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# $Eu(FOD)_3$ INDUCED SHIFTS OF ALKYL SUBSTITUTED ADAMANTANONES AND MOLECULAR GEOMETRIES OF THE ADDUCTS

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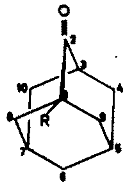
**Abstract**--The geometries of adducts of europium tris(fod) and a series of alkyl substituted adamantanones have been determined with the use of lanthanide induced $^1H$ shift measurements. The position of the Eu(III) cation relative to the substrate ligand appears to be strongly dependent upon steric interactions between the fod ligands and the alkyl groups in the substrate. The alkyl substitution causes distortions from the otherwise linear C-O-Eu array. In general the Eu(III) cation moves away from the alkyl substituents.

Lanthanide shift reagents have become valuable aids for structural analysis with NMR spectroscopy.[1-4] Their most frequent use is for the qualitative separation of overlapping multiplets in crowded spectra or for the assignment of signals. An even more powerful application employs the mathematical relationships between the lanthanide induced shifts (LIS) and the geometry of the complex, because these can provide information about the molecular structure of the substrate and about the position of the lanthanide nucleus with respect to the substrate moiety.

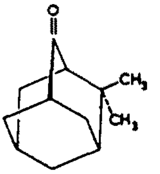
The bonds between Ln(III) ions and ligands are largely electrostatic in nature.[5] As a consequence, the general features of coordination geometries appear to be dominated by steric factors rather than by the directional properties of the lanthanide atomic orbitals. Nevertheless, the LIS of ketones have often been interpreted in terms of a two site model[6-11] according to which the observed lanthanide shifted spectra are time-averages resulting from rapid interconversion of two discrete complexes. In the two-site model the lanthanide cation is suggested to lie along the direction of the lone pairs of an $sp^2$ hybridized oxygen, and a C-O-Ln bond angle of about 120° is expected.

Other arguments have been presented in favor of a one-site model.[12-14] The complexes between formaldehyde and a series of cations were studied by ab initio molecular orbital calculations, and the results indicated that a bond angle of about 180° would be preferred in the absence of a strong sigma bond between oxygen and the cationic center.[12] In a detailed study of the adducts of Ln(fod)$_3$ (where fod is 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5- octanedionate) with the highly symmetric adamantanone using multinuclear LIS and gadolinium induced relaxation rate enhancements, we showed unambiguously that the complex can be properly described only by the one-site model.[13] These results confirmed our earlier conclusions that had been based just on proton LIS.[14]

In this paper we report the results of a LIS study of a series of alkyl substituted adamantanones, 2-6, which was undertaken in order to learn the effects of steric interactions between the substrate ligand and the shift reagent.



1 , R = H
2 , R = CH$_3$
3 , R = tert-C$_4$H$_9$



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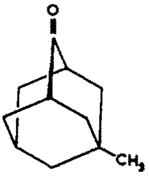

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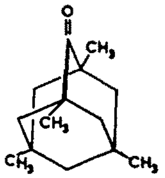

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We employed adamantane derivatives, because the rigidity of the adamantane skeleton would preclude significant changes in the substrate geometry when complexation to Ln(fod)$_3$ took place. Relaxation of any steric strain generated upon complexation must occur primarily via changes in the coordination geometry and in the geometry of the fod ligands.

## RESULTS AND DISCUSSION

For each of the adamantanones, 2-6, a series of LIS measurements with Eu(fod)$_3$ in CCl$_4$ or CDCl$_3$ was carried out over a large range of Eu(fod)$_3$/substrate concentration ratios. From these measurements the bound shifts and association constants were evaluated with the two-step method, which takes into account equilibria involving Eu(fod)$_3$, the substrate, the 1:1 adduct and the 1:2 adduct.[15,16] We have previously shown that the experimental bound shifts of some nuclei, particularly H$_\alpha$ in adamantanone, include substantial contact and diamagnetic shifts.[17] Because these contributions to the shifts are not very sensitive to small structural changes, the values determined previously[17] for 1 were used to correct the crude bound shifts determined for 2-6 The resulting pseudocontact shifts are compiled in Table 1.

The position of the Eu(III) cation in the Eu(fod)$_3$-ketone adducts was determined by a systematic search for the structure that afforded the best agreement when the pseudocontact shifts in Table 1 were compared with values calculated by the pseudocontact equation (eqn 1)[18] with the assumption of effective axial symmetry.[19,20]

$$\Delta = k(3\cos^2\theta-1)/r^3 \qquad (1)$$

Table 1. Lanthanide Induced Pseudocontact Shifts for Alkyl Substituted Adamantanones.[a,b]

| $H^c$ | $1^d$ | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1 | 13.59 | (11.25) | (7.96) | 14.43 | 12.97 | (10.30) |
| 3 | 13.59 | 14.33 | 13.07 | 16.32 | 12.97 | (10.30) |
| $4_{syn}$ | 7.81 | 8.28 | 6.77 | (7.54) | 7.19 | 8.42 |
| $4_{anti}$ | 5.04 | 5.17 | 3.93 | (3.89) | 4.64 | 5.98 |
| 5 | 4.11 | 4.57 | 4.20 | 4.49 | (2.36) | 2.89 |
| $6_{syn}$ | 3.63 | 4.02 | 3.89 | 4.00 | 3.39 | 4.06 |
| $6_{anti}$ | 3.63 | 4.02 | 3.28 | 4.54 | 3.39 | 4.06 |
| 7 | 4.11 | 4.57 | 4.20 | 4.39 | 4.04 | 2.89 |
| $8_{syn}$ | 7.81 | 9.57 | 9.14 | 8.31 | 7.38 | 8.42 |
| $8_{anti}$ | 5.04 | 5.94 | 5.98 | 5.09 | 4.84 | 5.98 |
| $9_{syn}$ | 7.81 | 9.57 | 9.14 | 8.37 | 7.19 | 8.42 |
| $9_{anti}$ | 5.04 | 5.94 | 5.98 | 5.02 | 4.64 | 5.98 |
| $10_{syn}$ | 7.81 | 8.28 | 6.77 | 9.24 | 7.38 | 8.42 |
| $10_{anti}$ | 5.04 | 5.17 | 3.93 | 5.90 | 4.84 | 5.98 |

[a] Pseudocontact shifts (ppm) were calculated from the bound shifts by subtracting diamagnetic and contact shifts by the procedure reported previously;[13,14] (corrections used were $H_{\alpha}$ -1.67, $H_{\beta\text{-syn}}$ -0.07, $H_{\beta\text{-anti}}$ +0.07, $H_{\gamma}$ -0.14, $H_{\delta}$ +0.01); [b] Induced shifts for methyl groups are shown in parentheses; [c] Syn and anti are relative to the carbonyl group, except for H-6, where they are relative to C-1; [d] Reference 13.

Here $\Delta$ is the pseudocontact shift for a given nucleus, k is a constant indicating the magnitude of the induced magnetic dipole for europium, r is the distance between Eu and the nucleus in question, and $\theta$ is the angle between the vector r and the Eu-O bond to the ketone oxygen, which is taken to be the effective magnetic axis. The geometries of the substrate moiety were obtained by molecular mechanics calculations using Allinger's MM2 force field,[21] and were assumed to be unchanged upon complexation with $Eu(fod)_3$. The agreement between the experimental pseudocontact shifts in Table 1 and those calculated with eq (1) was evaluated using the agreement factor (A.F.).[22]

In general, the fit between calculated and experimental data is rather soft, variations in the assumed complexation geometry leading to only small changes in the agreement factor. Such a soft fit is characteristic of an approximately linear C-O-Ln array.[13] The agreement factor is particularly insensitive to the choice of bond length, and an "acceptable" agreement factor[23] of less than 0.05 is observed despite considerable variation in the bond length used to predict the LIS. This is illustrated in Figure 1a for 1-*t*-butyl-2-adamantanone (3), for which Eu-O bond lengths in the range of 2.4-2.7 Å all afford agreement factors of 0.05 or less. For some of the other ketones even wider ranges of Eu-O bond lengths lead to low agreement factors. Optimization of the agreement factor as a function of the Eu-O-C bond angle or Eu-O-C-C torsion angle leads to fairly well defined minima for ketones 2-6, which are less symmetrical than adamantanone. The bond angles and torsion angles for 3 that lead to agreement factors less than 0.05 fall in a relatively narrow range, as shown in Figure 1b and 1c.

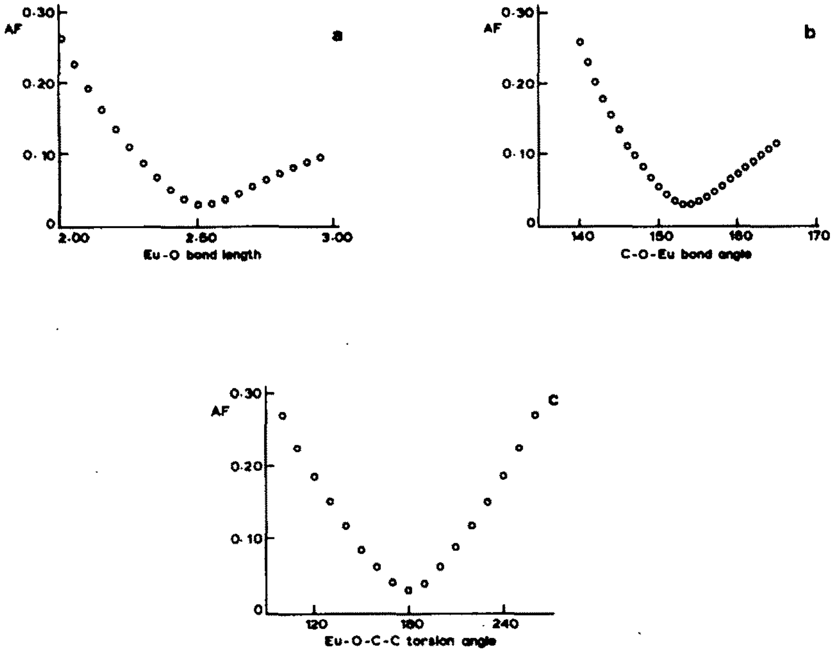

Figure 1. 1-tert-Butyl-2-adamantanone: dependence of agreement factor on variation in geometry parameters of the Eu(fod)$_3$ complex. Only one parameter was varied in each plot; the other two parameters were held constant at their optimized values.

Because the agreement factor is insensitive to some of the geometric parameters that define the coordination geometry, we restricted the Eu-O bond length to 2.5 Å[14] for all the ketones. The position of the lanthanide nucleus was further restricted so that the complex had the same symmetry as the free ketone. This is probably a good description of the time-average structure of the complex, even though the fod ligands preclude such symmetry for any discrete lanthanide-substrate adduct. The C-O-Eu bond angle was then systematically varied to locate the optimum structure of the complex. These geometry restrictions allowed us to avoid the false minima that are otherwise found on some of the very flat agreement factor surfaces. The results of these calculations are summarized in Table 2.

For each of the ketones 2-5 a unique position for the europium nucleus was found. In the case of 6 the optimum complexation geometry corresponded to two symmetry-equivalent structures. When no attempt was made to correct for contact and diamagnetic shift and the α-hydrogens were simply omitted from the computations,[14] the results were nearly the same. The positions of the europium nucleus in the complexes of 3-6 are depicted as projections along the Eu-O bond in Figure 2.

The observed deviations from linearity are all smaller than 60°, which is in agreement with the one-site model. The magnitude of the distortion for 1-t-butyl-2-adamantanone (3) is larger

Table 2. Structural Parameters for $Eu(fod)_3$-Adamantanone Adducts.

| Compound | Eu-O-C-$C_1$ (deg) | Eu-O-C (deg) | k | A.F.[a] |
|---|---|---|---|---|
| 1 | 0 | 180 | 921 | 0.0002 |
| 2 | 180 | 162 | 1080 | 0.028 |
| 3 | 180 | 154 | 1070 | 0.029 |
| 4 | 13 | 167 | 1050 | 0.025 |
| 5 | 90 | 176 | 870 | 0.015 |
| 6 | 90/270 | 135 | 1210 | 0.047 |

[a] The agreement factor is defined as:

$$AF = [\Sigma w(\text{obs-calc})^2/\Sigma w(\text{obs})^2]^{0.5}$$

where <u>obs</u> is an experimental bound shift, <u>calc</u> is the corresponding value calculated with eqn (1), and w is the weighting factor for a particular observation.[22]

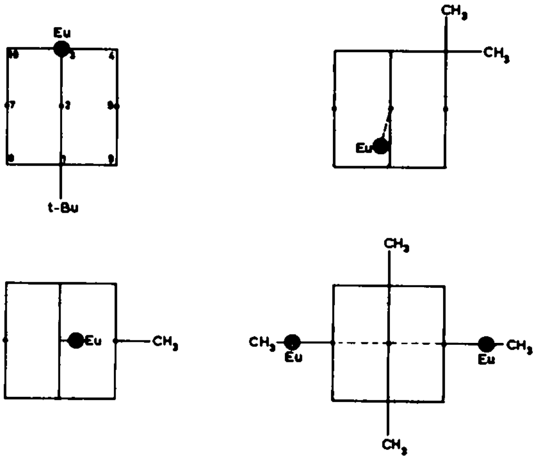

Figure 2. Optimum coordination geometries for 3-6 as determined by minimization of the agreement factors. Projections are in the x-y plane, viewed from the positive z-axis (i.e., along the C-O bond axis from above the oxygen atom).

than that for the 1-methyl-2-adamantanone (2), and this is consistent with repulsive steric interactions between the 1-alkyl substituent and the $Eu(fod)_3$ moiety. For 4,4-dimethyladamantanone (4) the distortion is away from the axial methyl group and is no longer in the plane of the carbonyl group. This is again consistent with repulsive steric interactions between the Eu(fod)$_3$ group and the alkyl substituent.

In the adduct of 5-methyl-2-adamantanone (5) the Eu-O-C array is almost linear, but our calculations show a small distortion in the direction *toward* the methyl substituent. We cannot be certain that this calculated distortion is significant, but it is nevertheless in agreement with steric interactions. The 5-methyl group is relatively distant from the carbonyl oxygen and hence from the Eu(fod)$_3$ moiety. Consequently, the van der Waals interactions between the methyl group and the fod ligands should be small but predominantly *attractive* in nature. Similar distortions toward remote alkyl substituents were previously found for substituted adamantanecarbonitriles.[23]

The behavior of the tetramethyladamantanone 6 is unique. From the results with 1-methyl-2-adamantanone we know that unfavorable steric interactions can be relieved when an otherwise preferred C-O-Eu angle of 180° is distorted by movement of the europium away from an α-methyl group. But for the adduct of 6, such a distortion would greatly increase the unfavorable interaction with the *other* α-methyl group. Only by movement out of the plane of the carbonyl group could the Eu(fod)$_3$ moiety simultaneously minimize steric interactions with *both* α-methyl groups. The ketone has $C_{2v}$ symmetry, but if the lanthanide complex has lower symmetry, four equivalent binding sites (symmetrically disposed about the $S_2$ axis) must be evaluated. The time-averaged pseudocontact shifts were calculated accordingly and were calculated over a wide range of lanthanide positions.

The optimum agreement between calculated and experimental LIS was found for the complexation geometry in which the europium remains above (or below) the plane of the carbonyl group and lies in the symmetry plane that is perpendicular to the carbonyl group. This result should not be confused with the previously rejected[13,14] 2-site model for which the lanthanide was assumed to occupy two coordination sites that would both lie in the plane of the carbonyl group.[6-11] In the structure that we propose, the lanthanide lies out of the plane of maximum electron density of the nonbonding electrons on oxygen, and this further supports the importance of steric effects in the formation of shift reagent adducts. Our interpretation of the geometry for the Eu(fod)$_3$ complex of 6 is reminiscent of the 4-site model of Abraham,[7] but that model was based on a steric perturbation of a 2-site model rather than of the 1-site model that we have since demonstrated to be correct.[13] In our earlier work we showed that the insensitivity of the agreement factor to the calculated C-O-Eu bond angle is typical of an approximately linear coordination geometry. We also investigated distinctly nonlinear complexation geometries by simulating the LIS for such structures. In those cases the agreement factor showed a very sharp minimum at the "correct" Eu-O-C bond angle. Similar behavior is found for the *experimental* LIS of 6, and any bond angle outside the range of 132-140° leads to an agreement factor of 0.06 or larger. This behavior supports our interpretation of a distinctly nonlinear complex.

The optimum k-values (eqn 1) determined from the fits between experimental and calculated LIS are all within 20% of 1000, and this is in agreement with earlier observations for other Eu(fod)$_3$ adducts with nitriles[23] and ketones.[14,24] The consistency in the k-values further increases our confidence in the geometries of the lanthanide-ketone complexes reported in Table 2. Our results are also in accord with those of a structural investigation of the adducts of halogen substituted adamantanones with lanthanide shift reagents.[25] We conclude that the geometries of Ln(fod)$_3$-ketone adducts are determined primarily by steric rather than electronic effects. In the absence of steric perturbations the C-O-Ln bond angle will be linear, but steric interactions between the Ln(fod)$_3$ moiety and substituents on the ketone will result in a single energy minimum geometry that is distorted from linearity. Only in highly unusual cases, such as that found for 6, will a combination of steric and symmetry constraints result in two or more equivalent binding geometries.

## EXPERIMENTAL

NMR spectra were obtained with Varian EM-360 and JEOL FX90Q spectrometers. All chemical shifts were measured with respect to TMS as an internal standard. Shift reagent runs utilized the incremental dilution method.[15,16] Spectra were recorded for a total of 25 different lanthanide:substrate concentration ratios. The bound shifts of the 1:1 complexes were calculated by the two-step method of Shapiro and Johnston.[15]

The signals were assigned using the splitting patterns, the induced shifts, and selective homonuclear decoupling experiments. The signals of the europium adduct of 4 were assigned with the use of a 2D COSY spectrum for a sample of 30.7 mg of 4 and 110 mg of europium tris(fod) in chloroform-d.

**Ketones:** Adamantanone (1) was obtained from Aldrich Chemical Co., and we described the synthesis of 1-*tert*-butyl-2-adamantanone (3) previously.[26] 1-Methyl-2-adamantanone (2),[27] and 4,4-dimethyl-2-adamantanone (4)[28] were synthesized by previously reported procedures.

**5-Methyl-2-adamantanone** (5)[29] was prepared by a several step-sequence, beginning with adamantanone. The adamantanone was converted to 7-*endo*-bicyclo[3.3.1]non-2-enecarboxylic acid,[28] and the acid was esterified in 90% yield with triethyloxonium fluoroborate.[30] A solution of 3 g (0.016 mol) of this ester in 40 ml of dry THF was added dropwise at -80°C to 0.020 mol of lithium diisopropylamide in 150 ml of dry THF. A 5 ml sample of iodomethane was added, and after stirring at -78° for 30 min, the solution was allowed to warm to room temperature. An additional 10 ml of iodomethane was added, and the reaction mixture was stirred at room temperature for 2 hr. The reaction was then quenched by addition of 80 ml of water, and the aqueous mixture was extracted with two 50 ml portions of chloroform. The combined chloroform extracts were washed successively with four 100 ml portions of water, four 50 ml portions of 1M HCl, two 50 ml portions of 1M potassium bicarbonate and two 75 ml portions of saturated sodium chloride. The solution was dried over sodium sulfate, and evaporation of the solvent followed by Kugelrohr distillation yielded 3.1 g (91%) of ethyl 7-methyl-7-bicyclo[3.3.1]non-2-enecarboxylate. The ester was reduced with lithium aluminum hydride to the corresponding alcohol.

The crude alcohol was cyclized to 5-methyl-2-adamantyl formate by dissolving it in a mixture of 75 ml of 88% formic acid, 30 ml of conc. sulfuric acid and 10 ml of trifluoroacetic acid and heating the solution at 90° for 48 hr. The solution was then poured over 100 g of ice. The resulting mixture was neutralized with 50% NaOH and was extracted with three 50 ml portions of chloroform. The combined chloroform extracts were washed with two 50 ml portions of water and a single 75 ml portion of saturated sodium chloride. The solvent was evaporated at reduced pressure to give the crude adamantane derivative (3.8 g, 0.014 mol) as an oil. This was dissolved in 75 ml of acetone and oxidized by the addition of 15 ml of 8N chromic acid solution.[31] The excess oxidant was quenched by the addition of 10 ml of 2-propanol, and the reaction mixture was poured over 300 g of ice. The aqueous mixture was extracted with three 50 ml portions of chloroform, and the combined chloroform extracts were washed with two 50 ml portions of 1M potassium bicarbonate and a single portion of saturated sodium chloride. The solution was dried over anhydrous potassium carbonate and evaporated at reduced pressure to give 1.0 g (42%) of crude 5-methyl-2-adamantanone (5). Chromatography on alumina afforded a sample melting at 124-124.5° (lit.[29] 125-126°, 126-127°).

**1,3,5,7-Tetramethyl-2-adamantanone** (6)[32] was prepared by Jones oxidation[31] of a sample of the corresponding alcohol that was generously supplied by Dr. Dieter Lenoir (Technische Universitat, Munchen). The sample had a melting point of 106-108° (lit.[32] 109-110°).

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