zn + X_2Zn \rightleftharpoons 2RZnX$$

This equilibrium lies well to the right.[56,66] Similar results from studies involving CdR_2 and CdX_2 have been noted.[74]

In view of the interest concerning exchange reactions of metal dialkyls, the ^{113}Cd nmr spectrum of an equimolar mixture of neat $(CH_3)_2Cd$ and $(C_2H_5)_2Cd$ was obtained. The spectrum is depicted in Figure 4. The results of the experiment are rather interesting in that three chemically shifted resonances appear with intensities 1:2:1. The corresponding ^{113}Cd chemical shifts are listed in Table II. The appearance of the center resonance (49.67 ppm) with intensity two is attributable to only $CH_3CdC_2H_5$. This unequivocally shows that self-exchange does occur in mixed species of cadmium dialkyls in the absence of catalyzing organic solvents. This exchange occurs within the limits of the ^{113}Cd nmr time scale. These data are consistent with the postulate concluded from former studies involving the formation of a four-centered transition state intermediate of the kind[61,62,65,69]



Moreover, the proton coupled ^{113}Cd spectrum of this reaction mixture is highly resolvable and such spin-spin coupling is also consistent with a slow exchange phenomenon. Elementary considerations allow one to conclude that the rate constant for this process must be slower than 4.5×10^{2} sec^{-1}.[75]

The utility of ^{113}Cd FT nmr is highly conductive to studies involving exchange kinetics between organometallic species in solution. The complexity of calculations associated with a many-site exchange problem (i.e., five or six) utilizing ^{1}H nmr and its corresponding ^{111}Cd and ^{113}Cd satellites is reduced to a three-site exchange problem in which the $Cd(CH_3)_2$ and $Cd(C_2H_5)_2$ are each separated by about 50 ppm from the center resonance. Concentration studies on the rate of exchange can also be applied to derive the order of these exchange reactions and from such studies preexchange lifetimes of Cd-C bonds can be determined.

Oliver[65] has discussed the coordinating ability of the solvent with Group IIB metal dialkyls in terms of the stability and longevity of these complexes. Such coordinating ability is proposed to be responsible for the reactivities and activation energies of these exchange processes.

Coordinating abilities of solvents may be further reflect-

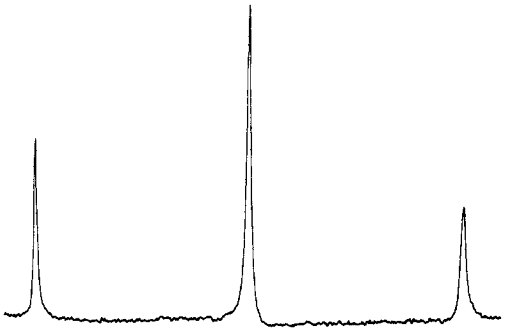


Figure 4. The ^1H-decoupled ^{113}Cd FT spectrum of $CH_3CdC_2H_5$ derived from mixing equimolar amounts of neat $Cd(CH_3)_2$ and $Cd(C_2H_5)_2$. Shielding increases from left to right and the spectral width is 2500 Hz. The center resonance is assigned to $CH_3CdC_2H_5$.

ed in changes in the ^{113}Cd chemical shift of a particular organocadmium compound in a variety of organic solvents. Since the ^{113}Cd chemical shift has been shown by Maciel and Borzo[23] to respond to changes due apparently to complexation, a study of dimethylcadmium in different organic solvents should reflect changes in coordination about the ^{113}Cd nucleus. Table IV summarizes a solvent shift study of 1.0 *M* solutions of $Cd(CH_3)_2$ in 15 organic solvents which differ in their relative Lewis basicities. Upon inspection, it is obvious that solvent interactions are quite substantial in that the overall range of ^{113}Cd chemical shifts listed in Table IV exceeds 100 ppm. The stronger bases such as THF, acetonitrile, and pyridine cause ^{113}Cd chemical shifts to higher shielding. These data are consistent with the donor ability and the coordinating nature of these basic solvents. This further supports evidence for the proposed transition state models[65] responsible for the observed exchange rate enhancements. Also of interest is that neat $Cd(CH_3)_2$ falls somewhat near the middle of the observed solvent-shift range in Table IV. This suggests that neat $Cd(CH_3)_2$ is associated in solvent. Furthermore, the observed deshielded shifts for 1.0 *M* $Cd(CH_3)_2$ in cyclopentane and cyclohexane are indicative of a destructuring of this association.

Spin–Lattice Relaxations. Cadmium-113 is of interest with regard to T_1 studies since its relaxation may arise from a variety of mechanisms. A separation of these mechanisms can yield pertinent information concerning the solution properties and dynamics of cadmium systems. These mechanisms can be related to the observed relaxation rate by a simple equation. The observed longitudinal relaxation rate can be expressed as a sum of terms for nonquadrupolar nuclei as

$$T_1^{-1}(\text{obsd}) = T_1^{-1}(\text{SR}) + T_1^{-1}(\text{DD-intra}) + T_1^{-1}(\text{DD-inter}) + T_1^{-1}(\text{CSA}) + T_1^{-1}(\text{SC})$$

in which $T_1^{-1}(\text{SR})$ is the spin-rotation contribution, $T_1^{-1}(\text{DD-intra})$ is the dipole-dipole contribution arising from intramolecular effects, $T_1^{-1}(\text{DD-inter})$ is the dipole-dipole contribution arising from intermolecular effects, $T_1^{-1}(\text{CSA})$ is the chemical shift anisotropy contribution, and $T_1^{-1}(\text{SC})$ is the scalar coupling contribution to $T_1^{-1}(\text{obsd})$, the observed relaxation rate. Detailed discussions of these relaxation mechanisms have been given elsewhere.[75-77] With regard to experimental considerations, a knowledge of T_1's will allow the most efficient use of spectrometer time that Fourier Transform methods can afford. Such considerations are essential to the study of dilute solutions of cadmium in slowly relaxing systems.[78,79] With these ideas in mind, a preliminary study of inorganic and organocadmium T_1's and their contributing mechanisms was undertaken. Table V summarizes these data.

The inorganic cadmium T_1's in D_2O solution range in value from 6.5 sec for 1.0 *M* CdI_2 to 84.4 sec for 1.0 *M* $Cd(ClO_4)_2$. Inorganic cadmium T_1's in H_2O were also determined. Of particular interest in this series of compounds is the $Cd(ClO_4)_2$ system since it is most representative of free Cd^{2+} ion in solution. Maciel and Borzo[23] have previously shown that the ^{113}Cd chemical shift for $Cd(ClO_4)_2$ exhibits a small concentration dependence (8.11 ppm) which extends over a concentration range of 1.0–4.2 *M*. The long T_1, reported here as 84.4 sec for 1.0 *M* $Cd(ClO_4)_2$ in D_2O, indicates that the relaxation mechanisms which are operative for this compound are not as efficient as those which are present in the more associated salts such as $CdBr_2$ and CdI_2. To further understand solvent-ion interactions in solution, it is necessary to be able to separate intra- and intermolecular effects. For this reason, a 1.0 *M* solution of $Cd(ClO_4)_2$ in H_2O was prepared. If the change in ^{113}Cd T_1 is due to a corresponding change in viscosity of the solvents D_2O and H_2O, then the ratio of the ^{113}Cd T_1's in D_2O and H_2O should be equal to the inverse ratio of the viscosities, i.e., 0.8. The resulting value for the T_1 in H_2O was 30.7 sec as opposed to 84.4 sec in D_2O. Since the ratio of these T_1's is 2.7 it is evident that H_2O provides an intermolecular dipole–dipole relaxation pathway for the ^{113}Cd nucleus. Since this mechanism arises through a dipole-dipole process, an observable nuclear Overhauser effect (NOE) should be present.

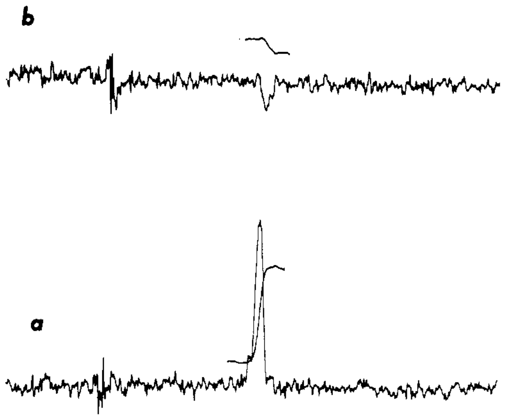


Figure 5. A quantitative NOE determination on 1.0 *M* $Cd(ClO_4)_2$ in H_2O. Figure 5a is the ^1H coupled spectrum, and Figure 5b depicts the same sample under the same conditions, except that the H_2O ^1H's are being irradiated. The resulting NOE is −1.2. Each spectrum represents 20 90° pulses separated by a pulse delay of 5 T_1's.

Figure 5 depicts the results of the heteronuclear NOE experiment on 1.0 *M* $Cd(ClO_4)_2$ in H_2O. For the case in which a pure dipole-dipole mechanism is operative, the value of the NOE enhancement factor is −2.5. The minus sign arises from the fact that the magnetogyric ratio, γ, is negative for ^{113}Cd. The value obtained for the experimental enhancement factor is −1.2 which corresponds to approximately 48% intermolecular dipole-dipole contribution to the ^{113}Cd relaxation rate at 35°. Unlike the $Pb(ClO_4)_2$ system in aqueous medium,[29] intermolecular dipolar effects in $Cd(ClO_4)_2$ are not eclipsed by spin-rotation interactions. At higher temperatures it might be expected that spin-rotation would become a more influential process than it is at 35°. Further studies, however, are needed to substantiate this.

For the halocadmium compounds it is found that the ^{113}Cd T_1 increases in the order I < Br < Cl whereas the degree of association for these cadmium salts increases in the order Cl < Br < I.[33] Preliminary NOE data at 35° indicate that in aqueous solutions of 1.0 *M* $CdCl_2$, intermolecular dipole-dipole interactions contribute about 20% to the $T_1^{-1}(\text{obsd})$ while analogous studies on $CdBr_2$ and CdI_2

show negligible effects due to intermolecular dipole-dipole interactions. For CdI_2 in H_2O, the temperature dependence on T_1 illustrates that mechanisms other than spin-rotation are responsible for relaxation in this system. That is, T_1^{-1}(obsd) is found to decrease with increasing temperature. Such a temperature dependence is consistent with either dipole-dipole, chemical shift anisotropy, and/or scalar coupling mechanisms. To test the possibility of an intermolecular dipolar interaction occurring between ^{113}Cd and the protons in H_2O at elevated temperatures, a heteronuclear NOE was determined for CdI_2 at 80°. Within experimental error, the resulting NOE is zero. Whether the observed temperature dependence is representative of a scalar coupling mechanism and/or a chemical shift anisotropy mechanism would require at least the determination of T_1 at two field strengths. For a pure scalar coupling process involving a spin ½ nucleus bonded to a quadrupolar nucleus, the following equation applies[76]

$$T_1^{-1}(\mathrm{SC}) = \frac{2}{3}A_{is}S(S+1)\left[\frac{\tau_s}{1+(\omega_i-\omega_s)^2\tau_s^2}\right]$$

when S is the nuclear spin of the quadrupolar nucleus, A_{is} is the scalar coupling constant for spins i and s, τ_s is the relaxation time of s, and $\omega_{i,s}$ is the Larmor frequency, in radians/sec, for spins i and s, respectively. Scalar coupling becomes important when the coupling constant is large and the correlation time very short, or when the coupled nuclei have very nearly equal Larmor frequencies. Scalar coupling constants for metal-halogen systems are generally large.[4] Assuming a pure scalar coupling mechanism and using a value for $\tau^{127}I = 1.5 \times 10^{-7}$ at 150°,[27] a $^{113}Cd-^{127}I$ scalar coupling constant of 312 Hz was calculated. This value for the coupling constant is well within the accepted range of metal-halogen coupling constants. Based on these considerations, it is possible that the CdI_2 relaxation time *could* be dominated by a scalar coupling mechanism.

The organocadmium compounds comprise a series of interesting systems from the standpoint of exchange phenomena, solvent association, and self-association. Also listed in Table V are some representative T_1 values for the neat organocadmium compounds $Cd(CH_3)_2$, $Cd(C_2H_5)_2$, and $Cd(n\text{-}C_3H_7)_2$.

Because of the labile nature of the other organocadmium compounds, photoinduced decomposition and thermodynamic instability, dimethylcadmium was used for studies involving the temperature dependence of T_1. Because of the proximity of the protons in $Cd(CH_3)_2$, intramolecular dipole-dipole effects between ^{113}Cd and ^1H might occur. It has been shown previously that within a 2% experimental error, the NOE for this compound is zero.[24] Therefore, the T_1^{-1}(DD) contribution to the observed T_1^{-1} at 35° is negligible.

The temperature dependence indicates that for this neat compound, spin-rotation is the predominant mode of relaxation above 25°. Below this temperature T_1^{-1}(obsd) increases with decreasing temperature. A scalar coupling mechanism can be ruled out on the basis that exchange is slow in neat $Cd(CH_3)_2$ and there is no quadrupolar nucleus undergoing rapid relaxation. Such a temperature dependence is thought to be due to chemical shift anisotropy. It is evident that further investigations involving the field dependence of T_1 for neat $Cd(CH_3)_2$ will have to be undertaken before a complete understanding of this system is available.

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Hydrogen-1 and Gallium-71 Nuclear Magnetic Resonance Study of Gallium Citrate in Aqueous Solution[1a]

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Abstract: Gallium citrate complexes which occur in aqueous solution were studied by ^{1}H and ^{71}Ga NMR and by equilibrium dialysis. In strongly acidic solution low molecular weight complexes having a Ga:citrate ratio of 1:1 form. At pH 2–6 gallium citrate polymers were detected by broadening of the citrate ^{1}H NMR resonance, decrease in the citrate ^{1}H spin–lattice relaxation time, and retardation of the rate of dialysis of the metal. Near neutral pH smaller gallium citrate complexes are observed. Chemical exchange between free and metal-bound citrate is slow on the NMR time scale. In highly basic solution (pH $\gtrsim$12) $Ga(OH)_4^-$ is the predominant species, even in the presence of citrate.

Localization of the radioisotope ^{67}Ga in malignant tissue has been employed in the clinical detection of a broad range of tumors.[2,3] The clinical procedure involves intravenous injection of gallium-67 citrate (typical dose: 2 mg of sodium citrate, 25 pmol (2 mCi) of carrier-free ^{67}Ga), clearance of the nuclide from normal tissue during a 2 day waiting period, and scintigraphic detection of γ radiation from regions of isotope accumulation. Our studies of the molecular mechanism of incorporation of ^{67}Ga in normal and malignant cells[4,5] have been directed toward improving methods of tumor detection, obtaining information about the nature of malignant cells, and gaining a better understanding of how cells bind metals which do not normally occur in their environment.

The impetus for the present study of the chemistry of gallium citrate in aqueous solution is the observation in this laboratory[4,5] that citrate inhibits in vitro uptake of ^{67}Ga by L1210 leukemic cells. It was suggested that formation of gallium citrate complexes, which had been detected by ion exchange chromatography[6] and by differential thermal analysis,[7] may cause this inhibition.[5] However, alternate mechanisms involving gallium citrate polymers may also explain this process.[8] Such polymers may be similar to gallium perchlorate polymers detected by Tyree and coworkers[9-11] and iron nitrate[12] and citrate[13,14] polymers characterized by Spiro et al. If tumor cells bind Ga polymers preferentially, then excess citrate may inhibit incorporation of the metal by favoring the formation of smaller citrate complexes. Additional data on the aqueous chemistry of Ga and on the structure of gallium citrate complexes is required for a better understanding of the molecular mechanism of cellular binding of Ga and the inhibition of this process by citrate and other buffers.[5] Characterization of gallium citrate complexes which occur in aqueous solution is the purpose of this investigation.

NMR spectroscopy is the principal method employed in this study. Other NMR investigations of Ga in solution include the demonstration by ^{17}O NMR that $Ga(NO_3)_3$ and $Ga(ClO_4)_3$ dissociate in aqueous solution to yield $Ga(H_2O)_6^{3+}$.[15-17] Fiat and Connick[16] also studied the exchange of water molecules between the solvation sphere of the metal and the bulk solvent. Employing broadline techniques, Akitt et al.[18] observed that ^{71}Ga resonances of a series of symmetrical Ga complexes had chemical shifts ranging over 1367 ppm. Lincoln[19] used ^{1}H and ^{71}Ga NMR to describe the solvation of $GaCl_3$ in acetonitrile.

In the present study we employed ^{71}Ga and ^{1}H NMR to monitor the chemical environment of both the metal and the ligands in gallium citrate complexes. ^{69}Ga and ^{71}Ga occur at natural abundances of 60.2 and 39.8%, respectively, and are both spin $\frac{3}{2}$ nuclei with large quadrupole moments. ^{71}Ga is generally the isotope studied by NMR because its lower natural abundance is offset by a greater sensitivity and lower quadrupole moment ($0.11–0.15e \times 10^{24}$ cm^2). Only resonances of Ga in a highly symmetrical local environment are sharp enough to be detected. The ^{71}Ga res-

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