Tetrahedron Vol. 38, No. 3, pp. 331 to 335, 1982
Printed in Great Britain.

0040-4020/82/030331-05$03.00/0

THE USE OF ^1H AND ^{13}C SPIN-LATTICE RELAXATION RATES IN THE STRUCTURE DETERMINATION OF ADDUCTS OF ADAMANTANE–1–CARBONITRILE AND LANTHANIDE CHELATES IN SOLUTION; COMPARISON WITH THE RESULTS OF MEASUREMENTS OF LANTHANIDE INDUCED SHIFTS

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(*Received in U.K.* 11 *June* 1981)

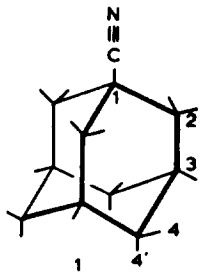
Abstract—$Gd(fod)_3$ induced enhancements of ^1H and ^{13}C spin-lattice relaxation rates showed the Gd-N distance in adducts of $Gd(fod)_3$ and adamantane–1–carbonitrile to be 2.60 Å. A good estimate of the intermolecular contribution to the enhancement of the relaxation appears to be essential in this method of structural analysis. The results of this investigation are compared with those of calculations based on lanthanide induced shifts.

Lanthanide shift reagents have become valuable tools in NMR spectroscopy.[1] These reagents have found widespread use in simplification of NMR spectra and, in addition, structural information can be obtained by fitting the dipolar portion of the lanthanide induced chemical shifts (LIS) to the McConnell-Robertson equation.[2] Generally, it is assumed that for the commonly used shift reagent $Eu(fod)_3$ the ^1H induced shifts are mainly of pseudo contact origin, while in ^{13}C induced shifts the contributions of contact and complex formation shifts may be significant.[3]

This approach, however, has met with several difficulties. The evaluation of bound shifts requires knowledge of the equilibria involved in the complexation of the compound under investigation (S) with the lanthanide shift reagent (L). For $Ln(fod)_3$ (fod = 1,1,1,2,2,3,3 - heptafluoro - 7,7 - dimethyl - 4,6 - octanedione), 1:1 and 1:2 adduct formation and self-association have been shown to play a role.[4-6] Recently, we have shown that complex self-association phenomena may hamper the accurate determination of bound shifts[7] in the fast exchange region.

For the $Yb(fod)_3$. quinuclidine adduct accurate bound shifts could be obtained under conditions, for which the exchange between adduct and free ligand was slow, *viz.* low concentration, low temperature and high field.[8] However, when the measurements were performed under fast exchange conditions unreasonable values for the bound shifts were obtained. Raber *et al.* developed a procedure for the evaluation of the structures of carbonitriles, using $Eu(fod)_3$ as the shift reagent, in which the number of assumptions is minimized.[9,10] With the aid of this procedure, however, an Eu–N distance of 2.1 Å was calculated for the $Eu(fod)_3$ adduct of the symmetric rigid compound adamantane - 1 - carbonitrile **1**, whereas from crystallographic data on related complexes an Eu–N distance of 2.4–2.6 Å should be expected.[10]

La Mar and Faller have shown that the effects of $Gd(fod)_3$ on the T_1 relaxation times may be useful in the



elucidation of molecular structure in solution.[11] The addition of $Gd(fod)_3$ to a solution of a Lewis base induces large enhancements of the relaxation rates of the nuclei in that compound. The magnitude of the enhancements enables measurements at low molar ratios $Gd(fod)_3$/substrate ($\rho \leq 10^{-2}$). Under these conditions contributions of products of the self-association of $Gd(fod)_3$ can be neglected.

Assuming that the mean residence time of the substrate ligand in a $Gd(fod)_3$-substrate adduct is short with respect to the longitudinal relaxation time of the ligand nuclei in this adduct, the measured relaxation rate can be related to the molecular structure via eqn (1).[12-14]

$$1/T_1 - 1/T_{1o} = K/r^6 + 1/T_{1inter}. \quad (1)$$

Here r denotes the distance of the nucleus under investigation to Gd(III). $1/T_{1o}$ is the relaxation rate in the absence of $Gd(fod)_3$ and $1/T_{1inter}$ is the contribution to the relaxation of intermolecular interactions. The latter is often assumed to be very small. From studies on the complexation of polycarboxylates with Gd(III), we obtained indications that $1/T_{1inter}$ may not be neglected.[15] Therefore, we decided to investigate the applicability of $Gd(fod)_3$ in structural analysis with a rigid substrate, taking into account T_{1inter}. Previously, Ernst *et al.*[16] and Inagaki *et al.*[17] have tested the use of $Gd(fod)_3$ in the

determination of molecular structure with borneol as the substrate. This compound, however, has the disadvantage that in its adducts several rotamers are possible. In the present study adamantane-1-carbonitrile **1** was chosen as the model compound. It may be assumed that in the $Gd(fod)_3$ adducts of this compound the Gd–N≡C–C array is linear, so rotations around the Gd–N axis have no influence on the relaxation enhancements. The enhancements of the ^1H and ^{13}C longitudinal relaxation rates were measured and the Gd–N distance was calculated. The results obtained were compared with those from LIS calculations for adducts of some other $Ln(fod)_3$ reagents and compound **1**.

EXPERIMENTAL

The ^1H NMR relaxation times (T_1) were measured at 300 MHz on a spectrometer built at the Department of Applied Physics.[18] As the T_1^{-1} value was taken the slope of the magnetization recovery curve at the time zero after the inverting 180°-pulse in a 180°-τ-12.5° pulse sequence.

The ^{13}C NMR relaxation times (T_1) were measured on a Varian CFT-20 spectrometer, with the use of the inversion recovery method (180°-τ-90° pulse sequence).

All solvents used were dried on zeolite KA. Since commercial $Ln(fod)_3$ compounds are often contaminated with impurities,[7] all lanthanide chelates were synthesized according to the procedure described by Sievers *et al.*[19] The $Ln(fod)_3$ reagents were recrystallized or sublimed and after that dried over zeolite KA *in vacuo*. The samples were prepared in a glove box flushed with dry nitrogen, degassed, and sealed under vacuum.

RESULTS AND DISCUSSION

^1H relaxation rates

In order to separate the resonances in the 300 MHz ^1H NMR spectrum of adamatane-1-carbonitrile **1** (0.137 mole/l in $CDCl_3$) the shift reagent $Eu(fod)_3$ was added (0.055 mole/l). With the aim to obtain an estimation of $1/T_{1inter}$ adamantane (0.139 mole/l) was added as internal standard. Adamantane, being roughly of the same size as compound **1**, will have about the same translational diffusion coefficient whereas it is not able to form adducts with $Gd(fod)_3$. The relaxation times (see Table 1) were measured in the absence of $Gd(fod)_3$ and at a ratio of added $Gd(fod)_3$/adamantane - 1 - carbonitrile (ρ) of 10^{-2}.

In the evaluation of the relaxation data several equilibria have to be considered:

$$E + S \rightleftharpoons ES \quad (2)$$

$$ES + S \rightleftharpoons ES_2 \quad (3)$$

$$G + S \rightleftharpoons GS \quad (4)$$

$$GS + S \rightleftharpoons GS_2 \quad (5)$$

$E = Eu(fod)_3$

$G = Gd(fod)_3$

S = adamantane-1-carbonitrile.

Under the conditions applied fast exchange exists between free and complexed S. Then the observed relaxation rate of a proton i can be described by:

$$1/T_1^i = f_{GS}/T_{1GS}^i + f_{GS_2}/T_{1GS_2}^i + (1 - f_{GS} - f_{GS_2})/T_{1o}^i + 1/T_{1inter}^i. \quad (6)$$

Here f_{GS} and f_{GS_2} are the molar fractions of GS and GS_2, respectively, and T_{1o}^i is the relaxation time in the absence of $Gd(fod)_3$. The intermolecular contribution ($1/T_{1inter}^i$) is proportional to the amount of $Gd(fod)_3$ added. Since ρ is very small equation (6) simplifies to:

$$1/T_1^i = f_{GS}/T_{1GS}^i + f_{GS_2}/T_{1GS_2}^i + 1/T_{1o}^i + 1/T_{1inter}^i. \quad (7)$$

When it is assumed that the Gd–N distances in the GS and the GS_2 adducts are the same, and that isotropic rotational diffusion applies to the system, (7) can be

Table 1. ^1H NMR relaxation data[a] of the system adamantane-1-carbonitrile[b], adamantane[c], $Eu(fod)_3$,[d] and $Gd(fod)_3$ in $CDCl_3$ solution at 300 MHz

Nucleus	T_{1o} (s)[e]	T_1 (s)[f]	$T_1^{-1}-T_{1o}^{-1}$ (s^{-1})	$T_1^{-1}-T_{1o}^{-1}-T_{1inter}^{-1}$ (s^{-1})
H_2	1.66	0.107	8.743	8.07
H_3	4.09	0.479	1.843	1.17
H_4	2.25	0.415	1.965[g]	1.32
$H_{4'}$	2.26	0.545	1.392[g]	0.70
H_5[h]	14.5	1.38	0.66	
H_6[h]	9.2	1.27	0.68	

[a] Average of 7 measurements. The reproducibility was better than 3%. [b] 0.137 M. [c] 0.139 M. [d] 0.055 M. [e] In the absence of $Gd(fod)_3$. [f] In the presence of $Gd(fod)_3$ (ρ = 0.01). [g] A correction is needed since the signals for H_4 and $H_{4'}$ are part of an AB system;[20] due to the line-broadening couplings of H_4 and $H_{4'}$ with the other protons are not observable. After this correction these relaxation enhancements are 1.989 and 1.368, respectively. [h] The tertiary and the secondary protons of adamantane are denoted H_5 and H_6, respectively.

converted into:

$$(1/T_1^i)_{corr} = 1/T_1^i - 1/T_{1o}^i - 1/T_{1inter}^i = K/r_i^6. \quad (8)$$

The intermolecular relaxation is determined by contributions of Gd (complexed as GS_2 and GS) to S, present as free S, ES, ES_2, GS, and GS_2. In view of the low ρ-values used, the contributions to GS and GS_2 can be neglected.

$$1/T_{1inter} = f_S/T_{1inter_S}^i + f_{ES}/T_{1inter_{ES}}^i + f_{ES_2}/T_{1\ inter\ ES_2}^i. \quad (9)$$

Here $1/T_{1inters}^i$, $1/T_{1inter_{ES}}^i$ and $1/T_{1inter_{ES2}}^i$ are the intermolecular contributions to the relaxation rates of free S, the ES adduct and the ES_2 adduct, respectively. As shown in the literature[21] the way in which corrections for the intermolecular contribution to the relaxation can be made depends on the relative magnitudes of the translational correlation time τ_t and the electron spin relaxation time τ_s:

(i) $\tau_t \ll \tau_s$. The correlation time responsible for the intermolecular relaxation is determined by τ_t. Since S, ES and ES_2 have different radii they also will have different translational correlation times, and $1/T_{1inter}^i$ of the reference compound must be corrected for these differences by means of the equations described in Ref. 21.

(ii) $\tau_s \ll \tau_t$. The electron spin relaxation time dominates $1/T_{1inter}^i$ and the intermolecular contribution of GS and GS_2 is the same for S, ES and ES_2. Literature values for τ_s range from 10^{-10} to 1.5×10^{-10} s.[21] τ_t can be estimated from the rotational correlation time τ_R; according to the hydrodynamic theory of liquids τ_R is determined by equation (10):

$$\tau_t = 9\,\tau_R. \quad (10)$$

From the $1/T_1^i$ values of a degassed dilute solution of adamantane in $CDCl_3$ τ_R can be calculated:

$$\tau_R \cong \left(\frac{\frac{3}{2}\gamma_H^4\hbar^2}{r_{H-H}^6}\right)^{-1} . T_1^{-1} \cong 5 \times 10^{-12}\ s. \quad (11)$$

γ_H and $\hbar$ have their usual meaning, r_{H-H} is the geminal proton proton distance (1.8 Å). The τ_t value of compound 1 is then about 4.5×10^{-11} s. By means of the method described in literature[21] and using molecular radii estimated from space-filling molecular models, the relative translational correlation times of S, ES and ES_2 with respect to GS_2 are calulated to be:

$$\tau_t(S\text{–}GS_2) = \tau_t(\text{adamantane–}GS_2) = 3.2 \times 10^{-10}\ s$$

$$\tau_t(ES\text{–}GS_2) = \tau_t(ES_2\text{–}GS_2) = 9 \times 10^{-10} s$$

So it seems that $1/T_{1inter}^i$ is dominated by τ_s. Therefore, the relaxation enhancement of the adamantane protons upon addition of $Gd(fod)_3$ is taken as $1/T_{1inter}^i$. The corrected values for the measured relaxation rates are given in Table 1.

^{13}C relaxation rates

In the 20 MHz ^{13}C NMR spectrum of compound 1 all resonances were well separated. So no addition of a shift reagent was needed. Here again adamantane was used as a probe for the intermolecular contribution to the T_1 relaxation upon addition of $Gd(fod)_3$, Due to the low ρ-value used, almost all S is present as free ligand. Therefore only the intermolecular contribution to free S needs to be determined. In an analogous way as in the previous section it can be derived that the enhancement of the relaxation rates of the ^{13}C nuclei of adamantane affords directly a good estimate for $1/T_{1inter}$. The measurements were performed at $\rho = 0$ and at $\rho = 4.6 \times 10^{-3}$. From these data the corrected relaxation enhancements of the ^{13}C nuclei were calculated (see Table 2).

Calculation of the Gd-N distance in the adducts

For the determination of the Gd–N distance in the adducts, the geometry of the adamantane-1-carbonitrile part of the adducts was assumed to be the same as in free **1**. This geometry was obtained from force field calculations, using the Allinger MM1 force field.[22] The ^1H and ^{13}C longitudinal relaxation rates for different Gd–N distances were calculated using eqn (8). The goodness of the fit between calculated and observed (corrected) relaxation enhancements was expressed in the crystallographic agreement factor RF:[23–25]

$$RF = \sqrt{\left[\frac{\sum_{i=1}^{n} w^i[(1/T_1^i)_{corr} - (1/T_1^i)_{calc}]^2}{\sum_{i=1}^{n} w^i(1/T_1^i)_{corr}^2}\right]}. \quad (12)$$

An optimum fit was obtained for a Gd–N distance of 2.60 Å, which is in good agreement with the value expected from X-ray analysis of analogous complexes.[10] The calculated longitudinal relaxation rates for this Gd–N distance are compiled in Table 3. The Gd–N distance obtained is rather insensitive for random changes in the relaxation rates, but very sensitive to variations in $1/T_{1inter}$: variation of 10% in $1/T_{1inter}$ results in a variation of 0.1 Å in the distance calculated. Therefore, a good estimate of $1/T_{1inter}$ is essential in structural analysis based on relaxation enhancements by $Gd(fod)_3$.

Comparison with the results of LIS measurements

Although the Gd–N distance obtained here is in agreement with the expected value, a rather large discrepancy exists with the results of the ^1H NMR LIS measurements of Raber *et al.* on the related $Eu(fod)_3$ complex of compound 1 (ES).[10] These authors calculated for this complex a Eu–N distance of 2.1 Å. We repeated these LIS measurements and obtained bound shifts which are excellent in agreement with those reported by Raber *et al.*[10] Moreover, it appeared that in a plot of the induced shifts of each of the protons at various amounts of $Eu(fod)_3$ vs those of protons H_2 excellent straight lines are obtained. This indicates that the bound shifts in the ES adduct are proportional to those of the ES_2 adduct.[25,26] Therefore, the Eu–N distances should be about the same in these complexes. It may be assumed that the same holds for the corresponding $Gd(fod)_3$ adducts. The relative bound shifts for $Yb(fod)_3$ were about the same as those for $Eu(fod)_3$ (see Table 4). The former shift reagent is known to give only small contact shifts in ^1H NMR spectroscopy. The diamagnetic analogue of these shift reagents, $La(fod)_3$, did not induce any ^1H shifts in compound **1**. Therefore, it can be concluded that contact and/or complex-formation contributions to the induced

Table 2. ^{13}C relaxation data[a] of the system adamantane-1-carbonitrile[b], adamantane[c], $Gd(fod)_3$ in $CDCl_3$ solution at 20 MHz

Nucleus	T_{1o} (s)[d]	T_1 (s)[e]	$T_1^{-1}-T_{1o}^{-1}$ (s^{-1})	$T_1^{-1}-T_{1o}^{-1}-T_{1inter}^{-1}$ (s^{-1})
$\underline{C}N$	57.6	0.0217	46.2	45.7
C_1	68.8	0.157	6.34	5.92
C_2	6.14	0.321	2.95	2.53
C_3	10.77	0.777	1.19	0.77
C_4	3.78	0.808	0.97	0.55
C_5[f]	23.7	2.18	0.416	
C_6[f]	13.8	1.99	0.430	

[a] Average of 3 measurements. The reproducibility was better than 2%. [b] 1.46 M. [c] 1.56 M. [d] In the absence of $Gd(fod)_3$. [e] In the presence of $Gd(fod)_3$ ($\rho = 4.63 \times 10^{-3}$). [f] The tertiary and secondary carbon atoms of adamantane are denoted C_5 and C_6, respectively.

Table 3. Comparison of experimental and calculated ^1H and ^{13}C relaxation enhancements for the system adamantane-1-carbonitrile $Gd(fod)_3$ (s^{-1})

Nucleus	experimental[a]	calculated[b]
H_2	8.07	8.23
H_3	1.17	1.14
H_4	1.32	1.30
$H_{4'}$	0.70	0.57
$\underline{C}N$	45.7	45.1
C_1	5.92	6.19
C_2	2.53	2.92
C_3	0.77	0.76
C_4	0.55	0.51

[a] See Tables 1, 2. [b] Calculated for a Gd-N distance of 2.60 Å.

Table 4. Relative Lanthanide Induced ^1H shifts in adamantane-1-carbonitrile (0.2 M) in CCl_4 at 35°

	$Eu(fod)_3$	$Yb(fod)_3$
H_2	1.000	1.000
H_3	0.390	0.381
H_4	0.408	0.402
$H_{4'}$	0.302	0.299

shifts cannot account for the discrepancy between the results of the LIS calculations and calculations based on relaxation enhancements.

These observations suggest that the evaluation of bound shifts from the LIS data is inaccurate. This might be due to the presence of a rather complex system of equilibria under the conditions needed for the measurements of the LIS data, which is obscured by the fast exchange between the adducts and the free ligand. We have observed that accurate bound shifts for the Yb(fod)$_3$.quinuclidine adduct could only be obtained, when the LIS measurements were performed under conditions where slow exchange exists between the adduct and the free ligand.[8] Unfortunately, we were not able to obtain slow exchange conditions for the system 1–Yb(fod)$_3$. Even at 300 MHz and at −90° (in toluene solution) averaged spectra of free ligand and adducts were observed.

It may be noted that in the fast exchange region the presence of complex equilibria does not interfere in the analysis of the relaxation data as long as the Gd–N distances in the various adducts are the same.

Acknowledgements—Thanks are due to Mr J. Vriend for experimental assistance and to Dr J. M. A. Baas for assistance with the force field calculations.

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