# CHEMICAL AND STEREOCHEMICAL APPLICATIONS OF PARAMAGNETIC LANTHANIDE CHELATE COMPLEXES

BY

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### ABSTRACT

Paramagnetic substances can produce two principal effects on the high resolution nuclear magnetic resonance (n.m.r.) spectra of any substrate molecule that will associate with them in solution. First of all the unpaired electrons can cause changes in nuclear relaxation times and secondly, paramagnetic substances produce changes in chemical shifts as a result of a pseudocontact or contact interaction or both.

This thesis describes some ways in which the chemical shift changes induced by paramagnetic chelate complexes of some lanthanide metals can be used to study the chemical and stereochemical properties of organic molecules. The predominance (for protons at least) of the pseudocontact interaction coupled with the rapid reversible equilibrium between lanthanide complex and organic substrate accounts for the unique suitability of these reagents for the present study.

In Chapter I, the <sup>1</sup>H n.m.r. spectra of a series of 1,2:5,6-di-<u>O</u>isopropylidene- $\alpha$ -<u>D</u>-hexofuranose systems have been studied in solution with tris(dipivaloylmethane)-(dpm)-derivatives of europium, thulium and praseodymium. All three reagents were found to induce large stereospecific <sup>1</sup>H chemical shifts in the carbohydrate spectra. Eu(dpm)<sub>3</sub> was particularly suitable; producing the optimum shift to line broadening ratio. The induced shifts were found to vary linearly with the amount of added lanthanide reagent thus facilitating the recovery of the "normal" chemical shift data. Some experimental optimizations for the use of these lanthanide shift reagents to induce chemical shift

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dispersion, with the minimal amount of broadening and hence the maximal number of measurable coupling constants, have been discussed.

The utility of lanthanide shift reagents to assist in assigning <sup>13</sup>C n.m.r. spectra has also been discussed. The model system, 2,2dimethyl-1-propanol was used for this study.

In Chapter II, a detailed theoretical analysis of the equilibrium which exists between a lanthanide shift reagent, L, and a substance, S, is presented and tested on several suitable substrate molecules interacting with a variety of lanthanide shift reagents.

Using this novel approach, it was possible to completely characterize the lanthanide-substrate equilibrium in terms of three parameters: the equilibrium binding constant,  $K_B$ ; the bound chemical shift,  $\Delta_B$ , for each proton of a substrate; the solution stoichiometry, n. Subsequent use of this knowledge was applied to studies of complex stability and to determination of molecular structure.

The dependence of  $K_{\rm B}$ ,  $\Delta_{\rm B}$  and n on the basicity of the donor group, the lanthanide reagent, the intramolecular steric hindrance at the substrate donor atom and the organic solvent has been thoroughly described. Substrates used for these studies included a variety of amines, alcohols and ketones and the organic solvents consisted of carbon tetrachloride, benzene and chloroform. Lanthanide shift reagents consisted of the tris(dipivaloylmethane) derivative of europium, thulium and praseodymium for which typical K<sub>B</sub>-values were <100 liter mole<sup>-1</sup> and the tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III), [Eu(fod)<sub>3</sub>], complex for which corresponding K<sub>B</sub>-values were increased by at least 10-fold.

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Perhaps the most important parameter to be unambiguously determined is the "bound" chemical shift for each proton of an organic substrate bound to a lanthanide shift reagent. This parameter reflects the stereospecific nature of the induced chemical shifts and can be used to determine the geometry of the lanthanide-substrate complex and thus presumably the conformation of the substrate itself.

In Chapter III, the potential use of lanthanide shift reagents in the determination of complex conformation has been rigorously investigated using a series of detailed computer programs which have been listed in the Appendices. Particular emphasis (from both a chemical and a mathematical point of view) is placed on the importance of internal rotation to the success of this approach to molecular conformations in solution. A variety of new models for free or hindered internal rotation is proposed and tested on four organic substrates (both alcohols and amines) which are rigid except at the point of attachment to the lanthanide. The studies presented are successful in arriving at well-defined and chemically reasonable substrate conformations.

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#### GENERAL INTRODUCTION

Proton nuclear magnetic resonance (<sup>1</sup>H n.m.r.) spectroscopy has achieved far reaching success when used for the study of small organic molecules in solution. However, one of the shortcomings of <sup>1</sup>H n.m.r. spectroscopy as a method for studying the structure of more complex organic molecules arises from the intrinsically low sensitivity of <sup>1</sup>H chemical shifts to changes in chemical and stereochemical environment; as a result, it often happens that a resonance of particular interest is obscured by the overlapping transitions of other resonances. Over the years, numerous methodologies and improved instrumentation have been developed to minimize the effects of this problem. These include: use of higher magnetic fields,<sup>1</sup> spin decoupling and double resonance experiments such as INDOR,<sup>2</sup> deuterium substitution,<sup>3</sup> solvent shifts,<sup>4</sup> and the study of heteronuclei (spin 1/2 nuclei other than protons) : present in the molecule (e.g. <sup>19</sup>F, <sup>2</sup>H, <sup>31</sup>P, <sup>13</sup>C).<sup>5</sup>

In addition to the above, as early as 1948,<sup>6</sup> it was recognized that the presence of any paramagnetic centre would influence the n.m.r. spectrum of a resonating nucleus. With respect to chemical applications, the most significant effects of the unpaired electrons in orbitals which have a finite existence at the magnetic nucleus are exhibited by the changes in nuclear relaxation times,<sup>7</sup> by nuclear spin polarization which gives rise to the Overhauser effect,<sup>8</sup> by chemical exchange spin decouplings,<sup>9</sup> and by large shifts in resonance positions.<sup>10</sup> This latter effect, certainly the most common, is that which has been studied in the pages which follow. For not only is the addition of a paramagnetic compound to the solution being studied likely to produce very large stereospecific chemical shifts over broader range of magnetic field strength (thereby resolving the complexity of overlapping transitions), but also it may provide detailed geometrical information of the paramagnetic species as well as of the interacting substrate.

Early studies in this area incorporated the paramagnetic properties of transition metal complexes<sup>11</sup> (e.g. nickel(II) and cobalt(II) diacetylacetonates). Peak broadening effects, low solubility of paramagnetic species, and weak interaction with organic molecules have prevented the widespread use of these complexes to resolve overlapping n.m.r. transitions.

The potential of paramagnetic lanthanide complexes as "chemicalshift" reagents has become the most important recent development in organic n.m.r. This field owes its beginning to Hinckley, who in early 1969,<sup>12</sup> performed experiments on a solution of cholesterol and the dipyridine adduct of tris(dipivalomethanato)europium(III),  $Eu(dpm)_3 \cdot 2py$ , in carbon tetrachloride, with the result that the <sup>1</sup>H chemical shifts of the cholesterol protons were stereospecifically shifted without being significantly broadened.

Our interest in this area was heightened by his paper and in the early months of 1970, we became fully engaged in the development of this novel technique as an aid to  ${}^{1}$ H spectral analysis of carbohydrates.

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Many other laboratories also followed suit and as a result, in three years there appeared in excess of 300 papers in this area. This is ample indication that the era of shift reagents is here to stay and will soon, if it has not already, become a routine and integral part of organic n.m.r. spectroscopy.

In spite of the enormous amount of attention afforded this area, it remains that a large number of the early, and even some of the more recent papers, have suffered from a serious lack of insight. Many have been entirely erroneous, a fact which has unfortunately distracted from the more than passing importance of this area. Our own <u>initial</u> investigations suffered from somewhat similar limitations. Indeed, it was the recognition of these limitations that led ultimately to the work described in Chapter II and III of this thesis.

It is neither appropriate nor intended that this thesis should present a comprehensive review of this area as it now exists. Rather it is hoped that the following summary will serve as a guide to some highlights which have developed over the past three years. Relevant papers will be discussed in greater detail in the text to follow. For those particularly interested, there are detailed reviews now available in the literature.<sup>13,14</sup>

Despite the diversity of the large number of existing applications pertaining to lanthanide shift reagents, a systematic approach to the area may still be achieved by the classification of the existing applications under the following three headings: (i) Inorganic, the chemical and physical properties of shift reagents, (ii) Qualitative, applications

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to different classes of organic compounds, (iii) Physical, the nature and mechanism of the induced chemical shifts.

# (i) Inorganic

The appropriateness of the paramagnetic,  $\beta$ -diketonate chelates of trivalent rare earth metals, of the following general formula,  $C_3 LnS_n$  (C = chelate, S = substrate) is a direct consequence of the variable co-ordination number of these rare earth elements. When n = 0 there are several free, acidic co-ordination sites available for the formation of stable adducts with a large number of substrates. Even complexes with n = 1 or 2, as is the case with Hinckley's reagent, which has a formal co-ordination number of 8, may still exhibit at least one free co-ordination site.



In addition, the undesirable line broadening associated with paramagnetic complexes of transition metal ions, is not nearly as critical for complexes containing unpaired 4f electrons. This result can be

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traced to their favourably short electron spin-lattice relaxation time, a property which renders them less effective for proton relaxation and hence n.m.r. line broadening. According to a systematic study of the relative proton resonance broadening abilities of the various  $ln(dpm)_3$  complexes by Horrocks,<sup>13</sup> complexes of Eu(III) and Pr(III) are best suited (i.e. exhibit the sharpest signal). Other factors which render these lanthanide complexes more suitable as "chemical-shift" reagents than similar transition metal complexes, are the increased solubility and the absence of interfering absorptions in the usual range of the substrate spectra.

Following Hinckley's initiative, Williams<sup>15</sup> demonstrated that the europium complex without the two moles of pyridine, which is commonly written Eu(dpm), and which had been first synthesized by Eisentraut in 1965,<sup>16</sup> produced shifts to lower field approximately four times larger in magnitude than those of Hinckley's dipyridine adduct. This was undoubtedly due to the lack of competition with pyridine for the available co-ordination sites. In addition interference resulting from pyridine resonances in the region of interest for the substrate is removed. Subsequently Rondeau and Sievers<sup>17</sup> found that with the incorporation of the anion of 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,5-octanedione (fod), an even superior n.m.r. shift reagent could be obtained with respect to both solubility and Lewis acidity. Presence of fluorocarbon on the  $\beta$ -diketonate ligand increases the solubility of the metal complex and, as we now recognize, the electron withdrawing fluorines increase the residual acidity of the cation, making it a better co-ordination site for weak donors. The usefulness of Eu(fod), as a shift reagent is hampered only slightly by ligand resonances at 8-9

 $\tau$  in the <sup>1</sup>H n.m.r. spectrum of Eu(fod)<sub>3</sub> plus substrate compared to 11-12  $\tau$  for ligand resonances of Eu(dpm)<sub>3</sub> plus substrate. In spite of the superiority of Eu(fod)<sub>3</sub> as a "chemical-shift" reagent, there are situations where the use of the Eu(dpm)<sub>3</sub> complex is preferable. One example of this occurs in the study of organic compounds which have more than one basic functional group capable of co-ordination to the lanthanide complex. In these cases, the weaker Lewis acid property of the Eu(dpm)<sub>3</sub> complex allows it to react more selectively with the polybasic substrate. This results in less broadening of the peaks in the n.m.r. spectrum than that which occurs when Eu(fod)<sub>3</sub> is similarly employed.

Workers in this area to date have incorporated, with some success, the complete range of lanthanide(III) metals with a variety of attached ligands. For the  $(dpm)_3$  and  $(fod)_3$  derivatives of praseodymium, neodymium, samarium, terbium, dysprosium, and holmium, upfield substrate ligand resonance shifts are obtained in organic solvents, while downfield shifts are observed for erbium, thulium, and ytterbium.<sup>14</sup> The acceptability of a shift reagent, however, depends not only on its ability to shift a substrate resonance but also on its line broadening effect which should be minimal. For example, shifts induced by Yb(dpm)<sub>3</sub> are <u>ca</u>. 4 times those for  $Eu(dpm)_3^{18}$  but the broadening is much larger with the result that all information derived from coupling constants is lost when this shift reagent is employed. In this respect, complexes of europium and praseodymium have been most widely used. Of these,  $Eu(dpm)_3$  or  $Eu(fod)_3$  appears to be more useful than  $Pr(dpm)_3^{19}$ or  $Pr(fod)_3$  because the latter reagents tend to shift the already low

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field resonances to a high field region which may already be complex, thereby increasing the complexity of a n.m.r. spectrum.<sup>20</sup>

Several  $\beta$ -diketonates of rare-earths have now been prepared and tested for their suitability as shift reagents. Complexes of europium(III) with ligands such as acetylacetonate and dibenzoylmethanate have been found inadequate principally because of the hygroscopic nature of the former and the low solubility of the latter.<sup>21</sup> All applications discussed thus far and those which follow are for shift reagent-substrate associations in organic solvents. It should be noted that the application of the water soluble salts of the lanthanide(III) ions (e.g.  $EuCl_3$ ,<sup>22</sup>  $Eu(NO_3)_3 \cdot 6D_20$ ,<sup>23</sup>  $Eu(ClO_4)_3 \cdot 6H_20$ ,<sup>24</sup>) to the studies of substrates in aqueous solutions has also been successful.

The magnitude of the induced shift has been observed to depend not only on the metal, the ligand attached, the substrate functionality (see later), and various experimental conditions (see Experimental Chapters I and II), but also on the position of the hydrogen relative to the lanthanide in the substrate-shift reagent complex. In this connection, the structure of the lanthanide complex has important implications as will be appreciated later.

(ii) Qualitative

It is now appropriate to consider the dependence of the induced shift on the substrate functionality. This will be followed by a brief review of some of the many applications of this dependence to organic systems.

It was soon realized that only substrates having a sufficiently polar and exposed donor atom could participate in complex formation

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with the lanthanide shift reagents. Other laboratories were quick to realize that the magnitude of the induced shift depended on the basicity of this co-ordination site as well as on the previously discussed factors of metal, ligand and position of the hydrogen relative to the lanthanide ion.<sup>21</sup>

Several systems containing suitable functional groups were investigated and the applicability of these lanthanide(III) complexes, which are Lewis acids, to form complexes with organic Lewis bases has now been shown for systems containing any one of the following functional groups; alcohols, amines, ketones, aldehydes, amides, phosphoryls, nitriles, phosphines, nitro groups, sulfoxide ethers, ethers and esters.

Shift reagents have been successfully used for the purpose of spectral analysis of and hence indirectly configurational assignment in a variety of molecular systems containing suitable donor groups of the sort already described. Included in the above are such classes of compounds as carbohydrates,<sup>20,25</sup> steroids and terpenoids,<sup>26</sup> pesticides,<sup>27</sup> polymers<sup>28</sup> and organometallics.<sup>29</sup> Shift reagents have also been used to determine the position of deuteration in deuterated borneols,<sup>30</sup> and optically active shift reagents<sup>31</sup> have been used in many instances to determine enantiomeric purity. Interesting applications have also been reported in the n.m.r. of nuclei other than <sup>1</sup>H, such as <sup>31</sup>P,<sup>23,32</sup> and <sup>14</sup>N,<sup>33</sup> and perhaps the most important <sup>13</sup>C <sup>22a,34,35</sup> where, as a result of recent advances in n.m.r. instrumentation such as Fourier Transform Spectroscopy, the observation of natural abundance <sup>13</sup>C n.m.r. spectra of complex organic substances has become possible. The principal

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problem remaining, which inhibits the generality of applications of the F.T. technique to  ${}^{13}$ C n.m.r., is the assignment of individual  ${}^{13}$ C resonances. At present, these assignments are generally made on the basis of either "off-resonance"  ${}^{13}$ C-( ${}^{1}$ H) heteronuclear decoupling experiments,  ${}^{36}$  by the internal consistency of the shifts of a series of closely related derivatives, or by studies of specifically deuterated derivatives. To this end, the application of lanthanide shift reagents has been shown to be an invaluable aid.

### (iii) Physical

This third classification has as its origin two basic components: (i) the nature of the hyperfine interaction of the nuclei in paramagnetic complexes with the unpaired electronic spin - whether pseudocontact (through space) and/or contact (through bond), (ii) a detailed analysis of the concentration dependence of the shifts.

A discussion of the relevant theory necessary to the understanding of the first of these points follows shortly. As will be shown, it is the pseudocontact interaction which contains the important geometrical dependence responsible for the stereospecific nature of the induced shifts. It is indeed significant, that right from the beginning Hinckley<sup>12</sup> recognized the potential of this aspect (which was well documented from earlier transition metal investigations) by showing the near linear slope of a plot of induced shift versus the cubed reciprocal distance  $(1/r_i^3)$  of the i<sup>th</sup> proton of cholesterol from the co-ordination site. This provided important evidence for the predominance of the pseudocontact mechanism. Although Hinckley chose to neglect the equally important angular dependence of the pseudocontact equation,

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he recognized its importance.

Clearly before any structural information can be ascertained, one is faced with the difficult task of resolving the observed shift into its contact and pseudocontact components. To this end, subsequent experimenters have addressed themselves but unfortunately many early workers chose simply to neglect the already firmly established theory concerning the mechanism of such interactions previously developed by McConnell. 37 Thus, initially there appeared in the literature many reports which completely ignored the existence of a contact term and proceeded to equate the observed shift to  $1/r_i^n$  where n = 1.6through to 3!<sup>38</sup> Before long, a large number of inconsistencies had developed and then the way of fate followed another ill-conceived path. Rather than incorporate the correct existing theory, numerous investigators continued to use solely the  $1/r_i^n$  (n = 1.6 to 3) dependence. This time any irregularities were equated to a contact interaction. 39,40 shown, 41-43,22b More recently, our own work and that of others has by equating the shift to the product of the angular and distance dependence of the pseudocontact equation, that a contact interaction is indeed negligible for protons, if present at all. This facet forms the basis of Chapter III where a more detailed account of these more recent applications will be discussed.

Hinckley<sup>12</sup> was also first to recognize the concentration dependence of the induced shifts which indicated the labile nature of the lanthanide-cholesterol complex. However, prior to the quantitative investigation of this aspect as presented in Chapter II of this thesis, no detailed analysis existed. Qualitative investigations into the

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effects of substrate, ligand and metal variations on the induced shift relied upon the entirely erroneous representation first proposed by Demarco.<sup>44</sup> Following our publication in this area,<sup>45,46</sup> numerous other papers have appeared delineating similar quantifications.<sup>47-51</sup> This area forms the foundation of Chapter II where a more detailed discussion will be found.

In summary, the work described in the literature has demonstrated that the more or less routine use of lanthanide shift reagents to provide access to a set of chemical shifts and coupling constants, the latter of which provides a useful structural probe, is of great significance to the organic chemist. However, more detailed information with respect to substrate geometry is possible and can be realized only when a full understanding of the chemical and physical processes involved in such interactions is attained. This need for a more quantitative investigation into the magnitude of chemical shift changes with respect to different lanthanide metals, solvent dependence, ligand dependence, substrate dependence, and temperature dependence has formed the basis on which the following thesis rests.

It has proved convenient to subdivide the main body of this thesis into three separate Chapters which demonstrate in a sequential order the quantification of our insight into this area.

In Chapter I we shall describe the experiments which were first performed (in 1970) and which had as their sole objective the development of understanding of the experimental procedure for using lanthanide shift reagents to obtain optimally dispersed  ${}^{1}$ H and  ${}^{13}$ C spectra. These experiments uncovered the need for quantifying some

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aspects of lanthanide shift reagents and this forms the core of Chapter II. Chapter II starts with the development of a theory for the molecular association. Use of this novel approach allowed an unambiguous determination of equilibrium constants,  $K_B$ , stoichiometry, n, and bound chemical shifts,  $\Delta_B$ , for the lanthanide-substrate complex of a range of model systems.

Subsequently, the application of this knowledge gave rise to further understanding of the chemical aspects of lanthanide shift reagents and in so doing some of the limitations of the procedure adopted in Chapter I were uncovered.

Finally in Chapter III we shall discuss some attempts to calculate absolute geometry using the correct values for bound chemical shift  $(\Delta_R)$  as evaluated in Chapter II.

Before introducing the particular facets of this area that we chose to study, it is appropriate to present a very brief summary of the salient features of the theory behind paramagnetic influences in n.m.r.; this being quite thoroughly described in the literature.<sup>52</sup> More detailed treatment may be found in papers by McConnell<sup>37</sup> and Bleaney<sup>53</sup> and in a review article by Webb.<sup>54</sup>

An electron spin in n.m.r. produces a characteristic chemical shift due to the very strong local magnetic fields resulting from hyperfine interactions. When we consider a paramagnetic ion in a solution with an isotropic hyperfine splitting 'a', the spin energy levels in a strong external field are given by the expression

[1]  $\mathcal{H} = g_N \beta HS_z - g_N \beta_N HI_z + aI_z S_z$ 

The abbreviations used in this and following equations are as follows: 'g' and ' $\beta$ ' are the electronic spectroscopic splitting factor and Bohr magneton; 'a' is the hyperfine interaction constant expressed in gauss; 'g<sub>N</sub>' and ' $\beta_N$ ' are the nuclear 'g' value and magneton respectively; 'H' is the applied magnetic field; 'S<sub>z</sub>' is the Z-component of the electron spin; 'I<sub>z</sub>' is the Z-component of the nuclear spin.

The part of the energy which depends on the nuclear spin orientation is

[2] 
$$\mathcal{H} = -g_N \beta_N I_z (H - \frac{aS_z}{g_N \beta_N})$$

The quantity  $\left(-\frac{as_z}{g_N\beta_N}\right)$  in the above equation is referred to as  $H_e'$  and represents the effective local field produced by the unpaired electron at the nucleus. For example a hyperfine splitting of a' = 84 Mc/s corresponds to a local field  $H_e'$  of  $\pm 10,000$  gauss, depending on the electron spin direction.



exceedingly fast for the nuclear resonance signals to be sharp enough to be observable. For the lanthanide(III) ions  $T_1 < 10^{-11}$  seconds and consequently even at liquid helium temperatures E.S.R. measurements to determine 'a' and 'g' values are not possible for these systems. In these situations where  $\frac{1}{T_1} >>$  'a' the nucleus sees only a timeaveraged local field proportional to the mean value  $\langle S_z \rangle$  of the electron spin component. Also in the presence of a magnetic field the degeneracy of the electron spin states is removed. The  $\alpha$  and  $\beta$  electron spin states now have significantly different populations with the effective field  $H_e = -\frac{a \langle S_z \rangle}{g_N \beta_N}$  and the nuclear resonance signal shifts to high field by an amount  $\Delta H = a \langle S_z \rangle / g_N \beta_N$  or to low field if the initial hyperfine splitting 'a' is say -84 Mc/s.

The above equation arising from the presence of unpaired spin at the resonating nucleus is that usually referred to as the contact interaction and will usually be written in the following form

$$[3] \qquad \frac{\Delta H_{i}}{H} = -a_{i} \frac{\gamma_{e}}{\gamma_{u}} \frac{g\beta S(S+1)}{3kT}$$

The abbreviations used in equations [3] and [4] are as follows: ' $\Delta$ H' is the difference in resonance field of the nucleus i at applied field 'H'; ' $\gamma_{e}$ ' and ' $\gamma_{N}$ ' the magnetogyric ratios of the electron and proton, respectively; 'S' the total spin quantum number; ' $r_{i}$ ' is the separation between the unpaired electrons and the resonating nucleus; ' $\theta_{i}$ ' is the angle between this distance vector and the principal axis of symmetry of the complex; ' $g_{||}$ ' and ' $g_{\perp}$ ' are, respectively the parallel and perpendicular components of the electronic g-tensor with respect to this axis; other symbols have their usual significance.

Another contributor, which can produce chemical shifts and is believed to be the major if not sole contributor when the paramagnetic substance is a lanthanide(III) ion, is the pseudocontact hyperfine interaction. This results from the combined interaction between the dipolar hyperfine coupling and an anisotropic g factor with the nuclear moment. The equation for this shift depends on the symmetry of the g-tensor and takes its simplest form for dissolved complexes with axially symmetric g-tensors (i.e.  $g_x = g_y \neq g_z$ ).

[4] 
$$\frac{\Delta H_{i}}{H} = \frac{-\beta^{2} S(S+1)}{45kT} \frac{(3\cos^{2}\theta_{i}-1)}{r_{i}^{3}} \times (3g_{\parallel} + 4g_{\perp})(g_{\parallel} - g_{\perp})$$

The importance of the geometric dependence of the pseudocontact shift, Eq.[4],will be rigorously evaluated in Chapter III. For the moment, it is clear that the magnitude of shifts for nuclei in the same complex will vary, perhaps even the sign, since the term  $(3\cos^2\theta_i-1)$  changes sign for angles of  $\theta_i \ge 54^\circ 44^\prime$ .

In summary, contact shifts provide information concerning the electron spin delocalization from the metal atom to the ligand, whereas the pseudocontact shifts are stereospecific and contain important geometrical information. Some justification for the use of Eq.[4], which pertains to complexes of axial symmetry only, will be presented in Chapter III. No attempt has been or will be made to analyze shift data with respect to the more complex equation derived for the general use of  $g_x \neq g_y \neq g_z$ .

### CHAPTER I

STUDIES OF THE CHEMICAL SHIFT CHANGES IN BOTH PROTON AND CARBON-13 N.M.R. PRODUCED BY THE ADDITION OF PARAMAGNETIC LANTHANIDE CHELATE COMPLEXES

### Introduction

Our systematic approach to the complete understanding of the nature of lanthanide-substrate interactions and subsequently to the determination of molecular geometry, began in 1970 as a result of the application of the lanthanide shift reagents to monosaccharide derivatives, an area in which no previous data were available. The sole objective in this investigation was to develop the necessary insight as to the optimal experimental procedure for using lanthanide shift reagents to obtain optimally dispersed <sup>1</sup>H spectra of this important class of molecules.

Such systems have previously been extensively studied by this laboratory and suitable systems were available in varying degrees of purity. From a practical point of view, these systems were conformationally relatively rigid and possessed one site likely to provide the major point for association with the lanthanide shift reagent. The importance of the above conditions will become apparent later. Also, the spectra of monosaccharide derivatives are not unusually complicated by the overlapping of different transitions. This results in little ambiguity in assigning individual resonances, thus minimizing any errors resulting from incorrect assignment of transitions. This latter characteristic was necessary because previously, workers had studied organic systems having a single "chelating" substituent, usually a hydroxyl group. The potentially polyfunctional monosaccharide on the other hand, could not be presumed <u>a priori</u> to follow the previously well established linear dependence of shift versus added lanthanide.

The applicability of lanthanide shift reagents to  ${}^{13}$ C n.m.r. spectroscopy as a means of assigning individual  ${}^{13}$ C resonances will also be discussed. As a result of instrumental limitations at U.B.C. at the time this research was initiated, it was not easy to study the  ${}^{13}$ C spectra of such interesting molecules as monosaccharides. The conclusions are, nevertheless, general.

In the following discussion, the optimal conditions under which to perform these particular experiments (i.e., to obtain the maximum shift with the least amount of line broadening) have been qualitatively assessed. In this respect, we have investigated the dependence of the magnitude of the induced shifts on variations in the rare earth metal for complexes with tris(dipivaloylmethane), the solvent system and the temperature at which the experiments were performed. It will be shown that the simplistic rationales concerning the relationship between the magnitudes of the induced shifts and the geometry of the substrate can in some instances be entirely misleading. In addition, an incisive experiment to distinguish between the contact as opposed to the pseudocontact mechanism will be presented.

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These investigations were responsible for introducing the need to quantify some aspects of lanthanide shift reagents, whereupon Chapter II originated. The results presented in Chapter II will reveal many of the limitations of the procedure presented in this chapter, nevertheless, qualitatively the conclusions drawn from this present study are unchanged. Thus the results presented here have useful significance for a large number of present applications seeking only optimally dispersed <sup>1</sup>H and/or <sup>13</sup>C spectra with still measurable coupling constants, the aim of many organic chemists.

## Results and Discussion

A. <u>Measurement of the <sup>1</sup>H Chemical Shift Changes of Carbohydrates</u> Induced by Lanthanide Shift Reagents

Initial studies using the lanthanide paramagnetic shift reagents involved the use of four derivatives of the 1,2:5,6-di-<u>0</u>-isopropylidene- $\alpha$ -<u>D</u>-hexofuranose system as the model substrate molecules. Instrumental


in this particular choice was the fact that all but one, 4, were available from previous studies in our laboratory and required only final purification. In addition, these derivatives have the necessary property that they all have reasonably well defined geometries and possess one group, either a hydroxyl or acetoxyl group, most likely to provide the major association site for the lanthanide reagent. Lanthanide shift reagents were synthesized for the tris(dipivalomethanato) derivatives of three typical lanthanide metals; europium 5, thulium 6, and praseodymium 7 following the standard literature procedures.<sup>16</sup> In all experiments, freshly sublimed lanthanide reagents and carefully dried solvents and substrates were used. It was essential to remove all traces of water. Water if present would "compete" many times more effectively for the lanthanide shift reagent than would the substrate, thereby reducing the resulting shift for an equivalent amount of lanthanide and possibly causing considerable line-broadening. A comparison between the spectra shown in Fig. 1A and B, typifies the effect of lanthanide reagent (in this case the europium reagent 5) on the <sup>1</sup>H spectrum of <u>1</u>. The outcome of adding water to this system is shown in Fig. 1C; clearly the added water has almost entirely eliminated the induced shift; from Fig. 1A,  $\tau_{H-1} = 4.080$ ,  $\tau_{H-2} = 5.489$  and from Fig. 1C,  $\tau_{H-1}$  = 4.060 and  $\tau_{H-2}$  = 5.463. This exemplifies the fact that water associates more strongly with 5 than does the carbohydrate derivative 1.

Preliminary experiments also established that the rather small quantities (<0.15 mol equiv; <25 mg; < $3.5 \times 10^{-5}$  mol) of lanthanide reagent needed to produce interesting chemical shift changes, were most



- Figure 1. The <sup>1</sup>H n.m.r. spectra (100 MHz) of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose (1, 0.0842 g) in CDCl<sub>3</sub> (0.5 ml). Tetramethylsilane was used for the internal field-frequency lock.
  - A. The normal spectrum.
  - B. The spectrum after the addition of  $Eu(dpm)_3$  (5, 9.84x10<sup>-2</sup> mol equiv).
  - C. As for B but with the further addition of water (0.01 ml, 1.55 mol equiv per mol of 1).

A diagrammatic representation of the first-order assignment is given above the spectrum shown in B. conveniently obtained by the addition of volume aliquots of freshly prepared stock solution of the reagent. This procedure also provided an automatic access to two important sets of data. These were, (i) plots of the magnitude of induced shifts as a function of the amount of added reagent and (ii) the spectrum of the compound having the optimal dispersion of chemical shifts and hence the maximum number of measurable coupling constants. This latter aspect is clearly illustrated in Fig. 1, which shows spectra of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose 1. The spectrum in Fig. 1B shows the effect of 9.84x10<sup>-2</sup> mol equiv of added europium 5; all seven ring-proton resonances are clearly resolved.

A routine series of spectra was then measured in which aliquots of each of the lanthanide reagents 5, 6, and 7 were added to each of the four sugars 1, 2, 3, and 4, using deuterochloroform solutions throughout.

The plots shown in Figs. 2, 3, and 4 are characteristic of those found for each of the lanthanide reagents interacting with each of the four sugars. They indicate that there is a linear relationship between the magnitude of an induced shift and the amount of added lanthanide reagent, at least up to <u>ca</u>. 0.15 mol equiv. The linearity of these plots implies that on the n.m.r. time scale, the exchange between the "free" and "complexed" lanthanide reagent must be in the fast exchange limit. Besides providing a convenient means for indicating the progress of an experiment and for obtaining the spectrum having the optimal dispersion of chemical shifts, this linear relationship provides for the important recovery of the chemical shift data. Thus, extrapolation of a shift-concentration plot back to zero concentration of the

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Figure 2. Chemical shifts observed for a solution of <u>1</u> (0.0842 g) in CDC13 (0.6 ml) following the dropwise addition of a solution of Eu(dpm)<sub>3</sub> (<u>5</u>, 0.0312 g) in CDC1<sub>3</sub> (1 ml). The dotted sections of the plots shown for the H-4, -3, and -5 resonances apply over the region where assignments were considered to be insufficiently accurate to be included here. Tetramethylsilane was used for the internal field-frequency lock.

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Figure 3. Plot of the chemical shift changes observed for a solution of 1 (0.0897 g) in CDCl<sub>3</sub> (0.6 ml) induced by Tm(dpm)<sub>3</sub>, <u>6</u>. The chemical shifts of the two H-6 resonances remained essentially the same throughout the experiment. The chemical shift of the H-5 resonance ran roughly parallel with that of H-4; it could not be measured with sufficient accuracy to justify its inclusion here. Tetramethylsilane was used for the internal field-frequency lock.





added lanthanide gives the "normal" shift of that particular proton. This useful procedure can, however, be subject to sizable experimental error, and this is illustrated in Fig. 3 for the thulium reagent 6. Here there appears a "lag" during the addition of the first 0.01 mdl equiv of 6; a lag which is identical for all protons in the substrate molecule. These observations are consistent with a small amount of water still present in the carbohydrate sample, which complexes preferentially with the thulium reagent. In accord with this suggestion the lag was decreased by further drying of the carbohydrate samples. The final magnitude of the error induced by this effect, which is greatly amplified the larger the slope, can fortunately be compensated This is accomplished simply by moving the y-axis to the right for. by the amount proportional to the lag - a quantity which can be measured provided that the normal chemical shift of one proton is directly measurable. The excellent agreement obtained between normal and extrapolations of shift-concentration plots when applying this correction factor is shown for the data listed in Table 1. These corrected extrapolated chemical shift values and coupling constants as measured from the first order spectrum achieved by the addition of the lanthanide shift reagent can now be used to simulate the original complex spectrum using LAØCN3. Fig. 5B illustrates this treatment for the highly complex portion of the spectrum of 1. Input parameters are those corrected extrapolated chemical shift values listed in Table 1 for 1, and coupling constants from the first order spectral

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Table 1. Chemical shifts ( $\tau$ -values) for compounds <u>1</u>, <u>3</u> and <u>4</u> in deuterochloroform solution, showing values obtained by direct measurements and by corrected extrapolations<sup>†</sup> to zero concentration of a shift-concentration plot for the addition of lanthanide reagents <u>5</u>, <u>6</u> and <u>7</u>.

0			Chemical shifts			
Compound	Proton	Corrected	Corrected extrapolated values			
		τ <sub>o</sub> (Eu)	τ <sub>ο</sub> (Tm)	τ <sub>o</sub> (Pr)	values	
	H-1	4.075	4.075	4.075	4.075	
	H-2	5.485	5.440	5.480	5.488	
1	H-3	5.710	5.800	5,700	<u>ca</u> .5.7	
	H-4	5.930	6.020	5,920	<u>ca</u> .5.9	
	H-5	5.670	*	5.700	5.669	
	H-1	4.152	4.152	4.152	4.152	
3	H-2	5.527	5.522	5.543	5.552	
	H-3	4.770	4.775	4.820	4.765	
	H-1	4.223	4.223	4.223	4.223	
4	Н-2	5.245	5.230	5.222	5.233	
	H-3	5.165	5.140	5.160	5.143	

\* Indeterminate

<sup>†</sup> In all cases, the correction factor was calculated from the 'normal' shift of H-1.

<u>Note</u>: Compound <u>2</u> has not been included because the shifts of a representative range of protons could not be determined with sufficient accuracy to justify its inclusion here.



analysis of Fig. 1B. The excellent agreement between Figs. 5A and B is proof of the reliability of this technique and, more important, indicates that for the concentration range studied, complexing with  $\operatorname{Eu}(\operatorname{dpm})_3$  <u>5</u>, does not alter the geometry of the substrate which would be displayed by a change in the measured coupling constants from Fig. 1B. Thus coupling constants measured in this way can be related to a Karplus-type curve<sup>†</sup> and this provides important geometrical information concerning the substrate molecule. True coupling constants for <u>1</u> are listed in Table 2.

For the compounds studied in this series, the thulium reagent  $\underline{6}$  always produces larger changes in chemical shifts than would an equivalent amount of the europium reagent. Insofar as the shifts induced by europium are already very large, there seems little advantage at this time in using the thulium reagent  $\underline{6}$ , except possibly for conformationally labile systems. Furthermore, the fact that for any particular amount of induced shift,  $\underline{6}$  causes significantly more line broadening than  $\underline{5}$ , (as has been shown elsewhere<sup>13</sup>) dictates in favor of  $\underline{5}$ . There may be occasions when the shift to high field induced by the praseodymium reagent  $\underline{7}$  is advantageous, but this was certainly not the case for the monosaccharide derivatives 1-4 of this study.

Several observations made during the course of this study provided

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<sup>\*</sup> The calculated number of transitions for this complexed seven spin system exceeded the storage capabilities of LAØCN3. It was necessary therefore, to analyze this region of the spectrum first for 5 spins then for 2 spins. This then, is responsible for the slight difference noticeable in the region of H-3, ca. 5.7 τ.

<sup>&</sup>lt;sup>†</sup> This is the well known dependence of the magnitude of the coupling constant between vicinal hydrogens (J<sub>HCCH</sub>) on the dihedral angle (\$\$) between the projected C-H bonds.

Table 2. N.m.r. parameters for 1,2:5,6-di-0-isopropylidene-α-D-glucofuranose 1.



Chemical shifts (τ-values) <sup>†</sup>							
H-1	H-2	Н-3	H-4	H-5	н-6 <sub>1</sub>	<sup>H-6</sup> 2	
4.08*	5.49*	5.69	5.95	5.68	5.85	6.01	

Coupling constants (Hz)

H-1,H-2	H-3,H-4	H-4,H-5	$H-4, H-6_{1}$	
3.7*	2.3	7.7	-0.2	
H-5,H-6 <sub>1</sub>	H-5,H-6 <sub>2</sub>	H-6 <sub>1</sub> ,H-6 <sub>2</sub>		
6.1	5.2	-8.6		

<sup>+</sup> Measured in deuterochloroform solution.

\* First order numbers only.

some interesting insights, and caused considerable skepticism against some of the simplistic rationalizations which have been implied elsewhere. Chapters II and III are a direct result of the need for a more complete method of analysis of the situation, which allows for a quantitative explanation of these and other observations. The following discussion will serve to demonstrate this need.

Prior to our work it had been shown that, for simple aliphatic derivatives, it was the protons which are nearest in terms of bond separation to the functional group predominantly engaged in complexing with the lanthanide, which undergo the largest shifts.<sup>15,21</sup> It would seem naive to anticipate that this same behaviour should necessarily pertain to more complex molecules, particularly rigid cyclic systems. For if the shifts induced by lanthanide reagents arise <u>via</u> the pseudocontact mechanism, as has generally been assumed, then as well as a distance dependence, an angular dependence must also be included in calculations of the induced shift-changes. From equation [4] in the Introduction, it will be necessary to calculate the complete factor

 $< \frac{3\cos^2\theta_i - 1}{r_i^3} >$  for each proton. Clearly the angular term will be a most important part, especially for those protons nearest to the donor group, because if  $\theta_i > 54.4^\circ$  this whole variable even changes sign. This function may be even more complicated if the complex does not possess axial symmetry as has been suggested.<sup>12,55</sup> This will be discussed in greater detail in Chapter III.

The results for 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose 1 indicate the complication which can arise for cyclic systems. From the

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many studies using aliphatic derivatives, one might have assumed that the C-3 hydroxyl group would be the principal donor group and therefore the H-3 resonance should undergo the largest shift. This is not the case. As seen in Fig. 1 H-5 shifts 1.35 times as fast as the H-3 resonance. The use of the praseodymium reagent  $\underline{7}$  with  $\underline{1}$  has a similar effect; the shift of H-5 is greater than H-3. Interestingly, the other three compounds  $\underline{2}$ ,  $\underline{3}$  and  $\underline{4}$  do behave in a "normal" fashion with  $\underline{5}$  and  $\underline{7}$ , with H-3 undergoing the largest shift. Further complexity arises with the observation that when  $\underline{1}$  is studied with the thulium reagent  $\underline{6}$ , H-3 does shift the most.

There are several possible reasons for this unusual difference in behaviour of 1 with 5 and 7 than with 6. These are, in increasing order of likelihood: (i) it could be that the geometry of 1 is uniquely suitable for forming a second donor bond with the europium reagent 5 and the praseodymium reagent  $\frac{7}{2}$  but not with the thulium reagent  $\frac{6}{2}$ , providing even further complexity in the symmetry of the complex and therefore the angular dependence; (ii) perhaps the angle  $\theta_i$  implicit in the  $\cos^2\theta_i$  term of the equation for the pseudocontact interaction with the axial complexes is different for 5 and 7, than it is for 6; (iii) the angle  $\boldsymbol{\theta}_i$  is the same for all three lanthanides but the thulium reagent 6 has some degree of contact contribution which is known to have the greatest effect on the protons nearest the donor site. Only by detailed computer study of the geometry term in the pseudocontact equation will the above inequality between the metals be solved. Interesting, in its own right, is the large value of  $J_{4.5} = 7.7$  Hz for 1 implying that H-5 is "transoid" with respect to H-4 and is hence

located quite near to the C-3 hydroxyl group. Nevertheless, based on the simplistic arguments applied elsewhere, the above unusual behaviour would certainly not have been expected.

A further observation is that the magnitudes of induced shifts appear to be significantly solvent dependent. For example the shiftchanges of the <u>D</u>-gluco derivative <u>1</u> induced by europium <u>5</u> have been measured for both chloroform (or deuterochloroform) and carbon tetrachloride solutions. As shown by the slopes of the lines for H-3 and H-5 in Fig. 6, the shift induced by a certain amount of europium <u>5</u> is approximately twice as large in a carbon tetrachloride solution (heavy lines) as it is for the same absolute concentration of <u>1</u> studied in a chloroform solution. This eventuality could result from a difference in bound chemical shift ( $\Delta_{\rm B}$ )<sup>\*</sup> between the two solvents; a larger equilibrium binding constant (K<sub>B</sub>) in CCl<sub>4</sub>; or from changes in both  $\Delta_{\rm B}$ and K<sub>p</sub>. This point will receive further treatment in Chapter II.

In a preliminary communication,<sup>18</sup> Williams and coworkers have commented that, "the shift ratios of protons in any given substrate remain the same whichever lanthanide is used". That our chemical shift changes appear to be in very poor accord with this suggestion is demonstrated by the data summarized in Table 3. Noteworthy is the similarity of the ratios for 3-Q-acety1-1,2:5,6-di-Q-isopropylidene- $\alpha$ -<u>P</u>-glucofuranose 3 with the europium 5 and praseodymium 7 reagent.

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<sup>\*</sup>  $\Delta_{\rm B}$  is defined as the chemical shift which would be observed for the substrate resonances when the substrate is rigidly bound to the lanthanide shift reagent.



Figure 6. Plot of the chemical shift changes observed for the H-3 and H-5 protons of <u>1</u> induced by Eu(dpm)<sub>3</sub> as a function of solvent. Light lines indicate the chemical shift changes observed for a solution of <u>1</u> (0.0842 g) in CDCl<sub>3</sub>. Heavy lines indicate the chemical shift changes observed for a solution of <u>1</u> (0.0817 g) in CCl<sub>4</sub>. Tetramethylsilane was used for the internal field-frequency lock in both cases.

 Table 3. Ratios of the chemical shift changes of selected pairs of protons for compounds  $\underline{1}$  and  $\underline{3}$  in deuterochloroform solution after the addition of lanthanide reagents  $\underline{5}$ ,  $\underline{6}$  and  $\underline{7}$ .

Compound	Protons	Numer	Numerical value of ratio				
	considered	Eu <u>5</u>	Pr <u>7</u>	Tm <u>6</u>			
1	H-1/H-2	0.82	0.84	0.65			
	H-1/H-3	0.35	0.47	0.29			
<u>3</u>	Н-1/Н-2	0.62	0.59	0.41			
	H-1/H-3	0.35	0.37	0.23			

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These ratios are identical, within experimental error and yet significantly different from those determined for the thulium reagent 6 whereas for the D-gluco derivative 1, this distinction is even more complicated.

If one could rest assured that all lanthanide shift reagents bound in the same manner and form, then from the variance in these ratios one must concede the presence of a contact shift in addition to the acknowledged pseudocontact shift. However, as will be shown later, the contact contribution must be negligible, if present at all. Therefore until studies have been performed to determine reliable values for the bound chemical shift  $(\Delta_{p})$ , the binding constant  $(K_{p})$  and stoichiometry (n) any such conclusion as the above is without grounds.\* Thus these ratios stand alone as strong critics of the simplistic rationalizations that are so often implied.

# Applications of Lanthanide Shift Reagents to the Identification Β. of <sup>13</sup>C Resonances

As commented earlier this study was initiated before the availability at U.B.C. of a Fourier Transform accessory; thus a  $^{1}H^{-}(^{13}C)$  INDOR spectrometer was used. The <sup>13</sup>C chemical shifts were measured for the model substrate 2,2-dimethy1-1-propanol 8 in the presence of varying concentra-

\* Interaction between lanthanide shift reagent and substrate can be represented as follows:

 $L + nS \xrightarrow{k_1} LS_n$  where L denotes lanthanide, S denotes substrate and the binding constant for substrate and the binding constant for  $K_{\rm B} = \frac{[\rm LS_n]}{[\rm L][S]^n}$ this process

tions of the tris(dipivalomethanato) derivatives of europium <u>5</u>, thulium <u>6</u>, praseodymium <u>7</u>, and gadolinium <u>9</u>. These measurements also provided the <sup>1</sup>H shift changes automatically.

Due to instrumental limitations, the substrate concentration was maintained constant during all experiments at a value of 2.27 M and the lanthanide concentration was varied from <u>ca</u>. 0.15 to 0.075 M. This procedure was carried out by first preparing a standard stock solution (5 mls) of 2.27 M <u>neo-pentanol 8</u>, then using 1 ml of this solution to dissolve <u>ca</u>. 0.100 g of lanthanide reagent. 0.5 ml of this latter solution was then placed in a n.m.r. tube. Chemical shift measurements were then made on this sample and the experiment continued by successive additions of aliquots (0.05 ml) of the standard 2.27 M stock solution. The resulting decrease in molar concentration of lanthanide reagent was monitored as a decrease in the induced shift.

Plots of the changes in <sup>1</sup>H and <sup>13</sup>C shifts versus  $\frac{[L]_o}{[S]_o}$  for three of the four metals studied are shown in Fig. 7 and Fig. 8. The data are summarized in Table 4. From the Figures, it is quite clear that for both <sup>1</sup>H and the <sup>13</sup>C resonance a direct relationship exists between the observed shift and the amount of added europium reagent <u>5</u> and praseodymium reagent <u>7</u>, up to <u>ca</u>. 0.15 M added lanthanide. The same is also true for the thulium reagent <u>6</u> up to <u>ca</u>. 0.05 M.

From the standpoint of  ${}^{13}$ C spectral assignments several points are noteworthy. It is encouraging to note that  ${}^{13}$ C shifts, like the  ${}^{1}$ H counterpart, were sufficiently sensitive to added lanthanide for this

<sup>[</sup>L] = total lanthanide shift reagent concentration; [S] = total substrate concentration.



Figure 7. Plot of the <sup>1</sup>H and <sup>13</sup>C chemical shift changes of 2,2-dimethyl-1propanol, <u>8</u>, in the presence of varying concentrations of Eu(dpm)<sub>3</sub>, <u>5</u>, using CHCl<sub>3</sub> as solvent. Tetramethylsilane was used for the internal field-frequency lock.



Figure 8. Plot of the <sup>1</sup>H and <sup>13</sup>C chemical shift changes of 2,2-dimethyl-1propanol, <u>8</u>, in the presence of varying concentrations of either Pr(dpm)<sub>3</sub>, <u>7</u>, or Tm(dpm)<sub>3</sub>, <u>6</u>, using CHCl<sub>3</sub> as solvent. CHCl<sub>3</sub> was used for the internal field-frequency lock for measurements with <u>7</u>, and tetramethylsilane for those with <u>6</u>.

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Table 4. Summary of the <sup>1</sup>H and <sup>13</sup>C chemical shifts of 2,2-dimethyl-lpropanol <u>8</u> in chloroform solution showing the effect of added tris(dipivalomethanato)europium <u>5</u>, thulium <u>6</u>, or praseodymium <u>7</u>.

Solution *	Chemical shifts				
studied	** Proton resonances		<sup>13</sup> C resonances <sup>§</sup>		
	CH <sub>3</sub>	CH <sub>2</sub>	<sup>13</sup> <sub>CH</sub> <sub>3</sub>	<sup>13</sup> CH <sub>2</sub>	
Normal	-0.90	-3.27	-26.26	-73.59	
With added $5^{\dagger}$	-1.63	-5.03	-27.38	-77.60	
With added $\underline{6}^{\dagger\dagger}$	-2.37	-7.26	-28.27	-80.00	
With added $\underline{7}^{\dagger}$	0.08	-0.81 <u>c</u>	<u>a</u> 24.90	-68.99	

\* The solutions all contained <u>ca</u>. 20% (w/v) of <u>8</u> in chloroform solution. Measurements were made at a probe temperature of <u>ca</u>.  $35^{\circ}$ C.

- <sup>+</sup> Values for 0.05 mol equiv of added lanthanide, interpolated from the shift concentration plots.
- <sup>++</sup> Values for 0.02 mol equiv of added thulium reagent.
- \*\*  $\delta$ -values based on tetramethylsilane as an internal reference: error + 0.02 p.p.m.
- §

Values in p.p.m. relative to tetramethylsilane calculated for a magnetic field at which the protons of tetramethylsilane would resonate at precisely 100 MHz; for details see reference 2, error  $\pm$  0.08 p.p.m.

approach to have some generality. Also, the carbon nearest the donor function of the organic substrate (C-1 in this case) undergoes a significantly larger shift than the more remote one. In this regard however, the angular dependence of the pseudocontact equation as well as the distance dependence must be considered, especially when studying cyclic organic substrates. This is clearly demonstrated by the work of Briggs and coworkers, <sup>34a</sup> for borneol <u>10</u>. Both C-1 and C-3 are



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adjacent to the hydroxyl donor group, yet their  $\Delta_{Eu}^{*}$  values as calculated by Demarco's method<sup>26a</sup> are -14.0 and -21.8 p.p.m. respectively. Clearly then, <sup>13</sup>C spectral assignments can be greatly facilitated with the proper use of the pseudocontact relationship. Subsequent extrapolations of suitable shift versus concentration plots can be used to determine the "normal" chemical shift values of individual resonances.

Again with regard to spectral assignments it is noteworthy that whereas both europium 5 and thulium 6 induce shifts to lower field with a Tm:Eu shift ratio of <u>ca</u>. 5.0, the praseodymium reagent 7 produces high-field shifts with a corresponding Pr:Eu shift ratio of

 $<sup>^{\</sup>circ}$   $\Delta_{Eu}$  represents the difference in chemical shift between the free substrate and that for 1 mole of substrate bound to 1 mole of shift reagent.

<u>ca</u>. 1.5. These shift ratios definitely dictate in favour of <u>6</u> as the preferred shift reagent. However, degenerate transitions are not nearly as common in <sup>13</sup>C spectra as in <sup>1</sup>H spectra and therefore the superior shifting ability of <u>6</u> is unnecessary and undesired in view of the increased broadening of resonances produced with this reagent.

In Table 5 are summarized the  ${}^{1}$ H and  ${}^{13}$ C shift ratios for the three lanthanides studied. It is important to note that for this <u>acyclic</u> system, the proton shift ratios with <u>5</u>, <u>6</u> and <u>7</u> are to within experimental error identical. These results further support the presumption, for lanthanide shift reagents, of an exclusively pseudocontact contribution to the observed proton shifts. On the other hand, the large variance observed for the  ${}^{13}$ C shift ratios may be indicative of a contact contribution, in addition to the pseudocontact contribution, to the observed shift mechanism. Recently Cushley,  ${}^{34f}$  and Willcott  ${}^{56}$ have demonstrated a dominant contact contribution in the  ${}^{13}$ C spectra for those carbons closest to the point of co-ordination with the lanthanide. These results will receive further discussion in Chapter III.

If a contact contribution was responsible for this difference in  $^{13}$ C shift ratios, then a different mechanism of electron spin delocalization into  $^{13}$ C orbitals would be indicated. This conclusion, resulting from not only our data but from that of others, demonstrated a need to be able to differentiate between the contributing mechanisms for induced shift. To that end, the following experiment was performed.

The experiment is based on previous studies by Kluiber and Horrocks<sup>10a</sup> and by Yonezawa, Morishima, and Ohmori<sup>57</sup> of main group

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Table 5. Ratios of the  ${}^{1}$ H and  ${}^{13}$ C chemical shift changes for compound <u>8</u> in chloroform solution after the addition of lanthanide reagent <u>5</u>, <u>6</u>, and <u>7</u>.

Nuclei considered	Numerical value of ratio				
	Eu <u>5</u>	Pr <u>7</u>	Tm <u>(</u>		
$^{1}$ H - $\frac{CH_{3}}{CH_{2}}$	0.40	0.41	0.3		
$^{13}C - \frac{CH_3}{CH_2}$	0.18	0.25	.0.3		

transition metals. Combining equations [3] and [4] from the Introduction one can write equation [5] which relates the observed chemical shift induced by a paramagnetic species in terms of both the contact and pseudocontact contributions. Any species having a spherically symmetric charge cloud (S-state) also has an isotropic g-value, that is

$$[5] \quad \left(\frac{\Delta H}{H}\right)_{i} = \frac{-a_{i}\left(\gamma_{e}\right)}{\left(\gamma_{N}\right)} \cdot \frac{g\beta S(S+1)}{3kT} - \Sigma(3g_{i} + 4g_{i}) \cdot \left[\frac{(g_{i} - g_{i})(3\cos^{2}\theta_{i}-1)}{r_{i}^{3}}\right]$$

 $g_{||} = g_{\perp}$ . Substitution of this equality into equation [5] results in the cancellation of the second term which is the pseudocontact term and leads to equation [3]<sup>\*</sup> which now describes the contact contribution.

[3] 
$$\left(\frac{\Delta H}{H}\right)_{i} = \frac{-a_{i}(\gamma_{e})}{(\gamma_{N})} \cdot \frac{g\beta S(S+1)}{3kT}$$

Gadolinium; in Gd(dpm)<sub>3</sub>, is in the +3 valence state and thus has a half-filled f-shell: it follows, then, that its orbital angular momentum, L, is zero and hence that it has an isotropic g-value. Consequently any shift induced by Gd(dpm)<sub>3</sub> must arise from the contact mechanism. If we now assume that the complex formed between a particular substrate molecule and Gd(dpm)<sub>3</sub> has the same geometry and distribution of unpaired electron spin as that of other  $Ln(dpm)_3$  complexes then the contact-shift of Gd(dpm)<sub>3</sub> should give an estimate of the contribution which the contact mechanism makes for the other lanthanide shift reagents. Thus, in this indirect fashion, it is possible to separate the shift contributions of the contact and pseudocontact mechanisms.

<sup>\*</sup> The abbreviations used in the equations [5] and [3] are as listed in the introduction with  $\Sigma = \beta^2 S(S+1)/45$  kT.

An experiment with  $Gd(dpm)_3 \ \underline{9}$  and <u>neo-pentanol 8</u> was performed following the same procedure adopted for the other experiments described previously and over the same concentration range. No detectable proton shift-change could be observed although the resonances of H-1 and H-3 were severely broadened which prohibited the detection of the  $^{13}$ C resonance via the INDOR technique.

Consequently it follows that if the assumptions of the above approach are correct then the contact mechanism makes very little contribution if any, to the proton shifts induced by Ln(dpm)<sub>3</sub> reagents, at least for non-aromatic substrates.

# C. <u>Temperature Dependence of the Paramagnetic Induced Shift in</u> <sup>1</sup><sub>H N.M.R.</sub>

As part of this qualitative evaluation of the lanthanide shift reagents, the temperature dependence of lanthanide induced chemical shift changes was investigated: as the temperature is reduced the magnitude of the shift increases. This behaviour, with decreasing temperature, is due to the large difference in population of the  $\alpha$ and  $\beta$  electron spin states and as a result, the local field  $H_e$  increases. It is therefore possible to increase the "effectiveness" of a lanthanide reagent by decreasing the temperature at which the measurements are made. This result may prove to be extremely useful where the limited solubility of the lanthanide complex is inadequate.

A chlorinated bicycloheptenol <u>11</u> was used as a model system in this study and the measurements are summarized in Table 6. For H-5 the shift induced at -47.5°C by 9.4 x  $10^{-2}$  mol equiv of 5 is 2.5 times

Table 6. Temperature-dependent chemical shifts<sup>\*</sup> data of protons of 5-hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene<sup>\*\*</sup> <u>11</u> in deuterochloroform containing<sup>†</sup> Eu(dpm)<sub>3</sub> <u>5</u>.

T (°C)	Н-6	H-6'	H <b>-</b> 5
-47.5	7.170	6.790	3.950
-38.0	7.230	6.840	4.150
-18.5	7.385	6.910	4.400
0.3	7.495	6.953	4.560
21.0	7.575	6.983	4.668
33.0	7.615	6.998	4.720
Ref <sup>††</sup>	8.028	7.155	5.238

\* τ-values.
\*\* 0.0951 g in 0.6 ml.
† 9.4 x 10<sup>-2</sup> M equiv.
†† <u>11</u> in CDC1<sub>3</sub> at 33°C.

that produced by the same amount of reagent at 33°C. Figure 9 represents these data in the form of a plot of the induced shift versus inverse temperature. The observed non-linear response, in contrast to a linear response fortuitously obtained elsewhere,<sup>26b,58</sup> is as expected from theoretical grounds.<sup>\* 53</sup>

No further experimental work in this area will be presented for it is hoped that with the above results and the relevant theory, (see Chapter II), the full potential of this area can be realized. One particularly important application would be in the use of shift reagent and temperature to raise the effective coalescence temperature of systems whose low barrier to inversion gives rise to a n.m.r. coalescence temperature too low for most normal spectrometers. Only just recently has the literature contained a report of the successful application of the above technique.<sup>59,60</sup>

In summary then, the preceding successful investigation of the <sup>1</sup>H spectra for a series of carbohydrate derivatives and the <sup>13</sup>C spectra of <u>neo</u>-pentanol interacting with a series of  $\text{Ln}(\text{dpm})_3$  complexes does nevertheless indicate the need for a more quantitative approach. We have demonstrated that the tris(dipivalomethanato)lanthanide(III) complexes do indeed produce useful chemical shift changes in the <sup>1</sup>H n.m.r. spectra of potentially polyfunctional carbohydrate derivatives; that these shift changes are dependent on solvent and metal used; that the induced shifts are very dependent on temperature; the <sup>13</sup>C spectra

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<sup>\*</sup> For a complete discussion of the theory involved, including a discussion of other investigations into this area, see Chapter II, Theory Section V.



Figure 9. Plot of the chemical shift changes versus inverse temperature for a solution of 5-hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene (<u>11</u>, 0.0951 g) in CDCl<sub>3</sub> (0.6 ml) with Eu(dpm)<sub>3</sub> (<u>5</u>, 9.4x10<sup>-2</sup> M equiv). Tetramethylsilane was used for the internal field-frequency lock.

is shifted to the same proportion (on a p.p.m. basis) as the <sup>1</sup>H spectra, with perhaps a somewhat different mechanism involved for <sup>13</sup>C; that the common assumption as to which proton is likely to undergo the largest change in shift based only on the  $\frac{1}{r_1^3}$  dependence can lead to erroneous results. These and other points form the basis on which Chapters II and III have been developed.

## CHAPTER II

QUANTITATIVE INVESTIGATION OF THE LANTHANIDE SHIFT REAGENT-SUBSTRATE EQUILIBRIA: THE UNAMBIGUOUS EVALUATION OF THE BINDING CONSTANTS, BOUND CHEMICAL SHIFTS, AND STOICHIOMETRY

#### Introduction

In spite of the successful use of lanthanide shift reagents to obtain optimally dispersed  ${}^{1}$ H and  ${}^{13}$ C spectra, a number of inconsistencies had developed in our own work and that of others, inconsistencies which originated most likely from the neglect to analyze with any degree of accuracy, the existing equilibrium. This was the incentive behind the detailed analysis to be presented in this chapter.

The problem of the determination of formation constants and other constants for weak intermolecular complexes in solution has received considerable attention during the past several years, particularly for the investigation of enzyme-inhibitor interactions, an area where n.m.r. has proved to be very useful. Realizing the many similarities between these lanthanide-substrate interactions and enzyme-inhibitor interactions (e.g. limited solubility of both lanthanide complex and enzyme), a method of approach similar to that for enzyme interactions was adopted. The following detailed analysis of the equilibrium process which occurs when a lanthanide shift reagent combines with a substrate molecule having a suitable donor function rests on the interpretation of the resulting experiments in terms of the following three parameters: (i) the equilibrium constant,  $K_B$ , which is important since it provides information concerning the stability of a complex; (ii) the bound chemical shift,  $\Delta_B$ , which is required before any determinations of molecular structure can succeed; (iii) the stoichiometry of the complex, n, also important for determination of molecular geometry. No account has been taken of the activity coefficients which may vary disproportionately with the change in substrate or lanthanide concentration or of the possibility of multiple equilibria of which some of the more likely are listed below.

 $L + S \rightleftharpoons LS$   $L + 2S \rightleftharpoons LS_2$   $2L + S \rightleftharpoons L_2S$   $2L \leftrightarrow L_2$   $L_2 + S \rightleftharpoons L_2S$   $L_2 + S \rightleftharpoons L_2S$   $L_2 + 2S \rightleftharpoons L_2S_2$ 

The possibility of all the above competing equilibria could undoubtedly discourage interested investigators. However, by placing certain restrictions on the range of concentrations of the reactants, it is possible to force the system to adopt certain preferred equilibria or at least minimize to a significant extent the number of competing equilibria. This was the approach chosen and which will be presented

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in the following text. Some attempts have been made to analyze the concentration dependence of the observed chemical shifts by the leastsquares fit of the parameters to a two-step equilibrium mechanism. This type of treatment can result in confusion in that a numerical solution can always be obtained but it may not be a chemically sensible one. It suffices to point out that the number of experimentally measurable parameters remains constant, while the number of unknown parameters increases by a factor of two for each competing equilibrium.

The most important result of this detailed analysis is the unequivocal determination of the "bound" chemical shift for each proton of an organic substrate (S) bound to a lanthanide shift reagent (L), a parameter which cannot be observed experimentally. When reliable bound chemical shifts have been determined for such complexes, it should be possible to establish with some confidence the <u>conformation</u> of the complex and hence the organic moiety itself, as will be shown in Chapter III. Thus a need for a full quantitative analysis of the chemical equilibria operating between the lanthanide shift reagent and the substrate molecule is essential for the full potential of this technique to be realized. Then, use of the correctly determined value of bound chemical shift,  $\Delta_{\rm B}$ , justifies the full computerized treatment for molecular geometry (Chapter III).

In the course of this study, it became obvious that the desired bound chemical shift,  $\Delta_{\rm B}$ , of a substrate while it is bound to the lanthanide, may be obtained from either of the following methods of investigation: (i) measuring the induced shift, $\delta$ , for several solutions having the same [S] but differing [L] or, (ii) measuring  $\delta$  for solutions

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having constant  $[L]_{o}$  but varying  $[S]_{o}$ . As a consequence of the theory, it will be evident that for method (i), the slope of a plot of observed shift versus  $[L]_{o}/[S]_{o}$ , as employed by the majority of investigators, yields an empirical number which can differ greatly from the actual  $\Delta_{\rm B}^{}$ , and that the error can even be different for different protons in the same molecule.

Thus, the theory to follow is intended to enable the reader to clearly distinguish between these two methods on the basis of a general and accurate evaluation of  $\Delta_B$ ,  $K_B$ , and n. Predictions based on this theory are then subjected to rigorous experimental testing which permits for the first time the quantification of the effects of metal and ligand variation, basicity of the donor group and solvent on the magnitude of the induced shift.

### Theory

The first step in analyzing the chemical shifts for a one step binding process, (in which L denotes lanthanide, S denotes ligand or

[1] L + S 
$$\frac{k_1}{k_{-1}}$$
 LS

substrate, and LS is the 1:1 lanthanide-substrate complex whose chemical shift we would like to obtain) is to establish whether the exchange rates are fast or slow on the n.m.r. time scale.<sup>13</sup> There are two simple limits, (a) and (b):

(a) If  $k_{-1}$ ,  $k_1[L] >> (\delta_{LS} - \delta_S)$ , the fast-exchange limit, then there will be a single resonance centered at

[2] 
$$\delta_{obs} = f_S \delta_S + f_{LS} \delta_{LS}$$

where  $\delta_{\rm S}$  and  $\delta_{\rm LS}$  are the respective chemical shifts for S and LS, and f<sub>S</sub> and f<sub>LS</sub> are the respective concentration fractions of S at the two sites. But f<sub>S</sub> = 1 - f<sub>LS</sub>, so an "induced chemical shift",  $\delta$ , may be defined as

$$[3] \qquad \delta = \delta_{obs} - \delta_{s} = f_{LS}(\delta_{LS} - \delta_{s})$$

[4] or simply 
$$\delta = f_{TS} \Delta_{B}$$

where  $\Delta_{\rm B}$  is the chemical shift for the LS complex relative to the chemical shift for free S. The relationship of these terms is shown in Fig. 10.

(b) If, on the other hand,  $k_{-1}$ ,  $k_1[L] << \Delta_B$ , the slow-exchange limit, then resonances are expected at  $\delta_S$  and  $\delta_{LS}$ , and even if the LS sites were so dilute that the  $\delta_{LS}$  resonance could not be detected, the  $\delta_S$  resonance would still be independent of  $f_{LS}$ .

Experimentally, then, observation of a single resonance whose chemical shift varies linearly with the fraction of substrate present as complex is direct evidence that the fast-exchange limit applies. Using this criterion, it was found that the fast-exchange limit was valid for all data reported, with the exception of the interaction between lanthanide shift reagent and a series of dimethylaminocyclophosphonitriles, where the slow-exchange limit was found to apply.



Figure 10. The relationship between the terms  $\delta$ ,  $\Delta_B$ ,  $\delta_{obs}$ ,  $\delta_S$  and  $\delta_{LS}$ ; see equations [3] and [4].
### I. Experiments in which [L] is Varied at Constant [S]

This was the method in general use at the time our research in this area was initiated. No theoretical justification for this method of approach had been presented and that which follows will demonstrate the limitations inherent in this manner of data reduction.

Let [L] and [S] be the initial concentrations of lanthanide and substrate - see Experimental section for mixing procedure. Then

$$[5] \qquad \delta = \frac{[LS]\Delta_{B}}{[LS] + [S]} = \frac{[LS]}{[S]}\Delta_{B}$$

Next, let the binding constant for the process, [1], be K<sub>p</sub>:

[6] 
$$K_{B} = \frac{[LS]}{[L][S]} = \frac{[LS]}{([L]_{o} - [LS])([S]_{o} - [LS])}$$

It is now necessary to solve Eq. [6] for [LS] and then substitute for [LS] in Eq. [5], so as to determine the desired quantity  $\Delta_{\rm B}$  in terms of the measured parameters [L]<sub>0</sub>, [S]<sub>0</sub>, and  $\delta$ . In order to avoid solving the quadratic equation, [6], and to minimize the occurrence of multiple equilibria, it is convenient to simply restrict the experiments to the range,

$$[7] \qquad [S] >> [L], \text{ then } [S] >> [LS]$$

thus guaranteeing that  $([S]_{o} - [LS]) \approx [S]_{o}$  in Eq. [6]. Using [7] to solve [6] for [LS], and substituting for [LS] in [5] gives,

[8] 
$$\delta = \frac{K_B[L]_o \Delta_B}{1 + K_B[S]_o}$$

Equation [8] is the principal result of this section. The immediate question now becomes, what will happen if one plots  $\delta$  versus  $[L]_0/[S]_0$ ? The answer is clear for two simple limits:

(a)  $K_B[S]_0 >> 1$ , i.e., strong binding or high substrate concentration. In this limit, Eq. [8] reduces to

$$[9] \qquad \delta = \Delta_{B}[L]_{o}/[S]_{o}$$

so that a plot of  $\delta$  versus [L]  $_{\rm o}/[{\rm S}]_{\rm o}$  will be a straight line through the origin, with slope,  $\Delta_{\rm R}.$ 

(b)  $K_B[S]_o \ll 1$ , i.e., weak binding or low substrate concentration. In this limit, Eq. [8] reduces to

$$[10] \qquad \delta = K_{B} \Delta_{B} [S]_{o} \left(\frac{[L]_{o}}{[S]_{o}}\right) .$$

In other words, a plot of  $\delta$  versus  $[L]_{0}/[S]_{0}$  will give a straight line but the slope is now proportional to  $[S]_{0}$ .

Results (a) and (b) from Eq. [8] suggest that in carrying out several sets of experiments (each set at a different  $[S]_0$  level), then for low  $[S]_0$  the slope of a plot of  $\delta$  versus  $[L]_0/[S]_0$  will be proportional to  $[S]_0$ , while for large  $[S]_0$  the slope will simply be  $\Delta_B$  independent of  $[S]_0$ . Therefore, <u>only at high substrate concentrations</u> is it permissible to take the slope of a plot of  $\delta$  versus  $[L]_0/[S]_0$  as  $\Delta_B$ . This conclusion is of quite practical significance, as will be shown in the Results section.

### II. Experiments in which [S] is Varied at Constant [L]

Since it is now clear that there is no simple way to extract  $\Delta_{\rm B}$  from a single plot of  $\delta$  versus  $[{\rm L}]_{\rm o}/[{\rm S}]_{\rm o}$  at constant  $[{\rm S}]_{\rm o}$ , one is led to seek out some other simple experiment which will yield the bound chemical shift. Returning to Eq. [6], suppose that only the  $[{\rm LS}]^2$  term is neglected;<sup>61</sup> then

[11] 
$$\delta = \frac{K_B[L]_o \Delta_B}{1 + K_B[S]_o + K_B[L]_o}$$
, which may be re-grouped to give

[12] 
$$[S]_{o} = [L]_{o} \Delta_{B}(1/\delta) - ((1/K_{B}) + [L]_{o}).$$

Equation [12] gives the important fact that a plot of  $[S]_0$  versus  $(1/\delta)$  gives a straight line whose slope is  $[L]_0 \Delta_B$  and whose y-intercept is  $-((1/K_B) + [L]_0)$ . Such a plot thus yields both  $\Delta_B$  and  $K_B$  unambiguously.

However, as pointed out by Dahlquist and Raftery for analogous enzyme kinetics experiments,<sup>61</sup> the approximations,  $(1/K_B) \ge [S]_o$  and  $\delta << \Delta_B$ , are necessary to reach Eq. [12]. The safest procedure is therefore to solve the full quadratic equation [6] according to the following computerized procedure first suggested by Sykes.<sup>62</sup> First, guess a value for  $K_B$  and use this value to compute [LS] from Eq. [6]; this gives [LS] expressed as a function of [L]<sub>o</sub> and [S]<sub>o</sub>. Next perform experiments in which [L]<sub>o</sub> is fixed and [S]<sub>o</sub> is varied. Use the expression for [LS] to compute [LS] for each of the experimental [S]<sub>o</sub> values. Next, plot  $\delta$  versus [LS]/[S]<sub>o</sub> to obtain  $\Delta_{\rm B}$  from Eq. [5]. This plot (since the wrong value of K<sub>B</sub> was probably guessed in the first place) will usually give a curve rather than a straight line. Thus, as a criterion of how well K<sub>B</sub> was chosen, let the computer calculate a least mean square slope for the plot and also the standard deviation for the slope. This whole procedure is now repeated for say, 100 values of K<sub>B</sub> spanning three powers of ten in magnitude, and the standard deviation of the slope is plotted as a function of K<sub>B</sub>. The correct value of K<sub>B</sub> is then taken as the one which gives the smallest standard deviation in the plots of  $\delta$  versus [LS]/[S]<sub>o</sub>.

For practical purposes, we have found that for low  $[S]_0$  concentrations (see Discussion) the graphical treatment based on Eq. [12] gives reasonable agreement with the full computer treatment outlined above, and may often be preferable, inasmuch as precise values for  $K_B$  from the computer treatment seem to require quite accurate shift measurements.

All values of  $K_B$  and  $\Delta_B$  reported in this text were taken from lowconcentration experiments in which  $[S]_o$  was varied at constant  $[L]_o$ . In principle, one might hope to extract  $K_B$  and  $\Delta_B$  from experiments in which  $[L]_o$  is varied at constant  $[S]_o$ , based on the slopes of plots of  $\delta$  versus  $[L]_o$  according to Eq. [8]. There are three reasons why this procedure is impractical. First, the slope of such a plot depends on  $[S]_o$ , so one would have to carry out several series of experiments at different  $[S]_o$  values, necessitating many more experimental measurements than a single "run" in which  $[S]_o$  is plotted versus  $(1/\delta)$ . Second, when  $[L]_o$  is changed, substantial changes in the bulk magnetic

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susceptibility of the solution are introduced, and even an internal standard may not compensate properly for them. Third, at high  $[L]_{o}$  concentrations, the possibility for self-association of  $[L]_{o}$  is increased.<sup>63</sup>

#### III. Stoichiometry

In this section, the implications of a one-step binding process,

[13] L + 2S 
$$\frac{k_1}{k_{-1}}$$
 LS<sub>2</sub>

are discussed, a reasonable assumption if the binding constant of this complex is large and/or the substrate molecule S is present in large excess. The actual binding process might involve several steps; in writing [13], it is simply assumed that there is a single step which is associated with the large change in chemical shift between "free" and "bound" substrate. It is only this step which will affect n.m.r. measurements.<sup>13</sup> It is easy to imagine multi-step binding phenomena which will not satisfy Eq. [13] even on an n.m.r. basis - such phenomena are not treated here, because it will not be possible in general to obtain separate binding parameters for even a two-step process, when the n.m.r. data fall in the fast-exchange limit.

For the one-step 2:1 binding model, [13], the criterion for fast exchange is readily shown to be the same as for the case of 1:1 binding; thus an observed proportionality between  $\delta$  and  $f_{LS_2}$  is direct evidence that the fast-exchange limit is satisfied.

The equilibrium binding constant for process [13] is

[14] 
$$K = \frac{[LS_2]}{[L][S]^2} = \frac{[LS_2]}{([L]_0 - [LS_2])([S]_0 - 2[LS_2])^2}$$

and it follows that

[15] 
$$\delta = \frac{[LS_2]}{[S] + [LS_2]} \Delta_B = \frac{[LS_2]}{[S]_0 - [LS_2]} \Delta_B$$

since  $[S] = [S]_0 - 2[LS_2]$ . Equation [15] applies if we assume that both S molecules have the same chemical shift when bound to the lanthanide. It is now possible to solve [15] for  $[LS_2]$  and then substitute for  $[LS_2]$  in Eq. [14] as in Section II, resulting in the cubic equation [16] for

[16] 
$$4[LS_2]^3 - 4([L]_0 + [S]_0)[LS_2]^2 + (\frac{1}{K} + 4[L]_0[S]_0$$

+  $[S]_{0}^{2}$  [LS<sub>2</sub>] -  $[L]_{0}$  [S]<sub>0</sub><sup>2</sup> = 0

the exact solution. In order to avoid solving the cubic equation, [16], experiments are again restricted to the range  $[S]_0 >> [L]_0$ , so that  $\delta \ll \Delta_B$ , and since  $[LS_2] \leq [L]_0$  then  $[LS_2]^3 \ll [S]_0 [LS_2]^2$  and equation [16] can be expressed in the quadratic form [17].

$$[17] \qquad 4[s]_{o}[Ls_{2}]^{2} - (\frac{1}{K} + 4[L]_{o}[s]_{o} + [s]_{o}^{2}) [Ls_{2}] + [L]_{o}[s]_{o}^{2} = 0$$

If now, one makes the further approximation  $4[L]_{0} << [S]_{0}$ , then  $4[L]_{0}[S]_{0} << [S]_{0}^{2}$  and equation [17] can be expressed in the following form

[18] 
$$[S]_{o}^{2} - \frac{\Delta_{B}}{\delta} [L]_{o}[S]_{o} + (\frac{1}{K}) = 0$$

[It may be noted that Eq. [18] has the same form as Eq. [12] if one makes the correspondence,  $K[S]_{o} = K_{B}$ ; the [L]<sub>o</sub> term in Eq. [12] is usually negligible.]

Now if one can restrict experiments to the range where  $4[L]_{0} << [S]_{0}$ a simple criterion for stoichiometry is available. One need simply specify [L],  $\Delta_{\rm R}$ , and K, and then use Eq. [18] to compute a set of  $\delta$ -values from a given range of [S] -values; the values may then be used to construct a plot of [S] versus (1/ $\delta$ ) as shown in Fig. 11. This figure shows the result for several choices of  $K_{\rm B}$  which span the range of  $K_{\rm R}$ -values actually determined in the present experiments. То facilitate comparison with the result for 1:1 binding, a plot of [S] versus  $(1/\delta)$  for 1:1 binding is also shown; to make the comparison as direct as possible, values of  $K_{\rm R}$  = 0.1 K were chosen since typical experimental [S] -values were about 0.1 M. The plots clearly show that for either large  $K_{R}$  (strong binding) or large [S], one cannot distinguish between 1:1 binding and 2:1 binding from a plot of this type. On the other hand, when  $K_{R}$  is small enough to be measurable, there are readily observable differences between 1:1 and 2:1 binding. Since all [S] versus  $(1/\delta)$  plots (vide infra) are linear, it is evident at once that the binding is either strong or 1:1 or both. \* If the experimental extrapolations to  $(1/\delta) = 0$  give a y-intercept which is more negative than -[L], then a straight-line experimental plot is

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<sup>\*</sup> In only one instance was a non-linear behaviour in a plot of [S] versus  $(1/\delta)$  observed (see Results).



Figure 11. Graphs of initial substrate concentration  $[S]_0$  versus  $(1/\delta)$  for a hypothetical substrate of  $\Delta_B = 2000$  Hz in the presence of shift reagent of concentration  $[L]_0 = 0.006$  M. For each graph, the binding is assumed to be either 1:1 with corresponding binding constant, K<sub>B</sub> or 2:1 with binding constant, K . (A) K = 32, K<sub>B</sub> = 3.2; (B) K = 126, K<sub>B</sub> = 12.6; (C) K = 501, K<sub>B</sub> = 50.1; (D) K = 1000, K<sub>B</sub> = 100.

definitive proof that the binding is 1:1 rather than 2:1.

When  $K_B$  is large (strong binding), there are no well-controlled measures of stoichiometry. However, some information may be obtained from (high-concentration) experiments in which  $\delta$  is determined as a function of  $[L]_o$  at constant  $[S]_o$ , and the data are displayed in a plot of  $\delta$  versus  $[L]_o/[S]_o$ . If either  $K_B$  or  $[S]_o$  were infinitely large, such a plot would simply be a straight line from the origin to the end-point,  $\delta = \Delta_B$  at  $[L]_o/[S]_o = 1$ . For smaller  $[S]_o$ , there will no longer be a sharp end-point and one will observe a family of curves which converge for large  $[S]_o$  (see Results). Experimentally, then, one need construct several such plots at increasing  $[S]_o$  concentration until the lines begin to converge; extrapolation of the limiting line to  $\delta = \Delta_B$  (where  $\Delta_B$  has been determined reliably from lowconcentration data according to the method of Part II of this section) will then give an x-intercept of (1/n).

In conclusion, the most critical test for 1:1 stoichiometry is the linearity of a plot of  $[S]_{o}$  versus  $(1/\delta)$ , where the range of  $[S]_{o}$  values should cover an order of magnitude in concentration, and include the lowest accessible concentrations for best results.

#### IV. Solvent Dependence

Whenever a diluting solvent, A, is used, there is the possibility

\* In principle, one might hope to obtain  $K_B$  in strong-binding situations by fitting the  $\delta$  versus  $[L]_{o}/[S]_{o}$  curve of the preceding paragraph. In the Discussion it is shown that this method may not work, even if an independently determined  $\Delta_B$  is used for the fit.

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of solvent competition for one or more components in the complex. Detailed theoretical treatment of competitive solvent binding to lanthanide only, has been presented elswhere.<sup>64</sup>

[19] L + A 
$$\xrightarrow{k_1}$$
 LA

and

$$[20] KA = \frac{[LA]}{[L][A]}$$

From a very qualitative sense, the practical significance of solvent effects has already been demonstrated in Chapter I, Fig. 6, however, the following brief discussion is necessary to the understanding of the more complete investigation of this effect (see text).

Even though the appropriate binding constant for [19] is small (of the order of 0.2 liter mole<sup>-1</sup> for  $CHCl_3$ , acting as a suitable donor), the large concentration of solvent (<u>ca</u>. 12 M) may cause a significant change in the apparent binding constant for the complex LS. For example, for solvent binding to lanthanide only, [20], then the concentration of L available to complex with S will be reduced. It can be shown that this can be related in terms of the appropriate binding constants in the following manner.

[21] 
$$K_{B(apparent)} = K_{B(real)} (1 + K_{A}[A])^{-1}$$

 $K_{B}$  values reported in the text are uncorrected for such competition and perhaps should be more correctly referred to as  $K_{B(apparent)}$ ,  $K_{B(app.)}$ .<sup>\*</sup> It is important to note that the above consideration does not predict a change in  $\Delta_{B}$  values obtained for the same substrate with the same lanthanide in different solvents. It may also be assumed that  $K_{B(real)} = K_{B(app.)}$  for the CCl<sub>4</sub> solution.

To what extent the above theoretical treatment is confirmed will be discussed in greater detail (see text). It is sufficient, at this point to say, that any observed discrepancies can most likely be attributed to complications arising from either: possible dimerization of  $Ln(dpm)_3$  or  $Ln(fod)_3$  complexes in solvents of differing polarities;<sup>63</sup> the possibility of solvent-substrate interaction for which no account has been made.<sup>\*\*</sup>

#### V. Temperature Dependence

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Although no further use was made of the temperature dependence of the chemical shift changes, it does seem appropriate at this stage, in view of the results presented at the end of Chapter I, to present the theory and perspective necessary for the proper analysis of such an effect. Numerous other groups have investigated the temperature dependence but all have suffered from an incomplete allowance for the processes involved.

Other researchers have investigated the temperature dependence of

For convenience only, we use the term  $K_B$  to denote the binding constant throughout the text.

\*\* An example of such an interaction is the well-known benzene-ketone interaction.<sup>4b</sup>

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the lanthanide induced chemical shift changes and have found a linear dependence for a plot of the induced shift versus inverse temperature.<sup>26b,58</sup> They conclude that this Curie behaviour is as expected on a theoretical basis. In fact, this resultant linear dependence is a mere coincidence of the temperature range investigated and the value of  $\Delta H^{\circ}$  for L + S  $\rightarrow$  LS. For the temperature dependence of the chemical shift to be a straight line would mean that a single type of chemical complex is under observation and that it would be very unlikely for there to exist any equilibrium between different configurations requiring rupturing of lanthanide-substrate bond. That this is certainly not the situation in the above investigations and our own is evident by the linear dependence of induced shift versus lanthanide to substrate ratio. Thus in addition to the inverse temperature dependence of the pseudocontact equation (Chapter I, Eq. [4]), there exists the additional temperature dependence of the equilibrium  $(d\ln K_{\rm R}/d(\frac{1}{\rm T}) = \frac{-\Delta {\rm H}^{\circ}}{\rm R}).$ 

Beauté et al.,<sup>65</sup> observing a similar behaviour to that of Fig. 9, Chapter I, attempted to combine the two temperature dependencies. He concluded that a plot of change in chemical shift versus  $1/\sqrt{T}$  would yield a straight line. However, this apparent temperature dependence is purely coincidental and has no theoretical basis. More recently Ritchey et al.<sup>66</sup> have attempted to evaluate the changes in chemical shift as a function of temperature. In so doing, a plot of  $\delta$  versus  $\begin{bmatrix} L \end{bmatrix}_{o}$  was prepared from the data collected at three different temperatures.  $\Delta H^{\circ}$  refers to the standard enthalpy.

For the temperature range employed, the slope of each of these lines was constant and decreased with increase in temperature. However, in view of Eq. [8], the above resultant linear dependence is indicative that one is in the limit  $K_B[S]_o >> 1$  where Eq. [9] applies. In general, this limit,  $K_B[S]_o >> 1$ , will not apply, particularly since  $K_B = f(T)$ . In such situations the slope of a plot of  $\delta$  versus  $\frac{[L]_o}{[S]_o}$  will be a function of  $\Delta_B$ ,  $K_B$ , and T. Thus a study of the temperature dependence of  $\Delta_B$  becomes impossible. A more general approach which suffers no limitations would be to perform the experiment as outlined in Section II for several different temperatures and then to construct the appropriate  $[S]_o$  versus  $1/\delta$  plot at each temperature. Such a representation allows one to determine unambiguously the changes in  $\Delta_B$  with temperature and also permits an evaluation of  $K_B$  at each temperature.

Just recently, following a complete re-evaluation of the pseudocontact equation, Bleaney<sup>53</sup> has arrived at a temperature dependence for Eu(III) somewhat >  $\frac{1}{T}$  but <  $\frac{1}{T^2}$ . This result alters but in no way affects the accuracy of the above approach to the study of the temperature effect.

#### Results and Discussion

The method believed to be best suited for the general and accurate evaluation of  $\Delta_{\rm B}$  and  ${\rm K}_{\rm B}$  will be discussed first with suitable examples, followed by a demonstration that the method currently used to determine  $\Delta_{\rm B}$  from the slope of a plot of  $\delta$  versus  $[{\rm L}]_{\rm o}/[{\rm S}]_{\rm o}$  can result in large errors in  $\Delta_{\rm B}$  and moreover that these errors can vary even among different protons in the same molecule. Thereafter, using only the method as outlined in Section II of the Theory, lanthanide-substrate interactions will be analyzed in an attempt to explain each of the specific behaviours, characteristic of this interaction.

- A. Stoichiometry
- B. Basicity of the donor group and the importance of steric effects on  ${\rm K}_{\rm R}$
- C. Explanation for the greater effectiveness of  $Eu(fod)_3$  as opposed to  $Eu(dpm)_3$
- D. Explanation for the differing magnitude of induced shifts for different Ln(dpm)<sub>3</sub> complexes
- E. Solvent effects on  $K_B^-$  and  $\Delta_B^-$ -values
- F. General applications

Finally, in Section G, the applicability of a Scatchard-type plot to the analysis of the interaction will be evaluated.

Solutions of <u>n</u>-propylamine, <u>12</u>, and of <u>neo-pentanol</u>, <u>8</u>, each with  $Eu(dpm)_3$  were prepared according to the procedure outlined in the Experimental Section as Method 2. The chemical shifts of these solutions were then measured, and the results plotted on a graph of [S]<sub>o</sub> versus  $(1/\delta)$ ; the plot for <u>n</u>-propylamine is shown in Fig. 12. The values of K<sub>B</sub>

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Figure 12. Graph of  $[S]_0$  versus  $(1/\delta)$  for the interaction of <u>n</u>-propylamine, <u>12</u>, (0.23 to 0.04 M) with Eu(dpm)<sub>3</sub> (<u>ca.</u> 0.006 M) in deuterochloroform solution. Tetramethylsilane was used as the internal-reference signal for the field-frequency lock. The separate lines are for protons H<sub>1</sub>, H<sub>2</sub>, and H<sub>3</sub> of <u>n</u>-propylamine. The precision of the K<sub>B</sub> evaluation is indicated by the close convergence of the three lines to the same y-intercept.

and  $\Delta_{\rm B}$  were obtained from these plots following the relationship given in Eq. [12]; the numerical values for these parameters are shown in the first four columns of Table 7. It is expected that the same value should be obtained for K<sub>B</sub> regardless of which proton is used for its determination. This may be confirmed experimentally by noting that the plots for protons H-1, H-2, and H-3, in Fig. 12, all intercept the y-axis at the same point. It may also be noted that the  $\Delta_{\rm B}$ -values obtained by this method vary inversely with distance from the co-ordination site, as expected for a pseudocontact shift.<sup>\*</sup>

Similar results were obtained for <u>neo-pentanol</u>, <u>8</u>, and the values of  $\Delta_{\rm B}$  and  ${\rm K}_{\rm B}$  for that substrate are also summarized in Table 7. Again, the high internal consistency between the evaluations of  ${\rm K}_{\rm B}$  based on different proton resonances is evident.

The experimental data obtained for the interaction of <u>8</u> and <u>12</u> with  $Eu(dpm)_3$  were then analyzed by the computer-based method outlined in Section II of the Theory. The values of  $K_B$  and  $\Delta_B$  calculated in this way are compared in Table 7 with the values obtained by the more approximate graphical method. The excellent agreement between the two sets of values indicates that the conditions which are implicit in the graphical analysis are satisfied in these experiments.

It is now useful to consider the evaluation of  $\Delta_{\rm B}$  from plots of  $\delta$  versus [L]<sub>0</sub>/[S]<sub>0</sub> according to Method 1 of the Experimental Section to show why the slope of such a plot<sup>44</sup> should not be taken as  $\Delta_{\rm B}$ .

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It must be remembered that an angular dependence must also be included in the calculation of induced shift-changes. This dependence will be treated in greater detail in Chapter III.

<u>Table 7</u>. Calculated values of bound chemical shifts  $(\Delta_B)$ , binding constants  $(K_B)$ , and stoichiometry for complexes of organic substrates with either Eu(dpm)<sub>3</sub> or Eu(fod)<sub>3</sub>.

Substrate				Eu (	(dpm) <sub>3</sub>	Eu(fod) <sub>3</sub>				
		Graph <sup>a</sup>	∆ <sub>B</sub> Computer <sup>b</sup>	Graph <sup>a</sup>	K <sub>B</sub> Computer <sup>b</sup>	Stoichiometry	$\Delta_{\rm B}$ Graph <sup>a</sup>	Graph <sup>a</sup>	K <sub>B</sub> Computer <sup>b</sup>	Stoichiometry <sup>C</sup>
	H-1	12.8	11.0	32.1	40.2	1.00 <u>+</u> 0.06	19.0	≥100	≥100	0.7 <u>+</u> 0.1
<u>n</u> -propylamine	H-2	7.7	6.5	32.9	43.1	~	12.7	≥100	≥100	
	н-3	4.1	3.7	37.8	44.6		6.6	≥100	≥100	
<u>neo</u> -pentanol	H-1	19.7	18.7	9.7	10.1	0.94 <u>+</u> 0.06	20.8	≥100	≥100	0.9 <u>+</u> 0.1
	н-3	7.6	7.0	9.8	10.5		8.3	<u>&gt;</u> 100	<u>&gt;100</u>	

<sup>a</sup> Values of  $\Delta_{\rm B}$  (parts per million) and  $K_{\rm B}$  (liter mole<sup>-1</sup>) derived from a least-squares fit of a plot of [S] versus (1/ $\delta$ ); precision of either result is  $\pm 10\%$ .

<sup>b</sup> Values of  $\Delta_{B}$  and  $K_{B}$  derived (from the same raw data) by a more exact formula, based on an iterative computer program (see text); precision of either result is  $\pm 10\%$ .

<sup>c</sup> Thése values should be regarded with some skepticism (see text).

As shown in Fig. 13 the slope of such a plot can vary markedly with the <u>absolute</u> concentration of substrate in a set of experiments with different [S]<sub>o</sub>-values. Both Uebel<sup>67</sup> and Williams<sup>18</sup> have reported similar behaviour. This variation in slope with concentration is related to the strength of binding of substrate to lanthanide and is readily accounted for by reference to the two possible limiting cases of Eq. [8] of Section I of the Theory.

For interaction of  $Eu(dpm)_3$  with <u>8</u> and <u>12</u>, the limiting condition,  $K_B[S]_{0} \ll 1$  pertains up to an [S]\_ level of at least <u>ca</u>. 0.04 M, so that Eq. [8] reduces to Eq. [10] rather than to the anticipated Eq. [9]. Only for the highest neo-pentanol concentration of 0.6 M, for which  $K_{B}[S]_{O} = 5.8$ , is the desired limit of  $K_{B}[S]_{O} >> 1$  effectively reached, since at this concentration the  $\Delta_{p}$ -value of 20.5 p.p.m. is within experimental error of the true value of 19.7 p.p.m. (derived from the H-1 proton resonance by the method of Section II of the Theory). It is thus neither correct, nor does it suffice to report values of  $\boldsymbol{\Delta}_{_{\mathbf{R}}}$  for different substrates - even if the molarity of a given substrate is kept constant - unless experimental evidence shows that the molarity of the substrate involved is large enough to satisfy the limit,  $K_{B}[S]_{O} >>$ 1, so that Eq. [8] reduces to Eq. [9]. However, Eq. [9] is no longer a function of  $K_{\rm R}$  and thus even under these optimum conditions,  $K_{\rm R}$ cannot be determined. Furthermore, at high concentrations of lanthanide which would be necessitated at high substrate concentrations, bulk susceptibility changes become substantial, and it is not clear that even an internal standard will properly compensate for them.

One issue of continuing concern was the need in Chapter I, to apply

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Figure 13. Plot of induced chemical shift  $(\delta)$  versus ratio of the initial concentrations of Eu(dpm)<sub>3</sub>, <u>5</u>, [L]<sub>0</sub>, to <u>neo-pentanol</u>, <u>8</u>, [S]<sub>0</sub>, in deuterochloroform solution. Tetramethylsilane was used for the internal field-frequency lock. Points on a given line represent experiments in which the concentration of Eu(dpm)<sub>3</sub> was varied, keeping the <u>neo-pentanol</u> concentration fixed at the value listed for that line.

a small correction factor in order to obtain the correct normal chemical shift for protons on a given substrate. The magnitude of the required correction factor varied with respect to the precautions taken to exclude moisture in the initial preparations. Thus it would seem that in part, the magnitude of the required correction factor was an indication of the purity of the lanthanide reagent used. However, even when the most rigorously anhydrous conditions were employed, discrepancies, though minimal, persisted as will be shown.

It follows from the Theory section that a plot of  $\delta$  versus  $[L]_{0}$  for any particular fixed concentration of  $[S]_{0}$ , Eq. [8], should intercept the x-axis at the origin if the lanthanide reagent is "pure". The results for just such experiments performed according to Method 1 of the Experimental are shown in Fig. 14. However, this figure reveals a finite x-intercept, which is unaccounted for by Eq. [8]. This behaviour is now known to be indicative of the change in <u>absolute</u> concentration of lanthanide as a result of solvent binding to lanthanide. Solvent used for the present experiments was deuterochloroform which as will be shown in Section E of this discussion, can participate in binding to the lanthanide. This result is consistent with the preceding discussion regarding the importance of the absolute concentration of the substrate and for that matter for any experiments which contain other suitable donors in addition to the substrate of interest.

#### A. Stoichiometry

Establishing the stoichiometry for the combination of a substrate with a lanthanide shift reagent is a prerequisite before any attempt

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Figure 14. Plot of  $\delta$  versus  $[L]_0$  for the interaction of <u>neo-pentanol</u>, <u>8</u>, (whose concentration was fixed at the value stated for each line) with Eu(dpm)<sub>3</sub> (<u>ca</u>. 0.02 to 0.005 M) in deuterochloroform solution. Tetramethylsilane was used for the internal fieldfrequency lock. All shifts are for the H-1 proton of <u>neo-</u> pentanol. The finite x-intercept of the lines is a result of a change in the <u>absolute</u> concentration of Eu(dpm)<sub>3</sub>.

can be made to fit calculated to observed  $\Delta_{\rm B}$ -values, to obtain molecular geometry. The reason for this will become clear in the following chapter; for now it is sufficient to point out that the angular dependence of the pseudocontact equation is dependent on the orientation of the principal magnetic axis relative to the bound organic substrate.

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Prior to this study, the stoichiometry was unknown, although Rondeau and Sievers' <sup>17</sup> experiments with Eu(fod)<sub>3</sub>,<sup>13</sup> left the impression that the leveling-off of a graph of  $\delta$  versus [L]\_/[S]\_ at a mole ratio of approximately 1:1 might be taken to indicate a 1:1 stoichiometry. In the Theory section, it was shown that such a conclusion is warranted only for cases where  $K_{\rm B}$  and [S] are large; Fig. 15 illustrates several such plots determined at different [S] levels, for the interaction of neo-pentanol with Eu(fod)3. In this case, the limiting line (the left most points in Fig. 15) extrapolated to the known  $\Delta_{\rm B}{\rm -value}$  gives a corresponding L/S ratio of 0.9:1, or about 1:1. However, the data points correspond to different [L] concentrations, and when  $[L]_0$  is changed there will be large changes in the bulk magnetic susceptibility of the solution, and these changes may not be compensated correctly even by an internal standard. Indeed, the poor internal consistency of the results is clearly evident in the dotted line of Fig. 15. This line was obtained by using the middle data point in the [S] = 0.1 M data set to compute  $K_{B}$ ; this value of  $K_{B}$ was then used to obtain the dotted line by using Eq. [5] and the full quadratic form of Eq. [6]. It is evident that the dotted line gives a poor fit to the remaining data points in the  $[S]_0 = 0.1$  M set. Since

 $22 \leq 1 \leq m_{\rm e} \leq 1_{\rm e}$ 



Figure 15. Plot of  $\delta$  (induced chemical shift for the H-1 proton) versus ratio of the initial concentration of Eu(fod)3, [L]<sub>0</sub>, to <u>neo-</u> pentanol, [S]<sub>0</sub>, in CDCl<sub>3</sub> solution with tetramethylsilane as the internal reference. The solid lines represent experiments in which [L]<sub>0</sub> was varied while keeping [S]<sub>0</sub> constant at the value listed for that curve. The dotted line (see text) is a theoretical fit to the [S]<sub>0</sub> = 0.1 M curve, based on a known value for  $\Delta_{\rm B}$  and with K<sub>B</sub> magnitude chosen to fit the middle data point of that curve exactly. it is now obvious that experiments in which  $[L]_0$  is varied can give inconsistent results, it is not surprising that for the interaction of <u>n</u>-propylamine with Eu(fod)<sub>3</sub>, the stoichiometry deduced from similar experiments is not even integral. In conclusion, when the binding is strong (large  $K_B$ ), these experiments do not reliably predict stoichiometry.

For the weaker binding of  $\underline{8}$  or  $\underline{12}$  to Eu(dpm)<sub>3</sub>, the outlook is much improved. As argued in Section III of the Theory, the linearity of a plot of [S]<sub>o</sub> versus (1/ $\delta$ ) is direct proof of 1:1 binding (compare Figs. 11 and 12). Since the range of choices of K<sub>B</sub> illustrated in Fig. 11 brackets the observed K<sub>B</sub>-values (see Table 7) for binding of  $\underline{8}$  or  $\underline{12}$ to Eu(dpm)<sub>3</sub>, there can be no doubt that the binding is 1:1 in each of these two cases.

For the interaction of norcamphor, <u>14</u>, with Eu(fod)<sub>3</sub> in carbon tetrachloride, the binding is sufficiently weak to allow for an accurate determination of K<sub>B</sub> (<u>ca</u>. 22.5 liter mole<sup>-1</sup>) from a plot of [S]<sub>o</sub> versus (1/ $\delta$ ). The linearity of this plot is direct proof of 1:1 binding. However, a similar plot for the above interaction in deuterochloroform produces a curve resembling that for 2:1 in Fig. <sup>11</sup> and when these same data were plotted in terms of the variables [S]<sub>o</sub><sup>2</sup> versus [S]<sub>o</sub>(1/ $\delta$ ), a linear plot was obtained. This is proof that 2:1 binding is occurring in deuterochloroform and that the limiting conditions, 4[L]<sub>o</sub> << [S]<sub>o</sub> applies.<sup>68</sup> For all other studies reported here where K<sub>B</sub> could be accurately determined, 1:1 binding was observed.

Practically speaking, then, when the binding is weak ( $K_B < 100$  liter mole<sup>-1</sup>), it is possible to obtain reliable, consistent values for

 $\Delta_{\rm B}$ ,  ${\rm K}_{\rm B}$ , and solution stoichiometry; when the binding is strong  $({\rm K}_{\rm B} \ge 100 \ {\rm liter mole}^{-1})$ ,  $\Delta_{\rm B}$  may still be determined <u>accurately</u>, a lower bound for  ${\rm K}_{\rm B}$  can be proposed, but the stoichiometry may be indicated only approximately.

## B. <u>Basicity of the Donor Group and the Importance of Steric Effects</u> on K<sub>B</sub>

From Table 7, it will be noted that the binding constant for <u>n</u>-propylamine is significantly larger (stronger binding) than that for <u>neo</u>-pentanol - for association with either  $Eu(dpm)_3$  or  $Eu(fod)_3$ . For  $Eu(dpm)_3$  where accurate determination of  $K_B$  is possible, the amine binds 3.5 times as strongly as the alcohol. This suggests that for a given shift reagent, the characteristic induced shift magnitudes, in the order  $-NH_2 > -OH > C= 0 > -O- > -CO_2R > -CN$  discussed by Williams,<sup>21</sup> may be correlated primarily with variations in the binding constants for substrates with different donor functionalities.

In Table 8 are listed the values for  $K_B^{}$  and  $\Delta_B^{}$  as determined by Method 2 of the Experimental, for a series of amines and alcohols. The values for  $K_B^{}$  clearly indicate a dependence on the basicity of the donor group as well as a steric dependence (see below).

An indication of the steric effect on  $K_B$ 's is shown in the values for this parameter for <u>n</u>-propanol <u>15</u>, and <u>neo-pentanol 8</u>, (Table 8). The greater steric hinderance in <u>neo-pentanol</u> is reflected in a  $K_B$ value which is <u>ca</u>. 0.5 that for <u>n</u>-propanol. The more basic character of amines is reflected in the overall larger  $K_B$ -values for these substrates as compared with the alcohols. Again even within a series

<u>Table 8</u>. Calculated values of bound chemical shifts  $(\Delta_B)$ , and binding constants  $(K_B)$  for complexes of organic substrates with  $Eu(dpm)_3$  in deuterochloroform solution.

Substrate		∆ <sub>B</sub> /p.p.m.ª	$K_{B}^{/1 \text{ mol}}$ -1 a
	H-1	12.8	32.1
<u>n</u> -propylamine	H-2	7.7	32.9
	H-3	4.1	37.8
	0	14.9	19.0
aniline	m	3.1	22.0
	р	3.7	20.0
	o	23.8	74.0
pyridine	m	7.8	80.0
	p	7.4	74.0
	H-1	13.9	19.0
<u>n</u> -propanol	H-2	8.1	19.5
	Н-3	5.0	17.9
	H-1	19.7	9.7
neo-pentanol	н-3	7.6	9.8

<sup>a</sup> Values of  $\Delta_{B}$  and  $K_{B}$  from least-squares fit of a plot of [S]<sub>o</sub> versus (1/ $\delta$ ); precision of values <u>+</u> 10%. The linearity of the [S]<sub>o</sub> versus (1/ $\delta$ ) plot for each of the above substrates implies 1:1 binding.

of amines,  $K_B^{-}$ -values determined in this manner indicate the change in basicity as displayed in the four-fold increase in  $K_B^{-}$  between aniline, <u>16</u>, and pyridine, <u>17</u>. From these results, it would appear that this parameter,  $K_B^{-}$ , is sufficiently sensitive to chemical and stereochemical environment and thus may be useful as a means of determining the potential reactivity at various donor sites. A more detailed evaluation of  $K_B^{-}$  dependencies can be found in Section F.

# C. <u>Explanation for the Greater Effectiveness of Eu(fod</u>)<sub>3</sub> <u>as Opposed</u> <u>to Eu(dpm</u>)<sub>3</sub>

Attention was next directed to the interaction of <u>8</u> and <u>12</u> with Eu(fod)<sub>3</sub>. Again using the form of data reduction as outlined in Section II of the Theory, attempts were made to process the experimental data by both the graphical and computer-based methods. With either treatment, it was possible to obtain  $\Delta_{\rm B}$  accurately, but K<sub>B</sub> was too large to be measured. Fig. 16 shows why.  $\Delta_{\rm B}$  is taken from the slopes of the lines in Fig. 16 and is readily determined. However, the y-intercept depends on (1/K<sub>B</sub>), and when K<sub>B</sub> is large, the y-intercept is so close to zero that K<sub>B</sub> cannot be determined with any confidence; in this case only a lower limit for K<sub>B</sub> may be deduced.<sup>\*</sup>

It should be appreciated that the graphical method is an approximation which is not expected to be valid when  $K_B$  is large. The computer-based method involves no approximations, but simply becomes numerically insensitive when the limit,  $(1/K_B) \ge [S]_o$ , is not satisfied. For the

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This limitation, intrinsic in our form of data reduction has been criticized and forms the basis for the discussion presented in Section G. As will be shown, Fourier Transform spectroscopy may perhaps offer the only possible solution to this problem.



Figure 16. Plot of [S] versus  $(1/\delta)$  for the interaction of <u>neo-pentanol</u>, <u>8</u>, (0.4 to 0.08 M) with Eu(fod)<sub>3</sub> (<u>ca</u>. 0.006 M) in deuterochloroform solution. Tetramethylsilane was used for the internal fieldfrequency lock. The separate lines are for protons H<sub>1</sub> and H<sub>3</sub> of <u>neo-pentanol</u>; the different slopes of the two lines are due to the different values of  $\Delta_{\rm B}$  for the two respective protons. Eu(fod)<sub>3</sub> experiments just mentioned,  $(1/K_B) \le 10^{-2}$  mole liter<sup>-1</sup>, while [S]<sub>0</sub> = 0.1 mole liter<sup>-1</sup>, so that even the computer method will yield only a lower limit for K<sub>p</sub>.

Similar experiments with <u>n</u>-propylamine and Eu(fod)<sub>3</sub> also gave precise linear plots. Again it was possible to obtain the  $\Delta_{\rm B}$ -values graphically to yield the data listed in Table 7, but again K<sub>B</sub> was too large to be measured; all that can be stated with certainty is that K<sub>B</sub> is at least 100 liter mole<sup>-1</sup>.

When this study was initiated, it was already known that for any particular substrate,  $Eu(fod)_3$  produced larger induced shifts than did  $Eu(dpm)_3$  on a weight-weight basis. From the data listed in Table 7, it is clear that the principal source of this enhanced effectiveness is the roughly ten-fold increase in binding constant,  $K_B$ , since the bound chemical shifts are nearly the same for a given substrate.

# D. Explanation for the Differing Magnitude of Induced Shifts for Different Ln(dpm)<sub>3</sub> Complexes

In contrast to the above, the differing effectiveness of various  $Ln(dpm)_3$  complexes can be accounted for by the differences in  $\Delta_B^-$  values rather than  $K_B^-$ -values. This may be confirmed experimentally by noting that the plots for <u>neo-pentanol</u> interacting with  $Eu(dpm)_3$ ,  $Pr(dpm)_3$  and  $Tm(dpm)_3$  in deuterochloroform solution, Fig. 17, all intersect the y-axis at the same point and thus have a common value of  $K_B$  whereas the slopes, therefore  $\Delta_B^-$ , vary markedly. The numerical



Figure 17. Plot of  $[S]_0$  versus  $(1/\delta)$  for the interaction of <u>neo-pentanol</u>, 8, with three different lanthanide shift reagents (<u>ca</u>. 0.006 M). For Eu(dpm)<sub>3</sub>, <u>5</u>, and Tm(dpm)<sub>3</sub>, <u>6</u>, CDCl<sub>3</sub> was used as solvent with tetramethylsilane for the internal field-frequency lock. For Pr(dpm)<sub>3</sub>, <u>7</u>, CHCl<sub>3</sub> was used as solvent and for the internal fieldfrequency lock. All shifts are for the H-1 proton of <u>neo-pentanol</u>. The precision of the K<sub>B</sub> evaluation is indicated by the close convergence of all lines to the same y-intercept.

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values for these parameters are shown in Table 9 along with the values of  $K_B$  and  $\Delta_B$  determined from a similar study with <u>n</u>-propylamine. For both substrates,  $K_B$ -values are found to remain constant while  $\Delta_B$ -values vary noticeably within a series of  $\text{Ln}(\text{dpm})_3$  complexes. Similar, though not as distinct behaviour has also been observed for the interaction of <u>8</u> with different  $\text{Ln}(\text{dpm})_3$  complexes in solvents other than deuterochloroform, (e.g. carbon tetrachloride and deuterobenzene, <u>vide infra</u>).

### E. Solvent Effects on $K_B$ and $\Delta_B$ -Values

For completeness in the investigation of the binding of substrates to lanthanide shift reagents in solution, the effects of typical solvents on the values determined for  $K_B$  and  $\Delta_B$  were examined. Quantitative investigations into this aspect of the interaction are not without complications, as is customary in any study of weak complexes, for not only is there the possibility of solvent binding to the shift reagent<sup>63a,b</sup> (binding in this context has the sense of solvent existing in the solvation sphere of the metal), but also solvent binding to substrate. In addition, there is the possibility of dimerization of shift reagents in different solvents.<sup>63a</sup> Solvent shifts in n.m.r. have long been the subject of lengthy investigations with perhaps one of the more common uses being to induce differential shifts which may often allow hidden resonances to become observable. Benzene-ketone: interactions are typical of this "solvent-induced shift" effect.<sup>4b</sup>

In the following discussion, all solvent effects will be analyzed with regard only to solvent competing with substrate for the shift

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Substrate		Eu	(dpm) 3	Pr(	(dpm) <sub>3</sub> <sup>b</sup>	Tm(dpm) <sub>3</sub>		
		∆ <sub>B</sub> /p.p.m.	$K_{\rm B}^{-1}$ mol $^{-1}$	∆ <sub>B</sub> /p.p.m.	K <sub>B</sub> /1 mo1 <sup>-1</sup>	∆ <sub>B</sub> /p.p.m.	K <sub>B</sub> /1 mol -1	
	H-1	12.8	32.1	46.8	∿32.3	71.7	25.4	
<u>n</u> -propylamine	H-2	7.7	32.9	30.8	22.0	39.5	26.6	
	H-3	4.1	37.8	15.6	25.0	21.6	27.3	- 86
	H-1	19.7	9.7	25.3	10.6	150.1	10.0	1
<u>neo</u> -pentanol	H-3	7.6	9.8	9.7	11.2	59.5	9.4	

<u>Table 9</u>. Calculated values of bound chemical shifts  $(\Delta_B)$ , and binding constants  $(K_B)^a$  for complexes of organic substrates with different  $Ln(dpm)_3$  in deuterochloroform solution.

<sup>a</sup> Values of  $\Delta_{B}$  and  $K_{B}$  from least-squares fit of a plot of [S] versus (1/ $\delta$ ); precision of values  $\pm$  10%.

<sup>b</sup> CHCl<sub>3</sub> was used as solvent and to provide a reference signal for the field-frequency lock; other metals, solvent was CDCl<sub>3</sub> with tetramethylsilane as the internal reference.

reagent. The deficiencies and discrepancies which result are then discussed with respect to competing solvent-substrate interactions<sup>\*</sup> which have not been allowed for in Section IV of the Theory.

In Section IV of the Theory, it was shown that if solvent binds to the shift reagent, the apparent  $K_B$  computed by our method would be smaller than the  $K_B$  which would be observed in a totally inert solvent but no change would be expected in  $\Delta_B$ -values. It should be pointed out that this in no way invalidates the fact that our reported  $K_B$ -values correctly measure the binding constant for the stated substrates to the stated shift reagent in the stated solvent.

In Table 10 are listed values for  $K_B$ ,  $\Delta_B$  and the ratios of  $\Delta_B$ 's for <u>neo</u>-pentanol interacting with Eu(dpm)<sub>3</sub>, Eu(fod)<sub>3</sub>, Pr(dpm)<sub>3</sub> and Tm(dpm)<sub>3</sub> in three different solvents. For Eu(dpm)<sub>3</sub> the K<sub>B</sub>-values are found to decrease in the order CCl<sub>4</sub> > C<sub>6</sub>D<sub>6</sub> > CDCl<sub>3</sub>, exactly the order one might expect from a chemical point of view with regards to either solvent-substrate interaction or solvent-lanthanide interaction or both. The fact that the  $\Delta_B$ -values for H-1 and H-3 are not identical within experimental error in all three solvents as theory predicts is not as clear but may be due to solvent-substrate interactions since binding of solvents CDCl<sub>3</sub> and C<sub>6</sub>D<sub>6</sub> to substrate may be of the same order of magnitude as the interaction of these solvents with Eu(dpm)<sub>3</sub>. On the other hand, this difference in  $\Delta_B$ -values may reflect the tendency of Eu(dpm)<sub>3</sub> to dimerize (<u>vide infra</u>) to differing extents in solvents <u>of varying polarity</u>. In this connection, dimerization would be expected

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Different substrates will be solvated to various degrees in different solvents and the extent to which a substrate is solvated should undoubtedly affect its ability to interact with the lanthanide shift reagent.

<u>Table 10.</u> Calculated values of bound chemical shifts  $(\Delta_B)$ , ratios of  $\Delta_B$  and binding constants  $(K_B)$  for complexes of <u>8</u> with Eu(dpm)<sub>3</sub>, Eu(fod)<sub>3</sub>, Pr(dpm)<sub>3</sub>, and Tm(dpm)<sub>3</sub> in three different solvents.

Substrate		Eu(dpm) <sub>3</sub>			Eu(fod) <sub>3</sub>		Pr(dpm) <sub>3</sub>			Tm(dpm) <sub>3</sub>			Solvent	
		$\Delta_{\rm B}^{*}$	к_в	Ratio	∆ <sub>B</sub> *	К_В	Ratio	$\Delta_{\rm B}^{*}$	к_в*	Ratio	$\Delta_{\mathbf{B}}^{*}$	к_*	Ratio	
8	H-1	19.7	9.7	2.59	20.8	<u>&gt;</u> 100	2.51	25.3	10.6	2.61	150.1	10.0	2.53	CDC13
	́H−3	7.6	9.8		8.3	tt		9.7	11.2		59.5	9.4	-	
	H-1	25.3	36.9	2.46	21.8	<u>≥</u> 200	2.43	43.4	37.0	2.47	115.9	<u>≥</u> 200	2.66	CC14
	H-3	10.3	34.0	•	9.0	11		17.6	35.0		43.6	**		
	H-1	22.5	31.7	2.53	20.7	≥100	2.52	40.3	10.7	2.52	172.6	22.4	2.68	C <sub>6</sub> D <sub>6</sub>
	H-3	8.9	30.0		8.2	11		16.0	10.5		64.5	22.9		00

\* Values of  $\Delta_{B}(p.p.m.)$  and  $K_{B}(1 \mod ^{-1})$  derived from a least-squares fit of a plot of [S] vs. (1/ $\delta$ ) precision of either result is + 10%.

\*\* CHCl<sub>3</sub> was used as solvent and to provide a lock signal; some TMS was added to provide a chemical shift reference. For all the other cases, TMS was used to provide a lock signal.

1 88 1 to be least probable in a donor solvent such as CDC1<sub>3</sub>.<sup>63a</sup> Even without shift reagent, the chemical shifts of H-1 and H-3 are not identical in the different solvents, indicating the effect of polarity or solvation of substrate on the measured chemical shift. It is not unreasonable then to expect that the complex LS would also show a notable variation in chemical shift with solvent.

Analogous ordering of  $K_B^{-}$ -values has been observed for <u>neo-pentanol</u> interacting with  $\text{Tm}(\text{dpm})_3$  and  $\text{Pr}(\text{dpm})_3$  (with the exception of the value of  $K_B^{-}$  determined for the latter in benzene) in these three solvents. However, the  $\Delta_B^{-}$ -values determined for these particular rare earth complexes in the three solvents are found to differ even more significantly than for Eu(dpm)<sub>3</sub>. This result, as previously stated, was not predicted from theoretical consideration and can only be rationalized as above.

Noteworthy are the ratios of bound chemical shifts shown in Table 10 which are constant to within experimental error for each metal in all three solvents.<sup>\*</sup> This must imply that the associated adducts have essentially the same shape and stoichiometry throughout, which thus favours the explanation of differing degrees of solvation in the three solvents and not that of dimerization or contact shifts.

The extent of solvation would be expected to be most important in

The value of these ratios for the Ln(dpm)<sub>3</sub> complexes in a particular solvent (across the table) allows one to speculate as to the possible contribution of a contact shift and/or the shape of the complex. From such a comparison it would seem that Tm(dpm)<sub>3</sub> behaves perhaps somewhat differently in CCl<sub>4</sub> and C<sub>6</sub>D<sub>6</sub>, either as a result of a contact contribution or more likely from a change in the shape of the complex.

 ${\rm CDCl}_3$  as is indicated by the nearly constant  ${\rm K}_{\rm B}$ -values shown in Table 9 for this solvent system. This ordering of  ${\rm K}_{\rm B}$ -values, which appears to reflect the extent of solvation, occurs to a somewhat lesser degree in benzene and even less so in  ${\rm CCl}_4$  where the large value for  ${\rm K}_{\rm B}$  with  ${\rm Tm}({\rm dpm})_3$  (Table 10) would seem to indicate a dependence on the ionic radius of the lanthanide which decreases across the row, in spite of the very bulky  $\beta$ -diketonate ligands attached. This finding is also in accord with the above ratios.

For a similar analysis, but this time using  $\operatorname{Eu}(\operatorname{fod})_3$ , a comparison of the K<sub>B</sub>-values in the three solvents is not possible because of the inaccuracies involved when K<sub>B</sub>  $\geq$  100. However, the values of  $\Delta_B$  determined from these experiments are identical within experimental error as are the ratios. In view of the range in  $\Delta_B$ -values observed for Eu(dpm)<sub>3</sub>, this result would seem to indicate the diminishing importance of solvent-substrate interaction (solvation), as a result of the much greater interaction of Eu(fod)<sub>3</sub> with both substrate and solvent.

In an attempt to better understand the influence of different solvents with  $\operatorname{Eu}(\operatorname{fod})_3$ , the interaction between the ketone, <u>18</u>, and  $\operatorname{Eu}(\operatorname{fod})_3$  was studied with the assumption that now the K<sub>B</sub>-values would be in a range (<100 liter mole<sup>-1</sup>), where accurate determination was possible. The result was not as anticipated, as shown for the values of K<sub>B</sub> ( $\geq 100$  liter mole<sup>-1</sup>), listed in Table 11.

Even though a comparison of  $K_B$ 's is not possible as was the original intent, this study did provide a bonus with regards to the stoichiometry and/or the shape of the complex in the three solvents.

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<u>Table 11</u>. Calculated values of bound chemical shifts  $(\Delta_B)$ , ratios of  $\Delta_B$  and binding constants  $(K_B)$  for complexes of 2,2-dimethyl-3-butanone, <u>18</u>, with Eu(fod)<sub>3</sub> in three different solvents.

Substrate			Eu(fod) <sub>3</sub>		Solvent
		∆ <sub>B</sub> *	к_*	Ratio	
	CH <sub>3</sub>	11.56	<u>≥</u> 100	1.74	CDC13
	(CH <sub>3</sub> )3 <sup>C</sup> 0	6.65	"		
<b>"</b> 0	сн <sub>з</sub>	16.12	≥100	1.96	cc1 <sub>4</sub>
(CH <sub>3</sub> ) <sub>3</sub> C <sup>+</sup> CH <sub>3</sub> <u>18</u>	(CH <sub>3</sub> ) <sub>3</sub> ∥ 0	8.21	11 '		
	сн <sub>з</sub>	14.90	<u>≥</u> 100	1.95	<sup>C</sup> 6 <sup>D</sup> 6
	(сн <sub>3</sub> ) <sub>3</sub> 0	7.64	11		

\* Values of  $\Delta_{B}(p.p.m.)$  and  $K_{B}$  (1 mol<sup>-1</sup>) derived from a least-squares fit of a plot of [S]<sub>0</sub> vs. (1/ $\delta$ ); precision of either result is  $\pm$  10%.

as depicted in the values for the ratio of the bound chemical shifts. This ratio is found to differ significantly in  $\text{CDCl}_3$  from that for  $\text{CCl}_4$  or benzene.<sup>\*</sup> If, of the above possibilities, one chooses to regard this as indicative of a change in stoichiometry, then this result is in accord with the change in stoichiometry observed for the ketone (norcamphor) with a similar change in solvent from  $\text{CCl}_4$  to  $\text{CDCl}_3$ .<sup>68</sup>

This rather unusual behaviour - possible change in stoichiometry which has only been observed for ketones in the polar solvent  $CDCl_3$ , may perhaps be related to the planar arrangement of the two lone pairs on the oxygen. Evans<sup>69</sup> has recently reported a situation where the stoichiometry for the interaction of dimethyl sulphoxide with Eu(fod)<sub>3</sub> in  $CD_2Cl_2$  can be directly determined as 2:1. Thus, in view of the similarity between all three systems - polar solvent, Eu(fod)<sub>3</sub>, and planar arrangement of the two lone pairs on the oxygen - it does not seem unreasonable to conclude that the change in observed shift ratios, Table 11, is in fact indicative of a change in stoichiometry of the lanthanide substrate complex.

In summary, it would appear that for quantitative investigation into the interaction of different shift reagents with suitable substrates, the solvent of choice would be CDCl<sub>3</sub>, at least with regards to alcohols and amines. This solvent would then allow the investigator to

As stated in Section III of the Theory, accurate determination of the stoichiometry is not possible when  $K_B \ge 100$  liter mole<sup>-1</sup> and thus from the present investigation, a plot of  $[S]_0$  versus  $(1/\delta)$  for CDCl<sub>3</sub> would yield a straight line. Analysis of the data on the basis of 2:1 binding, which also yields a staight line, resulted in different values for  $\Delta_B$  but as before the ratio for CDCl<sub>3</sub> (1.70) differed significantly from that for CCl<sub>4</sub> and C<sub>6</sub>D<sub>6</sub> (1.89).

quantitatively compare values of  $K_B$  and  $\Delta_B$  for different lanthanide shift reagents. However, for the eventual determination of substrate geometry utilizing ratios of  $\Delta_B$ 's, the solvent of choice for ketones would appear to be CCl<sub>4</sub>.<sup>\*</sup> On the more practical side, those investigators concerned solely with the magnitude of the induced shift for spectral simplification, CCl<sub>4</sub> would be the solvent of choice.

### F. General Applications

In Sections A to E of this discussion, we have described in detail the nature of lanthanide-substrate interactions. We shall now attempt to demonstrate the relevance of these detailed investigations to other areas of chemistry. In Chapter I, we described the usefulness of these reagents for obtaining optimally dispersed  ${}^{1}$ H and  ${}^{13}$ C spectra and in Chapter III we shall present what is perhaps the most important aspect of this area - the potential of lanthanide shift-reagents to the determination of substrate geometry. However, in addition to the above, there is a great deal more fundamental chemical insight to be gained from a quantitative understanding of the lanthanide-substrate equilibrium. The following discussion describes some of these more general aspects; it will be noted that many of the sections contain a discussion of experiments still in progress.

(i) An organic problem

The following Table 12, an extension of Table 8, lists the values of

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<sup>\*</sup> 

The significance of this statement will be appreciated in Chapter III. For now, it suffices to mention the importance of the symmetry of the complex for geometry determination.

<u>Table 12</u>. Calculated values of bound chemical shifts  $(\Delta_B)$ , and binding constants  $(K_B)$  for complexes of organic substrates with either Eu(dpm)<sub>3</sub> or Eu(fod)<sub>3</sub>.

	Substrate		∆ <sub>B</sub> /p.p.m.	K <sub>B</sub> /1 mo1 -	<sup>1</sup> Shift reagent
	Me O-CH <sub>2</sub>	H-1	4.46	32.7	Eu(dpm) <sub>3</sub>
·	Me 0-5	H-2	6.06	31.0	5
1 <sup>†</sup>	OR 2	H-3	15.70	29.0	
—	3 OL	le H-4	8.61	§	
	М́е R — Н	H-5	22.14	30.0	
	Me O-CH <sub>2</sub>	11 _ 1	2 07	60.9	Fulfed
	Me 0-5	H-1	2.9/	09.0	Eu(10a)3
_*	OR 2	H-2	7.41	65.2	
<u>3</u>	3 0/N	H-3	13.10	/9.0 §	
	Me	Н-4	4.91	<sup>5</sup> 6	
	R = CCH ∥	H-5 3	6.34		
	0	H-1	§	<u>≥</u> 100	Eu(fod) <sub>3</sub>
		H-2	4.62	·	
<u>4</u> *	Mer 0-5	H-3	12.80	11	
		H-4	8.57	11	
	RÒ Ò	Me H-5	14.37	· 11	
	ме				
	R = CCH	H-1	9.64	≥100	Eu(fod) <sub>3</sub>
<u>19</u> *	Ö	H-2	9.41	<b>11</b>	J
		H-2	15.95	. 11	
	6 <sub>0</sub>	H-3	6.67	11	
Ph	$6_{e}$	H <b>-</b> 4	2.33	11	
	0-15 kg	_1 H−5	§	§	
	3 2 <sub>e</sub>	Т н-6	3.39	>100	
	óн	OMe a H-6	6.61		
		e PhC-H	2.47	TT	
		= OMe	5.59	tt	

Table 12. (continued)

Substrate		∆ <sub>B</sub> /p.p.m.	$K_{\rm B}^{\prime/1}$ mol $^{-1}$	Shift reagent
· · ·	H-1	2.29	≥75	Eu(fod)
<u>20</u> *	H-2	9.93		
	н-2	8.17	11	
46 0	H-3	13.66		
	-1 H-4	<u>ca</u> . 6.3		
	н <del>–</del> 5	2.58	n	
3 ÓN	Ле н−6	<u>ca</u> . 9.4		
	H-6	5.41	**	
	PhC-H	3,98	**	
	OMe	1.33	11	
	H-1	3.00	<u>≥</u> 100	Eu(fod) <sub>a</sub>
21 <sup>*</sup>	Н-2	2.60	· 11	, ,
	Н-З	3.67	11	
0-50 1	H-4	7.83	**	
7 6 2	H-5	14.21	TF	
8 4 0	H-7	6.84	11	
3 Ó	ю H-8	5.84	11	
9	H-9	1.32	11	
	H-10	1.60		
18* 0	CH	11.56	≥100	Eu(fod)
(CH <sub>3</sub> ) <sub>3</sub> C-CH <sub>3</sub>	(C <u>H</u> 3)3C	6.65		S
	u_1	10 14	> 100	Fu (fad)
22 <sup>††</sup>	n-1 11 0	7 0/ 12•10	<u>~100</u>	Eu(roa)3
<u>~</u> 1){	п 112	2.04		
2	,7 ,7 ,7	1 /0		
	n=4 u≟5	1 55	11	
3	-6 п-ј и с	1 00	<b>†</b> ¥	
4 5	по 117	T*00		
	H-7	8.21		

Substrate		∆ <sub>B</sub> /p.p.m.	K <sub>B</sub> /1 mol <sup>-1</sup>	Shift reagent
<u>4</u> <sup>+</sup> 1 1	H-1	23.54	22.3	Eu(fod) <sub>3</sub>
$-\mathcal{A}^{*}$	H-2	24.09	22.7	5
	H-3	21.37	23.7	
3 1	H-4	7.79	22.3	

Table 12. (continued)

†

Solvent was carbon tetrachloride with tetramethylsilane for lock.

\* Solvent was deuterochloroform with tetramethylsilane for lock.

\*\* Solvent was deuterobenzene with tetramethylsilane for lock.

§ This value could not be determined with sufficient accuracy to justify its inclusion here.

 $\Delta_{\rm B}$ 's and  ${\rm K}_{\rm B}$ 's determined for a larger variety of organic substrates. Fig. 18 shows a plot of [S]<sub>0</sub> versus (1/ $\delta$ ) for <u>21</u> and is typical of the consistency observed in similar plots for the other compounds listed in Table 12. Several of the molecules listed are carbohydrates and most of these exist in a locked conformation, a necessary prerequisite to geometry investigations to be discussed in Chapter III. In the discussion which follows, the importance of being able to determine accurate values for K<sub>B</sub> and  $\Delta_{\rm B}$  will be analyzed with respect to the important chemical and configurational implications implicit in these parameters.

In many instances the values of  $\Delta_{\rm B}$  can be rationalized in terms of the distance dependence of the pseudocontact equation alone. However, the significance of the angular term in the pseudocontact equation, the importance of which is amplified for those protons closest to the donor site, is often unmistakable as is seen in the values of  $\Delta_{\rm B}$ determined for H-3 and H-5 of <u>1</u> and similarly for the values of  $\Delta_{\rm B}$ for H-3 and H-5 of <u>4</u>. In all other examples tabulated, distance alone is 'sufficient' for a configurational assignment to be made. The importance of this latter observation, which will be demonstrated for compounds <u>19</u> and <u>20</u>, is significant to the practising organic chemist.

Assignment of the configuration at C-3 for furanose and pyranose sugar rings is often possible only with great difficulty and even then a large amount of uncertainty remains. Methods currently used to make such assignments include n.m.r., o.r.d., c.d. and chemical derivatization. In many instances, even employing all the above methods does not

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Figure 18. Plot of  $[S]_0$  versus  $(1/\delta)$  for the interaction of 1,2:3,5-di-0methylene- $\alpha$ -D-glucofuranose (21, 0.02 to 0.102 M) with Eu(fod)<sub>3</sub> (0.0059 M) in deuterochloroform solution. Tetramethylsilane was used for the internal field-frequency lock. The precision of this plot is indicated by the close convergence of all lines to the same y-intercept.

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K,

unequivocally confirm the stereochemistry at C-3. We proposed to investigate the applicability of lanthanide shift reagents as a viable means for making such an assignment. Compounds chosen for this investigation were, methyl 4,6-<u>O</u>-benzylidene-2-deoxy- $\alpha$ -<u>D</u>-<u>ribo</u>hexopyranoside <u>19</u> and methyl 4,6-<u>O</u>-benzylidene-2-deoxy- $\alpha$ -<u>D</u>-<u>arabino</u>hexopyranoside <u>20</u>. These molecules were suitable as models for such an investigation because they possessed one group, a hydroxyl, likely to provide the major association site for the lanthanide reagent and configurational assignment could be confirmed in advance from the value of the H-3, H-4 splitting.

Comparison of the  $\Delta_{\rm B}$ -values for equivalent protons in <u>19</u> and <u>20</u>, Table 12, show substantial variations which, with the aid of a molecular model, appear to correlate well with the distance dependence of the pseudocontact equation.<sup>\*</sup> Most noticeable are the differences between  $\Delta_{\rm B}$ -values for H-2<sub>e</sub>, H-3 and OMe in compounds <u>19</u> and <u>20</u>. These values, significantly different as they are, agree on a first order basis considering distance alone, with the known stereochemistry at C-3. The magnitude of the  $\Delta_{\rm B}$ -values also reveal the steric effect on the position of co-ordination of the lanthanide shift reagent. This dependence has been demonstrated previously in Section B and will be discussed in a quantitative manner in Chapter III. It would appear, therefore, that the use of lanthanide shift reagents as a method for assigning configuration at C-3 for cyclic forms of sugars may prove to

As will be discussed in Chapter III, the angular dependence of the pseudocontact equation must never be neglected if one is seeking to calculate the absolute geometry; however, for many configurational assignments distance alone often suffices.

be a very attractive alternate technique.

The value of  $K_B = 31$  liter mole<sup>-1</sup> determined for the interaction of <u>1</u> with Eu(dpm)<sub>3</sub> in carbon tetrachloride compares favourably with that determined for the similarly sterically hindered <u>neo</u>-pentanol  $(K_B = 35.5 \text{ liter mole}^{-1})$  interacting with Eu(dpm)<sub>3</sub> in carbon tetrachloride. Such a comparison provides important evidence as to the reliability of the K<sub>B</sub>-values determined in this way. Quantitative comparison of K<sub>B</sub>-values determined for analogous interactions with Eu(fod)<sub>3</sub> is usually not possible for reasons which have been previously discussed. However, it is interesting to examine the K<sub>B</sub>-values determined for the interaction of compounds <u>18</u>, <u>22</u>, and <u>14</u> with Eu(fod)<sub>3</sub>.

The dependence of the  ${\rm K}_{\rm B}^{\phantom -} {\rm value}$  on the basicity of the donor group has previously been discussed (Section B). Thus, it was anticipated that for a ketone interacting with  $Eu(fod)_3$ , the  $K_B$ -value might be sufficiently less than that found for similar interactions with alcohols  $(K_{R} \ge 100 \text{ liter mole}^{-1})$ , thereby allowing for an accurate evaluation of  $K_{\rm p}$ . This was the case for compound <u>14</u> but not with <u>18</u> or <u>22</u>. The reason for the small value of  $K_{\rm B}$  = 22.5 liter mole<sup>-1</sup> with <u>14</u> is undoubtedly due to the steric hinderance at the point of co-ordination of the lanthanide for this substrate, an effect which would be much less significant for compounds <u>18</u> or <u>22</u> as reflected in a value of  $K_B \ge 100$ liter mole<sup>-1</sup> for these substrates. Also noteworthy was the observation of a single resonance for the H-1 protons of  $\underline{22}$  with and without shift reagent. This indicates that Eu(fod), binds to this ketone in such a way as not to alter the existing symmetry. This would seem to imply that the lanthanide must bind in such a manner as to bisect the angle

between these protons or alternatively, spends half of its time on each of the carbonyl lone pairs.

#### (ii) An inorganic problem

As part of another program, Paddock and Wingfield (Department of Chemistry, U.B.C) had prepared a series of dimethylaminocyclophosphonitriles  $[N_4P_4(NMe_2)_8 23, N_5P_5(NMe_2)_{10} 24, N_6P_6(NMe_2)_{12} 25, N_7P_7(NMe_2)_{14} 26, N_9P_9(NMe_2)_{18} 27]$  ranging in ring size from 4(P-N) to 9(P-N) units. <sup>1</sup>H n.m.r. proved unsuccessful as a means of characterizing these compounds for they all exhibited only a single resonance which was broadened (<u>ca</u>. 8.0 Hz) by the coupling to phosphorus. More recently, several complexes containing phosphonitrilic ring systems and transition metal ions have been prepared and detailed studies of the bonding and structure of such complexes have relied solely upon X-ray investigations which have been carried out on only a few of these molecules.<sup>70a,b</sup>

The present investigation of the interaction of  $Eu(fod)_3$  with the phosphonitrilic systems 23-27 (following Method 2 of the Experimental), was undertaken to measure the K<sub>B</sub> values for this series in anticipation that a systematic variation in K<sub>B</sub> would be observed corresponding perhaps to the differing basicities resulting from ring size. If successful, this study would then permit a better understanding of the differing abilities of these compounds to form complexes with transition metal ions.

The experiments which followed produced results which were totally unexpected although interesting in their own right. The following several points are noteworthy from this investigation: (i) in spite of the bulkiness of these substrates, <u>23-27</u>, and their polyfunctional donor qualities, all were observed to interact with  $Eu(fod)_3$ , (ii) for all except  $N_4P_4(NMe_2)_8$ , chemical exchange is slow - a separate peak was observed for both the free and complexed substrate, \* (iii) bonding with  $Eu(fod)_3$  occurs via the ring nitrogens - except perhaps for  $N_7P_7(NMe_2)_{14}$  - as is most always the case for transition metal complexes, (iv) for compounds 24, 25 and 26 a two-step binding process was observed, (v) for  $N_9P_9(NMe_2)_{18}$ , the stoichiometry can be trivally deduced as 1:1.

The implications of the above points with regards to the chemical properties of the phosphonitriles must await the final analysis of the result for the interaction of  $Eu(fod)_3$  with  $N_3P_3(NMe_2)_6$  and  $N_8P_8(NMe_2)_{16}$ , \*\* currently in progress. In the meantime, it is interesting to speculate into this aspect but more important are these results as they pertain to the chemical nature of the interaction with  $Eu(fod)_3$ .

For  $N_4P_4(NMe_2)_8$ , only one resonance is observed in the <sup>1</sup>H n.m.r. spectrum and for this compound ' $\delta$ ' is a function of the concentration of Eu(fod)<sub>3</sub>. Thus in contrast to the rest of the series, the fast exchange limit applies. This is in accord with previous findings for complexes with transition metal ions where the stability of the complex was found to increase with ring size. This result is likely a consequence

\*

\*\* Synthesis of this compound is currently in progress.

This implies that the induced shift is no longer a function of lanthanide concentration. This is the first reported case of slow exchange between lanthanide shift reagent and substrate at room temperature. Evans<sup>69</sup> has reported the only other similar occurrence for the interaction of Eu(fod)<sub>3</sub> with dimethyl sulphoxide where slow exchange was found to occur at  $-80^{\circ}$ C.

of the larger steric effect for the smaller ring systems. Performing the experiments as outlined in Method 2 of the Experimental allows one to calculate a bound chemical shift,  $\Delta_{\rm B} = 0.4$  p.p.m., and a  $K_{\rm B} \ge 100$  liter mole<sup>-1</sup>.

It is interesting to note that this calculated value of  $\Delta_B = 0.4$ p.p.m. is of the order of that observed directly for compounds <u>24-27</u>, where the slow exchange limit was found to apply;  $\Delta_B$  as measured from the spectra for compounds <u>24-27</u> ranges from <u>ca</u>. 1.0 p.p.m. to 1.5 p.p.m. This provides important proof as to the reliability of Method 2 of the Experimental for determining  $\Delta_B$  when the fast exchange limit applies.

Bonding of  $\text{Eu}(\text{fod})_3$  to the ring nitrogens can be confirmed in two ways. (i) For all those cases where the chemical exchange was slow with the exception of  $N_7 P_7 (\text{NMe}_2)_{14}$ , where more than one peak is observed for the complexed substrate - only one peak for the complexed substrate was observed. The equivalence of all the methyl groups could only result if the bonding occurred with the ring nitrogens. (ii) The magnitude of the bound chemical shift, <u>ca</u>. 0.5-1.5 p.p.m., which is a function of the angle and distance of Eu(III) from the protons, is small when compared with say the  $\alpha$  protons of n-propylamine, (Table 8).

For the concentration range of substrate employed, the shifted resonance for compounds  $N_5P_5(NMe_2)_{10}$ ,  $N_6P_6(NMe_2)_{12}$  and  $N_7P_7(NMe_2)_{14}$ appears to be somewhat dependent on lanthanide concentration even though a separate peak for free substrate exists - proof the slow exchange limit applies. This can only be explained in terms of a two-step binding process, with the first step being in the slow exchange limit

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and the second a fast exchange process. Thus, it is not possible to deduce a stoichiometry directly from the relative intensities of the resonances for these three substrates. For  $N_{9}P_{9}(NMe_{2})_{18}$  the situation is not as complexe, Fig. 19. Here only two resonances are observed, Fig. 19B, one for the free  $(7.42\tau)$  and the other for the bound substrate (6.52 $\tau$ ) (Resonance at 9.04 $\tau$  for the Eu(fod), protons is not shown). The resonance for the complexed substrate is not a function of the lanthanide concentration for this compound. Fig. 19C shows the observed spectrum for the compound obtained from reacting 0.255 grams of Eu(fod), with 0.292 grams of  $N_9P_9(NMe_2)_{18}$  (see Experimental for conditions used). The resonance at 6.52  $\tau$  is that of the Me's of 27 and that at 9.11  $\tau$ for the protons of Eu(fod)3. This is the first report of a stable complex of Eu(fod), with a substrate of this size and the resulting n.m.r. confirms the assignment of the n.m.r. spectrum shown in Fig. 19B. From the relative areas of the two peaks, Fig. 19C, it was found that each mole of shift reagent complexed  $1.0 \pm 0.1$  mole of 27, corresponding to a co-ordination number of 7 for the europium ion. \*\*

The above results are not only noteworthy from the point of view of providing important evidence as to the nature of lanthanide-substrate interactions as has been discussed, but have the potential of providing important information with regard to the chemical nature of these inorganic systems.

<sup>\*</sup> The chemical shift of the resonance for the free substrate in the presence of shift reagents is identical with the resonance observed in the absence of shift reagent. This result is proof that the first step is in the slow exchange limit.

<sup>\*\* 71</sup> Selbin<sup>71</sup> has reported the preparation and properties of other 7 co-ordinate Eu(III) complexes.



#### (iii) <u>A liquid crystal study</u>

As part of a preliminary investigation in conjunction with R.B. Malcolm of this laboratory, the suitability of paramagnetic lanthanide shift reagents to liquid crystal n.m.r. was investigated.

The theory required to understand and interpret the liquid crystalline n.m.r. spectra has been fully developed elsewhere and will not be discussed in this thesis.<sup>72,73</sup> For those who are unfamiliar with this form of n.m.r., it suffices to point out that in the liquid crystalline spectra, both the dipolar couplings and the normal J couplings from isotropic n.m.r. studies are observable. Analysis of the resulting liquid crystalline spectrum, which will therefore be many times more complex than the isotropic spectrum, has then been shown to provide a very sensitive means for determining the absolute geometry of the substrate in the liquid crystalline phase.

No previous reports existed on the applicability of lanthanide shift reagents to this area. It was our primary concern to determine whether these reagents would be effective in spreading out the complex liquid crystalline spectra.

Pyridine was chosen as the model substrate and its liquid crystal spectrum measured in the liquid crystalline solvent, N-(p-ethoxybenzylidene)- $p-\underline{n}$ -butylaniline (EBBA) in the presence of Eu(dpm)<sub>3</sub>.

For  $[L]_{o}/[S]_{o} = 0.1$ , the following shift was observed for the protons of pyridine: o = 260.0 Hzm = 82.5 Hz

$$p = 74.5 Hz$$

It is important to note that the magnitude of these shifts is <u>ca</u>. 1.5 times larger than for similar  $[L]_0/[S]_0$  ratio of pyridine and Eu(dpm)<sub>3</sub> in CDCl<sub>3</sub>. It is also noteworthy that the ratios of these induced shifts are identical to those found in the latter solution.<sup>\*</sup> No interpretation of the above results will be presented at this time but await the completion of a more detailed investigation which is currently in progress by R.B.M.

In addition, the generality of this method as a means of dispersing complex liquid crystal n.m.r. spectra cannot be commented on prior to a further more complete investigation of liquid crystalline solvents, temperature, and lanthanide.

From the point of view of furthering the understanding of the nature of substrate-shift reagent interactions, this area may have a great deal of potential. The following points indicate some of the more promising aspects further investigations may follow. (i) Studies of the mechanism of binding in the nematic phase - this would entail calculating values for  $K_B$  and  $\Delta_B$ . (ii) The possibility of using the magnitude of the induced shifts in this phase as an independent means of solving the controversy between the mechanism of the induced shift - contact versus pseudocontact. (iii) Geometry determinations based on liquid crystalline data determined in the presence of lanthanide shift reagent may provide important independent proof as to the accuracy of geometry determination resulting from lanthanide shift reagent studies in isotropic solutions.

· · · · *·* · · · · · · · · · ·

The implications of this statement are not yet fully understood.

In summary, the solid theoretical basis has allowed for a detailed and in most cases quantitative explanation of many of the characteristic behaviours exhibited by lanthanide-substrate interactions. In some areas, as that of solvent effects, more experiments are required before it will be possible to arrive at any firm conclusions and in this connection X-ray studies of 6, 7 and 8 co-ordinate lanthanide complexes may be useful.

## G. The Applicability of a Scatchard-type Plot to the Analysis of the Concentration Dependence of the Shifts

It will have been noticed throughout the preceding discussion that we have not discussed numerical values for  ${\rm K}_{\rm R}$  when this parameter is  $\geq$  100 liter mole<sup>-1</sup> (strong binding) as is most often the case when Eu(fod), is employed as the shift reagent. We have commented that both our graphical and computer methods were inadequate for  $K_{p}$  values in this region although values for  $\boldsymbol{\Delta}_{\operatorname{B}}$  could still be accurately evaluated (vide infra). In addition to the above recognized limitation of our method of analysis, some contention has originated regarding the use of Eq. [12] with its necessary approximations.<sup>74</sup> It has been suggested that the use of this equation may not always provide an accurate method for the evaluation of  ${\rm K}_{\rm B}$  and  ${\rm \Delta}_{\rm B}$  and that it is seldom a rigorous test for 1:1 complex formation. This objection is based on the assumption that in order to test for 1:1 complex formation, it is necessary to vary the concentration of all interacting reagents over as wide a range as possible and then to solve for the full quadratic form of Eq. [6].

The method proposed as a possible solution to the above points is that of a Scatchard plot. This plotting procedure has enjoyed considerable success in areas other than lanthanide-substrate interactions<sup>75</sup> and has sometime ago been the subject of a critical appraisal by Deranleau.<sup>76</sup> The following discussion is intended to provide an explanation as to why we chose not to use this method for our data representation.<sup>\*</sup> We shall show that although it is possible in principle, and perhaps experimentally to use the Scatchard plot to obtain a <u>numerical</u> evaluation of K<sub>B</sub> when  $\geq 100$  liter mole<sup>-1</sup> in practice any such evaluation is likely of little <u>chemical</u> significance. We will also show that a Benesi-Hildebrand plot is <u>always</u> the best source of  $\Delta_{\rm B}$ . It is for that reason that we have left this discussion to the end.

Let us start the discussion by reviewing the salient features of the Scatchard plotting method. Deranleau has concluded that, "obtention [sic] of roughly 75% of the data comprising the complete saturation curve seems necessary before the model can be considered proven by any single equilibrium technique". Representation of the resultant data by a Scatchard plot then provides for the most accurate evaluation of  $K_B$ and solution stoichiometry, n. In addition to the above requirement, it is important to note that Deranleau's treatment had been derived for the situation, (with  $[S]_0 >> [L]_0$ ), where [L] and [LS] are the measured quantities, (i.e. measurements are made on the dilute component). However, this is <u>not</u> the situation that would pertain to any lanthanide

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The following discussion is an evaluation of a Scatchard plot only as it pertains to the lanthanide-substrate interaction performed according to Method 2 of the Experimental.

experiments described thus far. In these investigations [S] and [LS] are the measured parameters. The importance of this difference between the two treatments is the basis on which rests the entire following discussion.

Representation of our data for the concentration dependence of the shifts (determined in the manner as outlined by Method 2 of the Experimental),<sup>\*</sup> in the form of a Scatchard plot corresponds to a plot of  $\delta/(\Delta_B-\delta)[L]_o$  versus  $\delta[S]_o/\Delta_B[L]_o$ . The slope of this plot is equal to  $-K_B$ , the y-intercept =  $K_B$ , and the x-intercept is 1.0.

Combining Eq. [5] and [6] and making no approximations, one can write the following expression,

$$[22] \qquad \frac{\delta}{(\Delta_{\rm B} - \delta)[{\rm L}]_{\rm o}} = {\rm K}_{\rm B} - \frac{{\rm K}_{\rm B} \delta[{\rm S}]_{\rm o}}{\Delta_{\rm B}[{\rm L}]_{\rm o}}$$

which is the form required for a Scatchard plot as discussed above, (i.e. when the measured quantities are [S] and [LS]). To the same level of approximation our own Eq. [12] can be expressed as follows;

[23] 
$$[S]_{o}(1 - \frac{\delta}{\Delta_{B}}) = [L]_{o}\Delta_{B}(\frac{1}{\delta}) - ((\frac{1}{K_{B}}) + [L]_{o})$$

It is obvious that either of these methods for data representation requires a knowledge, in advance, of the value for  $\Delta_{\rm B}$ . However, this value can seldom be measured experimentally (vide infra). Thus, for

This method imposes the restriction that  $[S]_0 >> [L]_0$ , thus forcing the systems to behave as a one step binding process. Also the concentration of lanthanide is kept low,  $\leq 0.006$  M, which significantly lowers the possibility of dimerization of lanthanide.<sup>63</sup>

either approach to yield itself to analysis, it is necessary to impose the restriction that  $\delta$  <<  $\Delta_{\rm B}$ . Eq. [22] now takes the form proposed by Deranleau,  $^{76}$ 

$$[24] \qquad \frac{\delta}{[L]_{o}} = \Delta_{B}K_{B} - \frac{K_{B}\delta[S]_{o}}{[L]_{o}}$$

and Eq. [23] becomes Eq. [12].

Interestingly, a Scatchard plot of our data in the form proposed by Deranleau,  $\delta/[L]_o$  versus  $\delta[S]_o/[L]_o$  (from Eq. [24]) produces a linear dependence only when  $\delta \ll \Delta_B$  and yields  $\Delta_B$  from the x-intercept and  $-K_B$  from the slope. However, because we impose the restriction that  $[S]_o \gg [L]_o$  and the fact that we are measuring [S] and [LS], the data points on such a plot will <u>always</u> fall in the region of the plot where the errors are a maximum.<sup>\*</sup> Thus,  $\Delta_B$ -values determined from these plots will be extremely imprecise. This is <u>not</u> the case if experiments are performed according to those discussed by Deranleau (i.e. [L] and [LS] are the measured quantities). For these experiments, the analogous limitation which is concomitant in Deranleau's treatment namely,  $[S]_o \gg [L]_o$ , now permits one to obtain data points throughout the entire saturation curve and thus  $\Delta_B$  can be accurately determined. This method, however, only applies when  $\delta \ll \Delta_B = 100$  liter mole<sup>-1</sup>).

On the other hand, to the same degree of approximation and for the same data as above, a plot of the form [S] versus (1/ $\delta$ ) (from Eq. [12]) will yield an accurate value for  $\Delta_{\rm R}$ . This result is in accord with the

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For a full error analysis of the plotting routines discussed here, the reader is referred to the paper by Deranleau.<sup>76</sup>

minimum errors for the region of this plot where these same data points fall.<sup>76</sup> Additional proof of the accuracy of the value of  $\Delta_{\rm B}$  determined from the slope of this [S]<sub>0</sub> versus (1/ $\delta$ ) was shown in the agreement between  $\Delta_{\rm B}$  and K<sub>B</sub> values determined in this way and those determined from a computer fit of the full quadratic function (Table 7).

From the preceding discussion, it seems reasonable to conclude that in view of the method in which present lanthanide experiments are performed, a plot of the form [S]<sub>o</sub> versus (1/ $\delta$ ) is most likely the best method for determining  $\Delta_B$ ,  $K_B$  and n, (at least for  $K_B < 100$ liter mole<sup>-1</sup>). It is also important to note that Scatchard plots, of the form proposed by Deranleau, will not be successful as a means for determining  $K_B$  when this parameter is  $\geq 100$  liter mole<sup>-1</sup>.

There remains only one possible significance to using the Scatchard plotting procedure - to obtain a numerical value for  $K_B$  when this parameter is  $\geq 100$  liter mole<sup>-1</sup> as is frequently the case only with Eu(fod)<sub>3</sub>. [When  $K_B \geq 100$  liter mole<sup>-1</sup>, the y-intercept from a plot of [S]<sub>0</sub> versus (1/ $\delta$ ) is obviously near zero, thus providing a very poor measure of  $K_B$ ; the  $\Delta_B$  value determined in this way is nevertheless correct as previously discussed.] In these situations, it is no longer possible to construct a Scatchard plot of the form proposed by Deranleau because the restriction  $\delta \ll \Delta_B$ , implicit in Deranleau's treatment, will no longer apply. One must therefore construct the <u>exact</u> Scatchard plot from Eq. [22]. To do so, it is necessary that  $\Delta_B$  be known in advance. For the interaction with Eu(fod)<sub>3</sub>, there are only two possible methods which may be employed to yield, in advance, a value for  $\Delta_B$ . They are as follows; (i) from a plot of [S]<sub>0</sub> versus (1/ $\delta$ )

where  $[S]_{o} >> [L]_{o}$  and (ii) from a plot of  $\delta$  versus  $[L]_{o}/[S]_{o}$  where high enough  $[L]_{o}/[S]_{o}$  ratios have been reached such that a constant value of  $\delta$  was obtained. Some practical limitations of this latter method will be discussed first, followed by an example of an <u>exact</u> Scatchard plot using the  $\Delta_{\rm R}$  values determined by both the above methods.

Using the  $\operatorname{Ln}(\operatorname{fod})_3$  complexes, a constant value of  $\delta$  can be obtained in plots of  $\delta$  versus  $[L]_0/[S]_0$ . However, the large molar ratio of  $\operatorname{Ln}(\operatorname{fod})_3$  needed to reach this saturation point, particularly for weak donors, may produce large changes in the bulk magnetic susceptibility of the solution, increasing the likelihood of the internal standard binding to  $[L]_0$  at large concentrations of  $[L]_0$ . In addition, when the concentrations of all interacting reagents are varied over the wide range required for Deranleau's treatment, the greater will be the importance of multi-step equilibria, (e.g. lanthanide dimerization), with the number of unknowns increasing by a factor of two for each additional equilibrium, while the number of observable parameters remains constant.

An evaluation of the <u>exact</u> Scatchard plot using  $\Delta_{\rm B}^{}$ -values determined by method (ii) will now be discussed. For the interaction of Eu(fod)<sub>3</sub> with 3,3-dimethyl-2-butanone in CCl<sub>4</sub>, the value of  $\Delta_{\rm B}^{}$  determined from the leveling off of a plot of  $\delta$  versus  $[L]_{\rm o}^{}/[S]_{\rm o}^{}$  was 11.0 p.p.m. for the C-4 protons. Using this value to construct the <u>exact</u> Scatchard plot produces the curve as indicated in Fig. 20. The K<sub>B</sub> value determined from the y-intercept of this plot would be unrealistic as this plot can not be made to intersect the x-axis at 1.0 as required by Eq. [22]. On



Figure 20. An exact Scatchard plot (Eq. [22]) for the interaction of <u>18</u>, (0.02 to 0.1 M) with Eu(fod)<sub>3</sub> (ca. 0.008 M) in CCl<sub>4</sub> solution. Dotted line represents the plot obtained using a value of  $\Delta_B = 11.0$  p.p.m. (see text). Solid line represents a similar plot but with  $\Delta_B = 16.12$  p.p.m. (see text). Error bars on this plot are approximately those shown in ref. 76.

the other hand, a similar plot was constructed using the same data as above, <sup>\*</sup> but this time using the value of  $\Delta_B = 16.12$  p.p.m. as determined from a plot of [S]<sub>o</sub> versus (1/ $\delta$ ). This plot is also indicated in Fig. 20. The straight line which can now be drawn through the data points, intersects the x-axis at 1.0 as required and yields a value for K<sub>B</sub> = 105 liter mole<sup>-1</sup>. It would appear therefore, that this second choice of  $\Delta_B$  is somewhat more precise, producing an x-intercept of 1.0 and a numerical value for K<sub>B</sub>.<sup>\*\*</sup> However, in view of the imprecision in this region of the saturation curve, little significance should be applied to this parameter.

In conclusion, for the method used to perform the present experiments, it does not appear advantageous to use even the <u>exact</u> Scatchardtype plots for the particular situations where  $K_B \ge 100$  liter mole<sup>-1</sup> and where some estimate of this parameter is desired. From the nature of the plot using  $\Delta_B = 11.0$  p.p.m., Fig. 20, the discrepancies (possibly of lanthanide dimerization or other multiple equilibria) inherent at high  $[L]_0/[S]_0$  ratios appear to be significant. Thus, it would seem that data reduction using Eq. [12] suffices both in ease and accuracy of parameters determined. If for any reason, one wishes to characterize the reactivity at a suitable donor site for a series of

\*\* In Fig. 20, an indication of the magnitude of the errors, in this region of the plot, has been shown for the data using  $\Delta_{\rm B}$  = 16.12 p.p.m. only. It is important to recall that the necessary restriction [S]<sub>0</sub> >> [L]<sub>0</sub> will always restrict the data to this region of the plot when the measured quantities are [S] and [LS].

<sup>\*</sup> δ-values used to construct these Scatchard plots were determined from experiments performed according to Method 2 of the Experimental.

related compounds by comparing  $K_B^{-}$ -values, then clearly the preferred shift reagent would be Eu(dpm)<sub>3</sub> where  $K_B^{-}$  values will most likely always be <100 liter mole<sup>-1</sup>. In principle it may be possible to extend the range where accurate determinations of  $K_B^{-}$  are possible by using a Fourier Transform spectrometer which will enable one to drop the substrate concentration by a factor of up to 100 (while maintaining a very low concentration of lanthanide to exclude possible dimerization), and still observe the n.m.r. spectrum.

#### CHAPTER III

# DETERMINATION OF MOLECULAR CONFORMATION IN SOLUTION USING LANTHANIDE N.M.R. SHIFT REAGENTS: SIGNIFICANCE OF

#### INTERNAL ROTATION

#### Introduction

In the General Introduction, reference was made to the potential use of lanthanide shift reagents for the determination of substrate geometry in solution. This potential use was first realized for the present series of lanthanide shift reagents by Hinckley.<sup>12</sup> It has since provided the motivation for most reported applications of these reagents, including our own.

Before discussing our own contribution to this particular aspect of lanthanide shift reagents, it is appropriate to discuss at somewhat greater lengths the historical sequence of events which has led to the present state of affairs with regards to the applicability of this approach for conformational determinations. In so doing, it will become apparent that the determination of molecular conformations from experimentally derived bound chemical shifts ( $\Delta_{\rm B}$ ) or ratios of bound chemical shifts is generally, a highly under-determined problem and becomes tractable only when several preliminary conditions are satisfied. Before continuing on this quantitative approach , it should be stressed that if the only purpose for using lanthanide shift reagents is to aid in assigning n.m.r. spectra (Chapter I), it matters little what reagents are used or how the experiment is conducted. However, for conformational conclusions, the situation is not as simple as will be shown.

The following equation is a repeat of Eq. [4] Chapter I, and is restated here for convenience.

$$\frac{\Delta H_{i}}{H} = \frac{-\beta^{2} S(S+1)}{45 kT} \frac{(3 \cos^{2} \theta_{i} - 1)}{r_{i}^{3}} \times (3 g_{||} + 4 g_{\perp})(g_{||} - g_{\perp})$$

The stereospecific nature of the induced shifts and thus the potential use of these shifts to determine absolute substrate geometry is a direct consequence of the quantity  $[(3\cos^2\theta_i - 1)/r_i^3]$ ; \*\* all other terms in the above equation being constant for different protons on the same substrate.

\*\*  $r_1$  is the separation between the unpaired electron and the resonating nucleus and  $\theta_1$  is the angle between this distance vector and the principle magnetic axis of the complex.

<sup>\*</sup> This equation is of the form stated by McConnell, <sup>37</sup> which only quite recently has been restated in a somewhat different form by Bleaney. <sup>53</sup> The significant difference between the two forms is that the new theory accounts for the shifts in solution from the anisotropy in the susceptibility rather than ascribing the pseudocontact shifts to anisotropic 'g' factors. In terms of practical applications, both expressions contain the same quantity relating the induced shift to substrate geometry. For this reason, I will not restate the equation as proposed by Bleaney. Differences do occur however, in the predicted temperature dependence between the two equations. Thus, in any temperature studies, it will be necessary to adopt this new expression.

In writing the above equation, we have already made one very important approximation - specifically that the complex has axial (n-fold,  $n \ge 3$ ) symmetry (see Discussion). For a complex with  $C_{2v}$  or  $C_2$  symmetry, the quantity relating the magnitude of the induced shift to substrate geometry is so complex as to make its use, we feel, technically impractical.<sup>\*</sup> This in no way justifies using the rather firmly adopted equation as stated above but, as will become apparent at the end of this discussion, for this technique to have any use at all, it is necessary to compromise between rigor and practical utility at this and other stages of the analysis. The reader may find this approach totally unacceptable. Nonetheless, even the most elementary analyses (<u>vide infra</u>) have already produced chemically significant information. Quite simply, the optimal procedure is dictated by the information desired and excellent fits have been obtained using only the quantity  $[(3\cos^2\theta_1 - 1)/r_1^3]$ .

Crystal structures have now been reported for a number of lanthanide n.m.r. shift reagents<sup>77</sup> including both the seven and eight co-ordinate complex with the most frequently used shift reagent -  $\text{Eu}(\text{dpm})_3$ .<sup>55,78</sup> None were found to even approximate axial (n > 2) symmetry. This result would seem to distract significantly from the credibility of using just the quantity  $[(3\cos^2\theta_i - 1)/r_i^3]$  as the geometry factor. However, in view of some of the excellent results obtained using only the above

<sup>\*</sup> The general equation for  $g_x \neq g_y \neq g_z$  can undoubtedly be solved, but in addition to the unknowns  $r_i$  and  $\theta_i$ , one would need to know the above three 'g'-values and an additional angle.

quantity, particularly R.J.P. Williams' work with mononucleotides,<sup>22b,79</sup> it is conceivable that the above X-ray results may not apply to the complexes in solution. Some justification for this 'belief' on our own part stems from the fact that the steric-directing effect of the f orbitals is negligible when compared to that of the d orbitals. As a consequence, according to Moeller, "neither the co-ordination sphere of the cation nor the geometry of the complex can be readily predicted in solution. Since the bonding forces involving the lanthanide cations are primarily electrostatic, solvent forces play an important role in determining co-ordination geometry. Thus, only rarely can it be assumed that the molecular structure found in a crystal will be the same in a solution of the substance in question."<sup>80</sup>

So far, discussion has been limited, perhaps somewhat prematurely, to the equation for the pseudocontact mechanism as being the one solely responsible for the observed induced shifts. In the General Introduction, it was argued that a paramagnetic complex may contribute to the induced chemical shift by two distinct mechanisms - contact and pseudocontact. In many instances, it has been assumed that all perturbations of proton resonances were attributable to the pseudocontact mechanism. \* Such an assumption stems from the fact that it is difficult to envisage a direct experiment which would permit an unequivocal determination between these two mechanisms in all situations. In Chapter I, the results

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This assumption has been based on the fact that the 4f electron shell is well screened. Therefore, there is little likelihood of overlap between the unpaired electron density on the lanthanide and the ligand electrons such as would be required for the 'through bond' contact mechanism.

from an experiment with Gd(dpm)<sub>3</sub>, implied the absence of a contact contribution to the induced shift.<sup>\*</sup> Another approach to this problem has been to compare the experimentally induced chemical shifts (or shift ratios) with those calculated on the basis of a pseudocontact interaction -  $[(3\cos^2\theta_1 - 1)/r_1^3]$  - for a rigid substrate whose geometry is already well established.<sup>34a,41-43</sup>

Interpretation of the pseudocontact model for n.m.r. shift reagents by comparing the experimentally observed induced chemical shifts with those calculated for the lanthanide-substrate complex using the quantity  $[(3\cos^2\theta_1 - 1)/r_1^3]$ , is the basis of existing conformational studies. This technique is usually performed in the following manner. One guesses the most likely configuration for the substrate (preferably of rigid stereochemistry) and then uses this configuration to compute the expected  $\Delta_{\mathbf{R}}$  ratios for all pairs of protons and for many different orientations of the lanthanide metal. For each orientation of the lanthanide complex, all calculated  $\Delta_{\mathbf{p}}$ ratios are compared with experimental ratios and the agreement is If no agreement is found for all reasonable orientations of the noted. lanthanide complex, then this whole process is repeated for a number of possible substrate configurations and the correct configuration is taken to be the one which gives the best agreement between calculated

\* No induced <sup>1</sup>H chemical shifts were observed for <u>neo-pentanol</u> interacting with Gd(dpm)<sub>3</sub> where a contact shift, if present in any of the lanthanide complexes, would be most likely.

A typical starting point for positioning of the lanthanide metal in this regression is that of least steric hinderance with Ln-donor bond distances and angles from related X-ray studies.

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and observed  $\Delta_{\mathbf{R}}$  ratios. The success (and ease) of such an approach is dependent on the analytical methods used to treat the experimental data. As a result, it is not surprising that there have been many attempts to correlate the induced shifts with those calculated, only with the distance variable  $(r_i^{-3})$ , assuming a constant angle term. \*38 Such an unwarranted neglect of the angular dependence can never be justified as we will show. Many of the recent applications 41,42 have used a computer to calculate the entire quantity  $[(3\cos^2\theta_i - 1)/r_i^3]$ and have, for rigid substrates with known conformations, achieved notable success over the conventional method of measuring angles and distances from a Dreiding model. The excellent correlations from a number of these studies have served to further confirm the predominance of the pseudocontact mechanism at least for protons. \*\* These results also substantiate results from similar investigations on substrates of unknown conformation. However, in spite of the apparent success achieved while employing the above technique, inconsistencies have developed and often without justification, these inconsistencies are attributed to the existence of a contact contribution to the induced shifts. 39,40

We have even further optimized this existing procedure in such a way that accurate determinations of substrate-lanthanide complex (and thus substrate) conformation are possible without the necessity of incorporating a contact contribution.

Our approach to the use of lanthanide shift reagents to obtain

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<sup>&</sup>lt;sup>^</sup> In order to correct for the inconsistencies which originated, other orders of the distance variable were tried (from  $r_i^{-1.6}$  to  $r_i^{-3}$ ). <sup>38c,e,81</sup>

<sup>\*\*</sup> For C-13, Cushley and Willcott have both observed a contact contribution to the induced shift.34f,56

molecular geometry from the pseudocontact type contribution to the induced chemical shifts has as its basis the following two distinct aspects: (i) Experimental determination of reliable values for the bound chemical shifts,  $\Delta_{\rm B}$ , for each proton involved; (ii) Proper use of the  $[(3\cos^2\theta_i - 1)/r_1^3]$  dependence in  $\Delta_{\rm B}$  (see Theory).

When, as in the present instance, the ultimate goal is molecular conformation, the experiment should be designed to yield  $\Delta_B$  and stoichiometry while suppressing the complication of intermediate steps in formation of the complex. Such was the reason and justification behind the detailed theoretical treatment presented and tested in Chapter II, which provides a simple and direct way to obtain accurate  $\Delta_B$ -values, stoichiometry, n, and binding constant,  $K_B$ , for the substrate-shift reagent complex.

All previous determinations of molecular geometry using the lanthanide shift reagents (from the angle- and distance-dependence of bound chemical shifts,  $\Delta_{\rm B}$ ), have treated the substrate-shift reagent complex as <u>rigid</u>.<sup>\*\*</sup> However, if there is appreciable flexibility at the site of attachment to the lanthanide or elsewhere in the complex (certainly a possibility if there are minimal intramolecular steric interactions at the point of attachment), then the substrate is permitted to sample many orientations during its residence on the shift reagent. In these circumstances, it is necessary to first average over all available

For particular examples of this see references 34a, 41, 42 and 43.

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<sup>\*</sup> The importance of knowing the stoichiometry is related to the previous discussion regarding the symmetry of the complex in solution. It suffices to point out that it may be reasonable to assume effective axial symmetry only for a 1:1 complex.

conformations <u>before</u> comparing observed and calculated  $\Delta_B$ 's or ratios of  $\Delta_B$ 's as will be shown in the Theory which follows. For the time being, this condition can be stated quite explicitly as follows:

$$<[(3\cos^2\theta_i - 1)/r_i^3] > \neq [(3\cos^2\theta_i > - 1)/(r_i^3)],$$

where <> indicates a weighted average over all possible configurations.

A variety of new models for free or hindered internal rotation are proposed and tested on three organic substrates which are rigid except perhaps at the point of attachment to the lanthanide. Moreover, examples are provided which show that "good" fits between observed and calculated shift ratios are not in themselves <u>proof</u> for the predominance of that conformation. However, the use of several models for internal rotation, interpreted by means of contour plots of "fits" as a function of geometry of the complex, can provide a means for sorting out the correct from the spurious calculated conformations. In addition, a rather unique experiment, unique in the sense that no geometry was chosen for the substrate in advance, will be discussed.

While present treatments were successful in arriving at welldefined and chemically reasonable substrate conformations, the interpretation rests on the fulfilment of a number of requirements (some of which have already been discussed), which will be stated below.

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#### Theory

As stated previously the determination of molecular conformation from experimentally derived bound chemical shifts ( $\Delta_B$ ) is a highly under-determined problem. The analysis becomes tractable only when several preliminary requirements are satisfied.<sup>82,83</sup>

(1) The  $\Delta_{\rm B}$ -values themselves are obtained in the most direct and reliable way (Chapter II).

(2)  $\Delta_{\rm B}$  is wholly pseudocontact in origin, as seems to be the case for proton shifts induced by Eu or Pr shift reagents.<sup>13</sup> This assumption does not appear to be valid for <sup>13</sup>C shifts from either of these shift reagents. Yb(dpm)<sub>3</sub> has been found to give the least amount of contact contribution in <sup>13</sup>C shifts, <5%.<sup>56</sup>

(3) The geometry of the substrate bound in the complex is the same as that of free substrate in solution.

(4) Only a single stoichiometric species exists in solution in equilibrium with uncomplexed substrate.

(5) Only a single geometric isomer of this complex species is present.

(6) The substrate ligand exists in a single conformation or an appropriate averaging over internal motions is carried out.

(7) The effective electronic g-tensor is axially symmetric, with principal magnetic axis along the Eu-donor atom bond. Without this assumption, the problem is too under-determined to solve. Determination of stoichiometry for the complex thus becomes important, since the g-tensor principle axis will most easily be located in a 1:1 adduct. Since the g-tensor in the solid can deviate markedly from axial symmetry,<sup>77</sup> we require sufficient internal rotational motion about the Eu-donor atom bond to ensure effectively axial symmetry for the complex in solution.<sup>\*</sup> This motion need merely be fast compared to  $\Delta_{\rm B}$ , which seems highly likely in view of the rather long Eu-donor bond distances observed by X-ray diffraction.<sup>55</sup>

Realizing the importance of this latter requirement, Roberts<sup>84</sup> has recently proposed a method of analysis which does not assume in advance that the Eu-donor atom bond of the complex is collinear with the principal magnetic axis. This treatment requires that the induced shifts be compared with those calculated using 2 angles and 1 distance to define the position of the metal atom, (vide infra) and an additional two angles to define the orientation of the magnetic axis, a total of 5 unknown geometric parameters.

His results are significant in that they confirm the assumption that the principal magnetic axis of alcohol-lanthanide complexes are essentially collinear with the Ln-donor atom bond. The validity of this result is, however, questionable for the following reasons: (i) their treatment rests on the assumption that the complex is rigid at the point of attachment to the lanthanide (vide infra), (ii) if the complex does not possess axial symmetry, then  $\Delta_{\rm B}$  is proportional to  $[(3\cos^2\theta_{\rm i} - 1)/r_{\rm i}^3] + [\sin^2\theta_{\rm i} \cos^2\theta_{\rm i}/r_{\rm i}^3]$  and must be evaluated as such.

For fast internal rotation, averaging of  $\cos 2\Phi$  over  $2\pi$  makes the second term go to zero, leaving the desired Eq. [4], Chapter I.

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<sup>\*</sup> For non-axial magnetic symmetry, the induced shift is of the form,  $\Delta_{\rm B} = {\rm const}[3\cos^2\theta_{\rm i} - 1)/r_{\rm i}^3] + {\rm const'}[\sin^2\theta_{\rm i}\cos^2\theta_{\rm i}/r_{\rm i}^3]$
In addition to the above requirements, it has been suggested that:<sup>85</sup> "(i) A variety of lanthanide shift reagents must be employed in each study and the ratio of shifts at different proton sites then compared for the different lanthanides. If these ratios are independent of the lanthanide cation then the shifts have their origin in dipolar coupling (pseudocontact) and, (ii) the observed shifts must be corrected by observing shifts due to complex formation with diamagnetic lanthanides, La<sup>3+</sup> and Lu<sup>3+</sup>." In Chapters I and II we have presented the results for studies using a variety of lanthanide shift reagents and these results alone indicate that at least as far as proton shifts are concerned, complexes, either (dpm), or (fod), with Eu(III) are the most appropriate for conformational investigations. With regards to the second point, the experiments discussed in this text are all performed in the region [S] >> [L] with the maximum concentration of [L] ca. = 0.006 M. At these low lanthanide concentrations, the internal standard is satisfactory in correcting for bulk susceptibility effects and there is no need to make use of corrections possible by using diamagnetic lanthanides.

With these requirements, Fig. 21A defines the starting point for determination of molecular geometry. This right-handed co-ordinate system has been designed to facilitate computer fits of shift data. The donor atom (atom #1) defines the origin; proceeding from atom #1 to #2 defines the positive x-direction; atom #3 is then assigned a positive y-value in the x-y plane.  $\Omega$ ,  $\phi$  and R unambiguously fix the position of the lanthanide atom relative to the molecular frame.

Since the molecules of present interest are rigid except at the

- 128 -Ζ Eu Φ Ω Figure 21A. Co-ordinate system for substrate-shift reagent complex. R is the lanthanide-donor atom bond direction vector; |R'| =  $|\mathbf{R}| \sin \Omega$ . Origin is at donor atom 1, proceeding to atom 2 Х then defines the positive

x-axis; atom 3 is then assigned a positive y-value in the x-y plane; z-direction then follows from right-hand convention.  $\Omega$ ,  $\phi$  and R unambiguously define the position of the lanthanide relative to the substrate molecular frame.

point of attachment to the lanthanide, a "determination" of the conformation of the complex consists of finding the "best" values of R,  $\Omega$  and  $\phi$  (if a unique  $\phi$  exists), given the conformation of the substrate molecule itself. Appendix A gives a rapid method for obtaining the desired parameters,  $r_1$  and  $\theta_1$  for the i'th proton, from (guessed) values of the Eu-donor atom bond distance, R, the polar ( $\Omega$ ) and azimuthal ( $\phi$ ) angles which locate the Eu-donor bond axis relative to the molecular frame, and the co-ordinates of all atoms in the substrate, (Fig. 21B). Assuming a perfectly rigid complex, one could proceed as follows. First put into the geometry program the cartesian co-ordinates for the protons of the substrate molecule as well as the corresponding shift ratios, then estimate a starting location for the lanthanide atom (i.e., choose values for R,  $\Omega$  and  $\phi$ ) and compute  $[(3\cos^2\theta_i - 1)/r_i^3]$ for each proton of the substrate; \*\* then calculate the normalized variance (the "R-value")<sup>41</sup> between ratios of this quantity and observed shift ratios for all possible independent pairs of protons. \*\*\*

$$R = \frac{\left(\sum_{\substack{j \neq 1 \\ j \neq 1}}^{\Sigma W_{j}} \left(\frac{\Delta H_{1}}{\Delta H_{j}}\right)_{obs} - \left(\frac{\Delta H_{1}}{\Delta H_{j}}\right)_{cal}\right)^{2}}{\left(\sum_{\substack{j \neq 1 \\ j \neq 1}}^{\Sigma W_{j}} \left(\frac{\Delta H_{1}}{\Delta H_{j}}\right)_{obs}^{2}\right)}, \text{ where } W_{j} \text{ is a weight}}$$

\* A modified version of the computer program COORD which is listed in Appendix B was used to calculate cartesian co-ordinates for all atoms in the substrate. Input data to COORD were bond lengths, bond angles and dihedral angles taken from X-ray studies of related compounds.

\*\*

The computer programs used to perform these geometry calculations are listed in Appendix C and D.

\*\*\*

An "R-value" of 0.04 or less for the present calculations corresponds to agreement well within experimental error for each of the experimental "bound" shift ratios.



Figure 21B. Co-ordinate system for substrate-shift reagent complex. r is the distance vector from the lanthanide atom to the i'th proton of the substrate;  $\theta_i$  is the angle between R and  $r_i$ . Internal rotation of R about the x-axis consists of permitting a range of  $\phi$ -values, shown as the circle in the figure.

Repeat the procedure many times for different values of R,  $\Omega$  and  $\phi$  then choose the most probable conformation as that which gives the best "fit" (smallest normalized variance, smallest "R-value") to the observed shift ratios. The difficulty with this treatment is that it is quite possible to obtain correct shift <u>ratios</u> from incorrect <u>absolute</u> shifts, so that sometimes the best "fits" are obtained at chemically unreasonable values of R and  $\Omega$  (see Results).

The source of the difficulty lies in attempting to fit the observed shifts to those computed for individual conformations - this procedure will at best indicate the average values of  $\langle \mathbf{r} \rangle$  and  $\langle \theta_i \rangle$ . However, the observed quantity is  $\Delta_{\mathbf{R}}$ 

[1] 
$$\Delta_{B} \alpha < \frac{3\cos^{2}\theta_{i} - 1}{r_{i}^{3}} > \neq \frac{3\cos^{2}<\theta_{i}> - 1}{< r_{i}>}$$

where the brackets denote an average over all possible bound conformations during the residence of a substrate at a shift reagent. Whenever rapid internal rotations are present, it is necessary to average the <u>entire quantity</u>,  $[(3\cos^2\theta_i - 1)/r_i^3]$  on account of the inequality just written, <u>before</u> comparing observed and calculated shift ratios, and any analysis based on a best single conformation should not be expected to succeed. The three simplest models for internal rotation are free rotation, no rotation, and jumps between the minima of an n-fold potential. Fig. 22 may be used to visualize what is meant by these three models. The remainder of this discussion concerns application of these three models to the internal motions in selected molecules



Figure 22. A diagrammatic illustration of the weight distribution as a function of  $\phi$  for three simple models of internal rotation.

which are expected to fall into these categories.

<u>Free rotation</u> about the atom #1 - atom #2 axis is readily simulated by multiplying the quantity  $[(3\cos^2\theta_i - 1)/r_i^3]$  by a normalized unit weight factor.

$$[2] P(\phi)d\phi = (1/2\pi)d\phi,$$

followed by integration over all  $\phi$  from 0 to 2 $\pi$ , where this operation is carried out <u>before</u> comparing observed with calculated shift ratios. The same procedure may be used for the opposite limit of a <u>rigidly</u> locked complex by use of the weight factor,

$$[3] P(\phi)d\phi = \delta(\phi - \phi_{\alpha})d\phi ,$$

where  $\phi_0$  is the (fixed) azimuthal angle in the Dirac  $\delta$ -function. Since no real molecule will be perfectly rigid, it is desirable to relax the distribution, [3], to span some specified angular range in  $\phi$  in the vicinity of  $\phi_0$  - we have for convenience chosen a Gaussian weight factor.<sup>\*</sup>

[4] 
$$P(\phi)d\phi = (A/\sqrt{\pi}) \exp[-A^2(\phi - \phi_0)^2]d\phi$$
.

In Eq. [4], a large value of A corresponds to a narrow distribution of possible angles; the values of A =  $(8)^{1/2}$  or A = 1 in the next section correspond to rms widths of about 14° or 40° about  $\phi_0$ , respectively.

The normalization implied in Eq. [4] corresponds to an infinite domain in  $\phi$ , whereas the physical domain of integration is only from  $\phi = \phi -\pi$ to  $\phi_0 + \pi$ . Thus it is correct to compute induced shift ratios for any given A, but one should not compare <u>absolute</u> shifts computed from different choices for A.

Finally, the possibility of <u>rapid random jumps</u> between n equally likely values of  $\phi$  may be simulated by use of the periodic weight function,

[5] 
$$P(\phi)d\phi = (1/\pi)\cos^2[(n/2)(\phi - \gamma)]d\phi$$
,

where  $\gamma$  is the  $\phi$ -distance between  $\phi = 0$  and the nearest potential minimum in  $\phi$ . Random jumps may also be simulated by  $\delta$ -function distributions,

$$[6] P(\phi)d\phi = a\delta(\phi - \phi_1) + b\delta(\phi - \phi_2) + \dots + f\delta(\phi - \phi_n)d\phi$$

where a,b,...,f represent the probability of finding the complex with  $\phi$ -value  $\phi_1$ ,  $\phi_2$ , ...,  $\phi_n$ , respectively. Numerical integration (when necessary) was carried out by low-order Gauss-Legendre quadrature (i.e., 6, 8, or 10 point) and in most cases checked against higher order formulas to verify its validity. The Appendix contains a complete listing of the computer programs used in the analysis of complex conformation according to the above models. Only the programs for completely free rotation and that for a rigidly locked complex are listed. The programs used with a Gaussian weight factor are similar to that for free rotation, requiring only a change in weight function from Eq. [4].

## Results and Discussion

Determinations of molecular geometry from chemical shift ratios appear to be best illustrated by contour plots of the type shown in Figs. 23-28. The contours are simply paths of constant normalized variance ("R-value", agreement factor) between observed and calculated shift ratios, as a function of possible positions of the lanthanidedonor atom distance (R), the angle ( $\Omega$ ) between the europium-donor bond and the bond between atom #2 and the donor atom, and the azimuthal angle ( $\phi$ ) shown in Fig. 21A. A small normalized variance (< 0.04) thus indicates very good agreement between observed and calculated shift ratios.

The first substrate considered was the monofunctional donor, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 1.



Only those protons directly bonded to the rigid "furanose ring were

\* Rigid in the sense that the isopropylidene ring substituent prevents the furanose ring from adopting all but a few possible conformers in the pseudorotation cycle. For the purpose of this present study, a single rigid conformer has been assumed. used to derive the complex geometry. The co-ordinates for these protons can be accurately defined whereas use of the other protons would necessitate a much more detailed analysis which allowed for internal rotation within the substrate itself. This particular molecule was chosen to represent the model where there was unlikely to be any rotation about the  $C_3$ -donor atom bond as a result of the intramolecular steric hinderance. This was only an intuitive assumption based on visual inspection of a Dreiding model of <u>1</u> and will be tested by comparing the results from all three models for internal rotation.

Table 13 lists the values of the shift ratios which were used to determine the geometry of the furanose ring. These ratios are calculated from the appropriate  $\Delta_{\rm B}$ -values listed in Table 12, Chapter II. The stoichiometry for this complex can be accurately determined to be 1:1. Several attempts were made to fit the observed shift ratios to those calculated, with the assumption that there was no internal rotation about the C<sub>3</sub>-donor atom bond, for several reasonable conformations of the furanose ring. All conformations tested had bond lengths and bond angles in accord with X-ray and neutron diffraction data for related furanose ring systems.<sup>86</sup> A number of different values for the dihedral angles, which were estimated from X-ray data and n.m.r. coupling constant data, were tested (e.g. the near zero coupling for H-2, H-3 is indicative (Karplus) of a H<sub>2</sub>C<sub>2</sub>C<sub>3</sub>H<sub>3</sub> dihedral angle near 90°).

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Substrate	$\Delta_{\rm B}^{\rm -ratios}$	Shift Reagent	Solvent	
Aniline, <u>16</u>	o/m=4.79 o/p=4.00	Eu(dpm) <sub>3</sub>	CDC13	
Pyridine, <u>17</u>	o/m=3.05 o/p=3.22	Eu(dpm) <sub>3</sub>	CDC13	
1,2:5,6-d1-0-1sopropy1- idene- $\alpha$ -D-glucofuranose, $\underline{1}^{c}$	H-3/H-2=2.59 H-3/H-1=3.52	Eu(dpm) <sub>3</sub>	CDC13	
	H-3/H-4=1.82	1		

Table 13. Induced chemical shift ratios for association of four

a	Shift ratios were determined from bound chemical shifts which were obtained from plots of $[S]_0$ versus $(1/\delta)$ , as explained in Chapter II. For <u>16</u> , <u>17</u> , and <u>1</u> , binding was unequivocally shown to be 1:1.
Ъ	For binding of $\underline{11}$ to Eu(fod) <sub>3</sub> , the binding was too strong to measure, and the listed shift ratios correspond to the induced shifts for an

H-5/H-6(exo)=1.40

H-5/H-6(endo)=2.90

5-hydroxy-1,2,3,4,7,7-

hexachloronorborn-2-

ene, <u>11</u>b

CC14

Eu(fod)<sub>3</sub>

substrates with lanthanide n.m.r. shift reagents.

- For binding of <u>11</u> to  $Eu(fod)_3$ , the binding was too strong to measure, and the listed shift ratios correspond to the induced shifts for an [L]<sub>0</sub>/[S] ratio of 0.3. The shift ratios for <u>11</u> are in good agreement with those in ref. 44 for the unsubstituted alcohol.
- <sup>c</sup> The H-5 proton was not used in the analysis because of the possibility of internal rotation about the C-4 C-5 bond which would complicate the analysis.

The conformation which finally allowed for a successful geometric fit to be obtained has bond lengths, bond angles, and dihedral angles as shown in Table 14. This conformation is signified as  $V_4$  from the pseudorotation cycle and differs only very slightly from the  ${}^3T_2$  conformer arrived at from high resolution n.m.r. studies. It should be emphasized that, although all likely conformations were investigated, this method does not test whether the conformation used is the <u>best</u> possible one, only that this conformation is preferred over other proposed conformations.

The data in Table 14 are then input to the program COORD which produces a set of cartesian co-ordinates for the atoms shown with oxygen at the origin. These cartesian co-ordinates for the protons, H-1, H-2, H-3 and H-4 as well as the corresponding shift ratios (Table 13) are then put into the appropriate geometry program.

Fig. 23A,B shows the contours which are obtained, under the assumption that there is no internal rotation about the carbon-donor bond. Two features are evident. First, for some choices of  $\phi$ , there are no "good" fits (i.e. having normalized variance, R, smaller than 0.04). Second, among the range of  $\phi$ -values for which good fits are obtained, some  $\phi$ -values lead to unreasonably short europium-oxygen bond distances. Based on these results, if <u>1</u> is rigid with respect to internal rotation about the carbon-donor bond, then the most likely position of the europium is R = 2.2 Å,  $\Omega$  = 114°, and  $\phi$  = 116°. It is significant that these parameters appear to correspond with an

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<sup>\*</sup> The numbering scheme here is as shown on the structure, it is not numbered in the conventional manner. For the purpose of these geometry calculations, atom #1 is <u>always</u> the donor atom.

<u>Table 14</u>. Bond distances, bond angles and dihedral angles used to calculate a set of cartesian co-ordinates from COORD for 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. Numbering scheme is as shown below with atom #1, the oxygen of the hydroxyl group.



1-2 Bond Distance = 1.40 Å; 2-3 Bond Distance = 1.523 Å; 123 Bond Angle = 115.7°.

Atoms	Bond Distances(A)	Bond Angle(deg.)	Dihedral Angle <sup>*</sup> (deg.)
ABCD	CD	BCD	ABCD
1234	1.450	105.8	105.0
2345	1.427	109.3	15.0
3456	1.523	105.8	345.0
1238	1.083	109.0	210.0
3459	1.083	109.0	225.0
4 5 6 10	1.083	109.0	240.0
5627	1.083	109.0	150.0

\* Dihedral angle of CD relative to AB, measured clockwise along the direction B to C.



Figure 23A. Contours of normalized variance ("R-value", agreement factor) between observed and calculated induced chemical shift ratios as a function of possible positions of the lanthanide atom relative to the donor atom of the substrate for <u>1</u>. It has been assumed that there is no internal rotation about the bond from carbon to donor oxygen.



Figure 23B. Contours of normalized variance ("R-value", agreement factor) between observed and calculated induced chemical shift ratios as a function of possible positions of the lanthanide atom relative to the donor atom of the substrate for <u>1</u>. It has been assumed that there is no internal rotation about the bond from carbon to donor oxygen. orientation of Eu(dpm)<sub>3</sub>:1 which has the metal in a sterically favourable position. The position of the metal is also in accord with the observed shift for H-5 being greater than H-3.

Fig. 24A,B shows the effect of varying degrees of internal motion on the agreement between observed and calculated ratios for <u>1</u>. Beginning (as in Fig. 23) with a static molecular frame, we now allow for a Gaussian distribution of  $\phi$ -values, centered at the most likely  $\phi$ -value of 116°, with a root-mean-square width of either 14° ("narrow Gaussian" in Fig. 24A) or 40° ("wide Gaussian" in Fig. 24B). It is clear that this greater latitude in internal rotational position produces less reasonable fits, with respect both to agreement with experiment (normalized variance) and also intuition (too-short values for Eu-O bond distance). In fact, the contour plot for the assumption of completely free internal rotation about the carbon-donor bond (Fig. 24B) shows that free rotation is simply not possible in this complex.

Thus we have demonstrated that the 1:Eu(dpm)<sub>3</sub> complex is relatively rigid and thus the geometry of the complex may be determined with confidence.

The above model (that of a rigid complex) can hardly be expected to hold for a substrate such as aniline, <u>16</u>, where there should be little preference for the shift reagent to be rigidly attached at any one value of  $\phi$ . This presumption is reasonable in view of the rather large bond distance for europium-nitrogen bonds. X-ray determinations of this distance put it in the range of <u>ca.</u> 2.65 Å.

Table 13 lists the values of the shift ratios which were used to



Figure 24A. Contours of normalized variance as a function of lanthanide position for 1. For the "static plot", there is no internal rotation about the carbon-donor bond. For the "narrow Gaussian",  $\phi$ -values are first weighted by the factor,  $(A/\sqrt{\pi})\exp[-A^2(\phi-\phi_0)^2]d\phi$ , and then integrated over all  $\phi$  (with  $A = \sqrt{8}$ ) before comparing observed with calculated shift ratios (see Theory).



Figure 24B.

AB. Contours of normalized variance as a function of lanthanide position for 1. For the "wide Gaussian",  $\phi$ -values are first weighted by the factor,  $(A/\pi) \exp[-A^2(\phi-\phi_0)^2]d\phi$ , and then integrated over all  $\phi$  (with A = 1) before comparing observed with calculated shift ratios (see Theory). For the "free rotation" plot,  $\phi$ -values are averaged over all  $\phi$  from 0 to  $2\pi$  using unit weight factor.

determine the geometry of the 16:Eu(dpm)<sub>3</sub> complex. These ratios are calculated from the appropriate  $\Delta_{\rm B}$ -values listed in Table 8, Chapter II. The stoichiometry for this complex can be accurately determined to be 1:1.

Table 15 lists the bond lengths, bond angles, and dihedral angles which are in accord with X-ray and microwave data for related compounds<sup>87</sup> and which were used as input to COORD to calculate a set of cartesian co-ordinates for <u>16</u>. The cartesian co-ordinates and the observed shift ratios for the o, m and p protons were then put into the appropriate geometry program.

Fig. 25 shows the contours which were obtained for this substrate, <u>16</u>, under the assumption of completely free internal rotation about the C-N bond; "good" fits were obtained. The value of 2.55 Å for the Eu-N bond distance (R) and 111.0° for the Eu-N-C bond angle ( $\Omega$ ) computed in this way compares favourably to typical X-ray values of about 2.65 Å for R. This "good" fit obtained under the assumption of free internal rotation will now be compared to the fits obtained when other models for internal motion for aniline were examined.

The results for these other models are shown in Fig. 26 and are a particularly incisive illustration of the danger of literal interpretation of shift reagent results. As for the case of free internal rotation discussed above, three protons (o, m and p) formed the basis for the calculation, but now under the assumption that there was no internal rotation about the C-N bond. Excellent fits were obtained in

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Table 15. Bond distances, bond angles and dihedral angles used to calculate a set of cartesian co-ordinates from COORD for aniline. Numbering scheme is as shown below with atom #1, the N donor atom.



1-2 Bond Distance = 1.37 Å; 2-3 Bond Distance = 1.40 Å; 123 Bond Angle = 123.0°.

Atoms	Bond Distance(A)	Bond Angle(deg.)	Dihedral Angle <sup>*</sup> (deg.)
ABCD	CD	BCD	ABCD
1234	1.40	125.0	180.0
2345	1.39	119.0	0.0
3456	1.39	117.0	0.0
4567	1.39	125.0	0.0
7238	1.07	120.0	180.0
2349	1.07	120.0	180.0
3 4 5 10	1.07	122.0	180.0
45611	1.07	120.0	180.0
5 6 7 12	1.07	120.0	180.0

\* Dihedral angle of CD relative to AB, measured clockwise along the direction B to C.



Figure 25. Contours of normalized variance as a function of lanthanide position for aniline. Internal rotation about the C-N bond is assumed to be completely free (unhindered).







Figure 26. Contours of normalized variance as a function of lanthanide position for aniline. Top: fits based on experimental shifts for o, m and p protons, assuming no internal rotation about the C-N bond. Middle: fits based on experimental shifts for o, m and p protons assuming no internal rotation about the C-N bond. Bottom: fits based on experimental shifts for o, m and p protons, assuming rapid jumps between fixed \$\phi\$-values of 0° and 180°.

the vicinity of  $\phi = 66^\circ$ , and the fit at  $\phi = 90^\circ$  was very poor. This leads to the conclusion that the complex is rigid, with R = 2.55 A,  $\Omega = 124^{\circ}$ , and  $\phi = 66^{\circ}$ . The problem with this conclusion is that the experiment shows a single resonance for both o and m protons on opposite sides of the aromatic ring! Thus, the symmetry of aniline must be maintained in the complexed state. Here then is a case where the agreement with experimental shift ratios for three protons is excellent, the Eu-N bond distance which results is reasonable, but the "determined" geometry is wrong. Since the "static" fits at  $\phi = 90^{\circ}$ were poor, apart from free rotation, the remaining possibility, which is chemically unreasonable (vide infra), is that of random jumps between  $\phi$ -values of 0° and 180°; the contours from this model are shown as the bottom plot of Fig. 26. The "fit" for this "jump" model is very sharply-defined, with R = 2.75 Å,  $\Omega$  = 115°. These "good" fits obtained for random jumps between  $\phi$ -values of 0° and 180°, although in agreement with experimental shift ratios, are unreasonable from a point of view of steric hindrance which would be a maximum in this position.

Thus in conclusion, only the free rotation model produces chemically meaningful results for the aniline:Eu(dpm), complex.

So far a distinct chemically meaningful fit has been obtained after treating each molecule with several possible models for internal

<sup>\*</sup> When all five protons were included in a static model at the (only possible) φ-value of 90°, a contour plot identical to that in the middle graph of Fig. 26 was obtained, with even poorer agreement (higher "R-value" contours).

rotation. This situation is considerably altered for the binding of 5-hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene, <u>11</u>, to a lanthanide shift reagent.

-Cl

This compound was particularly suitable for geometry determinations of the sort described here because of its rigid stereochemistry and because the chemical shifts of the individual protons were well separated initially, thus permitting very accurate measurement of the changes which occurred with added lanthanide. In addition, related compounds (borneol and isoborneol) had previously been used as model compounds to study complex geometry by several other groups,<sup>34a,41,43</sup> none of which had made any allowance for internal rotation about the carbon-donor atom bond. It is not possible to predict in advance what model for internal rotation is applicable to the complex, nevertheless, it is improbable that the lanthanide will be rigidly attached.

Table 13 lists the values of the shift ratios which were used to determine the geometry of this Eu(dpm)<sub>3</sub>:11 complex. The binding

constant for this complex was too large to be measured and thus the stoichicmetry can only be assumed 1:1. Table 16 lists the bond lengths, bond angles and dihedral angles which were used as input to COORD to generate a set of cartesian co-ordinates which were subsequently used in the geometry program.\*

Fig. 27 shows the contours which were obtained for this substrate, 11, under the assumption of completely free internal rotation about the C-O bond. "Good" fits (perhaps not quite as well defined as that for aniline, free rotation) were obtained, but at a value of 2.9 A for the Eu-O bond distance which is quite large in comparison with the X-ray range of 2.3-2.4 Å. This result would seem to indicate the need to examine other models for internal motion in this substrate. Fig. 28 illustrates some of the other models considered and some of the difficulties which may be encountered. The top plot gives the contours for a  $\phi$ -value giving an excellent "static" fit at  $\phi = 236^\circ$ ,  $\Omega = 112^\circ$ and R = 2.65 A. This "fit" is reasonable except perhaps in view of the rather long Eu-O bond distance and consequently other models for internal motion were investigated. The middle plot of Fig. 28 shows that the above fit can be made to give even better agreement with experiment, if a Gaussian weight factor is applied to the  $\phi$ -values, with the Gaussian still centered at  $\phi = 236^{\circ}$  with 14° rms width. However, the very best fits (smallest normalized variance) were obtained in the bottom plot, Fig. 28, which is a Gaussian distribution in  $\phi$ centered at  $\phi = 248^{\circ}$  with rms width of 14°. The embarrassing feature of this plot is the very wide range in values of R and  $\Omega$  over which

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Only the ethane fragment need be defined for this chlorinated bicycloheptenol.

Table 16. Bond distances, bond angles and dihedral angles used to calculate a set of cartesian co-ordinates from COORD for 5-hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene. Numbering scheme for portion analyzed is as shown below with atom #1, the oxygen of the hydroxyl group.



1-2:Bond Distance = 1.43 A; 2-3 Bond Distance = 1.54 A; 123 Bond Angle = 108.9°.

Atoms	Bond Distance(A)	Bond Angle(deg.)	Dihedral Angle*(deg.)
ABCD	CD	BCD	ABCD
1235	1.107	108.9	120.0
1236	1.107	108.9	0.0
6324	1.107	108.9	240.0

\* Dihedral angle of CD relative to AB, measured clockwise along the direction B to C.



Figure 27. Contours of normalized variance as a function of lanthanide position for <u>11</u>. Internal rotation about the C-O bond is assumed to be completely free (unhindered).





Figure 28. Contours of normalized variance as a function of lanthanide position for <u>11</u>. Top: no internal rotation about C-O bond. Middle: Gaussian distribution in  $\phi$ ,  $(A/\sqrt{\pi}) \exp[-A^2(\phi-\phi_0)^2] d\phi$  with A = 1, centered at  $\phi_0 = 236^\circ$ . Bottom: Gaussian of the same width, but centered at  $\phi_0 = 248^\circ$ .

equally good fits could be obtained; so that virtually no information about R and  $\Omega$  can be derived from the experiment. For substrate <u>11</u>, the bound conformation probably exhibits some internal rotation, with the Eu more often opposed than adjacent to the apical chlorines. This result would seem to have guite a severe consequence on the results reported elsewhere for related compounds where a claim to a single unique static fit has been made.

The results for the substituted bicycloheptenol, <u>11</u>, provide one final point of interest. Although the method of fitting shift ratios from the best number of individual conformations is not determinative as to Eu-O distance or even Eu-O-C angle, there is a dependence on  $\phi$ (see Fig. 28) which shows for the present compound a definite minimum at <u>ca</u>. 250°, the orientation expected for the <u>exo-hydroxyl position</u> on the grounds of minimal intramolecular steric interaction. In confirmation of this claim, comparison of shift ratios for <u>11</u> with those for the <u>exo-</u> and <u>endo-bicycloheptanol<sup>44</sup></u> shows that the shift ratios for <u>11</u> match nicely with those for <u>exo-bicycloheptanol</u>, but do not match the rather different values for <u>endo-bicycloheptanol</u>. This assignment of configuration at C-2 (numbering scheme as shown in Table 16) could not have been made on the basis of coupling constant data.

For the analysis of complex conformation in the systems discussed up to now, it has been necessary to first define a particular (most reasonable) configuration of the substrate whose co-ordinates were then calculated using the computer program COORD. These cartesian co-ordinates and the observed shift ratios were then put into the appropriate geometry program for internal rotation and several metal co-ordination schemes were examined.

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The molecule, pyridine, 17, appeared at first sight to present a rather well defined rigid system on which to perform a geometry calculation according to the above procedure. Bond lengths and bond angles were available from a number of X-ray<sup>87a</sup> and microwave studies<sup>87b,c</sup> and could be used to generate a set of cartesian co-ordinates using the computer program COORD. The directional lone pair of the nitrogen donor group left little doubt as to which model for internal rotation was most likely - namely a rigidly locked complex where only internal rotation about the Eu-N bond was possible, which would not affect either r or  $\theta$  in Eq. [1]. In addition, X-ray data for  $Eu(dpm)_3(py)_2$  were available which reported an average Eu-N bond ; distance of 2.65 Å. Even though this value was for an eight co-ordinate lanthanide complex whereas our present analysis was for a seven co-ordinate lanthanide complex, \* (vide infra), there seemed little doubt as to what the value for the Eu-N bond distance determined from the present system of analysis could be.

Table 13 lists the values of the shift ratios which were used to determine the geometry of the pyridine:Eu(dpm)<sub>3</sub> complex. These ratios were calculated from the appropriate  $\Delta_{\rm B}$ -values listed in Table 12, Chapter II. The binding constant was in the range where accurate determination was possible and thus the stoichiometry can be accurately determined to be 1:1. Using the computer program for a rigidly locked complex, several attempts were made to fit the observed shift ratios with those calculated for several reasonable conformations of the

<sup>\*</sup> Selbin<sup>71</sup> has reported the preparation and properties of the stable Eu(dpm)<sub>3</sub>(py) complex and other seven co-ordinate lanthanide complexes.

pyridine ring. No fits were obtained over any reasonable Eu-N bond distance (2.2 to 3.5 Å); even when the geometry of the pyridine ring was defined using X-ray data for transition metal complexes with pyridine.  $^{88}$ 

The inability to fit the observed shift ratios was particularly disconcerting, especially when one considers the well-defined nature of this system. There are three possibilities which may contribute to the above result. They are, in order of ascending importance: (i) the principle magnetic axis may be other than along the Eu-N bond, (ii) the possibility of a contact contribution to the induced shift if present, this would be most probable for the o-protons \*. and. (111) the geometry of the substrate bound in the complex may be different than that for the free substrate in solution. We still allow for rapid internal rotation about the Eu-N bond which, as discussed in the theory, ensures effective axial symmetry. Also, it can hardly be assumed at this juncture that a contact contribution is present in the induced shift, even in view of the aromatic character of this system.<sup>89</sup> This brings us to the third possibility about which we are unable to make any definite comments and which if correct, would inhibit the success of the present system of analysis unless fortuitously the required conformation for pyridine was chosen.

A specific computer program was written to attempt to resolve the problems encountered with pyridine. This program will not be listed and although written specifically for pyridine, it would be applicable, in a slightly modified form, for any planar system.

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<sup>\*</sup> It should be emphasized, however, that for geometry determinations, protons with small r and wide angle θ will be the most sensitive to configurational changes.

The only molecular dimension which is input to this program is the C-3 - H-3 bond distance, which is taken as 1.02 Å.  $^{88}$ In addition, a minimum value for the Eu - H-3 distance, and as before, the observed shift ratios are input. It is assumed (and not unexpectedly), therefore, that the Eu atom lies in the plane of the pyridine ring and along the  $C_2$  axis. The computer then varies the Eu - H-3 distance in increments of 0.06 A to a maximum possible value which would correspond to a Eu-N bond distance of 3.5 Å. At each increment the quantity, [( $3\cos^2\theta_i$  - $1/r_{i}^{3}$ ], is calculated for H-1 and H-2 and the ratio compared with the observed (Table 13). The output of this program is a series of plots to which one manually fits a structure of pyridine, assuming C-C bond lengths of 1.40 Å and C-H bond distances between 1.02 and 1.08 Å. The geometry of pyridine which resulted from such a treatment is shown below.



The significant difference in this structure with any tried in the previous treatment, is the position of the o-protons which are displaced towards the point of complexation with the shift reagent. This result may reflect a possible stabilized structure with these hydrogens participating in H-bonding with the (dpm) ligand of the lanthanide complex. Although this change in geometry of the pyridine ring is not large, it was enough to prevent any fits being obtained for the several proposed geometries when treated in the regular manner. The resulting Eu-N bond distance,  $R = 2.67 \text{ Å} \pm 0.1 \text{ Å}$  ( $\Omega = 118^{\circ} \pm 2^{\circ}$ ) is in excellent agreement with the reported X-ray value for R of 2.65 Å.

The method of analysis used above can be applied, in principle, to molecules which are not planar but the display of the results would best be viewed in 3-D, using graphical displays of the sort used by R.J.P. Williams.<sup>22b</sup> No attempt was made to develop our technique to this degree.

The results for pyridine provide one final point of interest. We have stated that one of the distinct aspects necessary, before any attempt can be made to determine molecular geometry, is the experimental determination of reliable values for the bound chemical shifts, for each proton involved. Other less precise ways for determining this parameter were discussed in Chapter II, but it was not until the data

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<sup>\*</sup> Using this calculated geometry, a set of cartesian co-ordinates was generated and these plus observed shift ratios were put into the regular geometry program for the static case (Appendix C). An excellent fit was obtained (expected) thus confirming the above treatment.

for pyridine had been collected and reduced as a plot of  $[S]_0$  versus  $(1/\delta)$  that the vital importance of this particular aspect became apparent.

In Table 17 are listed the  $\Delta_{\rm B}$ -values for the protons of pyridine determined by ourselves and those from twoother independent groups.<sup>90,91</sup> It can be seen that the values for this parameter differ significantly from one group to another. It is particularly interesting that the limiting shifts of Group I <sup>90</sup> (for [S]<sub>0</sub> of 0.5 M) are larger than the limiting shifts from Group II <sup>91</sup> (for [S]<sub>0</sub> of 0.15 M). This is consistent with a probable dependence of the slope of a plot of  $\delta$  versus  $[{\rm L}]_0/[{\rm S}]_0$  (method used to determine  $\Delta_{\rm B}$ -values by groups I and II<sup>44</sup>) on [S]<sub>0</sub> as discussed in Chapter II. This dependence of the slope on IS]<sub>0</sub> suggests that the binding constant is small enough to affect the bound shift determinations and in fact we have measured the binding constant and found it to be 76 liter mole<sup>-1</sup> and thus from our data can accurately determine the stoichiometry to be 1:1.

Of particular significance in Table 17 is the variation in shift ratios among the various measurements. Other than ourselves, only Group II has made use of the shift ratios to determine the complex geometry and thus the geometry of the pyridine ring. Using the ratios as shown, they found the best agreement with calculated shift ratios was with a Eu-N bond distance of  $4.0 \pm .4$  Å. This calculated value for the Eu-N bond distance was based on measurements taken from a molecular model and not from a detailed computer analysis. However, the results from a detailed computer analysis using the ratios reported by Group II were even best encouraging. The best "fits" between calculated and

Group -	Pyridine	∆ <sub>B</sub> -Values, <sup>d</sup> p.p.m.	$\Delta_{B}^{-Ratios}$	Solvent
	Q	28.7	o/m = 2.90	CDC13
I <sup>a</sup>	m	9.9	o/p = 3.12	
	р	9.2		
	0	25.9	o/m = 2.88	cc1 <sub>4</sub>
II <sup>b</sup>	m	9.0	o/p = 3.16	
	p	8.2		
C	• <b>O</b>	23.8	o/m = 3.05	CDC13
IIIC	m P	7.8	o/p = 3.22	
a From	ref. 90.			
b From	ref. 91.			
c Our c	own work.			
d For (	(a) and (b)	, this parameter was $d$	letermined by linea	rly extrapolatin
a plo	ot of $\delta$ ver	$\frac{1}{[S]}$ to a $\frac{1}{[S]}$	<sup>2</sup> ratio of 1.0 (s	ee ref. 44).
For (	(c), the $\Delta_{\rm H}$	-values were obtained	from a plot of [S]	o versus (1/δ)
as ex	plained in	Chapter II.		

Table 17. Induced chemical shift data for association of pyridine with  $Eu(dpm)_3$ : three independent determinations.

experimental shift ratios were obtained with a Eu-N bond distance of  $\underline{ca}$ . 3.5 Å and with the Eu some 40° out of the plane of the ring. It is difficult to find any chemical evidence which would substantiate either of these values and there is obviously little interest in doing so in view of the excellent and chemically meaningful results presented previously.

This chapter has provided a number of models for derivation of molecular conformation in the presence of internal rotational motion by use of lanthanide shift reagents. All four molecules studied were rigid except at the point of attachment to the lanthanide and so provided the simplest type of problem for the analysis. The results show that determination of molecular geometry is straightforward and gives chemically reasonable results only in cases where: (i) the entire complex is relatively rigid as with 1 and 17 and, (ii) there is completely free internal rotation as with 16. For 16 and 11 it was shown that the presence of internal rotational motion, even when present only at the site of attachment to the lanthanide, can lead to either erroneous or un-determinative results respectively for attempts to find the "best" single (static) conformation of the bound complex. These results clearly demonstrate the difficulties, even for rigid substrates, which may be encountered when attempting to determine the bound conformations of substrates bound to lanthanide shift reagents. Thus, there is need for considerable caution (and a variety of motional models) in any attempt to treat polyfunctional and non-rigid substrates or both.

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#### GENERAL CONCLUSIONS

The foregoing investigations warrant a few general conclusions to bring the work presented in this thesis into perspective with present and certainly the future application of lanthanide shift reagents to organic n.m.r. spectroscopy. More specific conclusions have been presented within the Chapters and will not be reiterated

The primary theme and objective throughout this thesis has been to develop the necessary chemical and theoretical understanding for the ultimate use of lanthanide shift reagents to the determination of molecular conformation in solution. As a whole, therefore, this thesis represents the successful progression of our understanding and evaluation of the applications of lanthanide shift reagents to organic n.m.r. spectroscopy.

We have described numerous experimental optimizations and in addition have presented a detailed theoretical analysis of the lanthanide-substrate equilibrium which has permitted, for the first time, the chemical aspects of this equilibrium to be fully understood. In addition, this latter understanding has provided the basis on which rests present and future applications of lanthanide shift reagents to the determination of molecular structure. In Chapter III, we have successfully described in detail this particular aspect, as it pertains to a series of rigid organic substrates. We have demonstrated that geometry determinations are possible but not simple and considerable caution is advised in future applications to polyfunctional and/or nonrigid systems. In this connection, the use of <sup>13</sup>C shift ratios in conjunction with <sup>1</sup>H shift ratios, the use of broadening reagents, chemical derivatization and more detailed computer programing will assist in overcoming some of the problems which will be encountered when attempting to determine solution conformations of these more complex molecules.

In conclusion, it is the belief of this author that lanthanide shift reagents have become and will continue to be a routine and integral part of organic n.m.r. spectroscopy.

#### EXPERIMENTAL

The Experimental for this thesis has been divided into two parts. A. Techniques and experimental methods, synthesis and/or purification of compounds, for Chapter I.

B. Techniques and experimental methods, synthesis and/or purification of compounds not previously described in part A, for Chapters II and III.

The reason for this partitioning of the Experimental is twofold. (i) All <sup>1</sup>H and <sup>13</sup>C n.m.r. measurements discussed in Chapter I were made with a modified Varian HA-100 spectrometer, operating in the frequency-swept mode with a probe temperature of  $32.0^{\circ}$ C. Whereas, all <sup>1</sup>H n.m.r. measurements reported in Chapters II and III were made on a Varian XL-100 spectrometer, operating in the frequency-swept mode with a probe temperature of  $40.0^{\circ}$ C. (ii) In Chapter I, chemical shift changes induced by various  $Ln(dpm)_3$  complexes were measured as a function of the change in the concentration of the lanthanide shift reagent. In Chapters II and III on the other hand, the concentration of the lanthanide shift reagent was maintained constant (<u>ca</u>. 0.006 M) and the substrate concentration was varied. For both parts A and B, extreme precautions were taken to exclude moisture at all stages of the experiments.

<u>A</u>.

#### General Methods

(a) All <sup>1</sup>H n.m.r. measurements were made with a modified Varian HA-100 spectrometer, operating in the frequency-swept mode with a probe temperature of  $32.0^{\circ}$ C. For experiments using the europium, thulium, and gadolinium reagents, <u>5</u>, <u>6</u>, <u>9</u>, deuterochloroform solutions were used, with internal tetramethylsilane (TMS) as the reference signal for the field-frequency lock. Experiments with the praseodymium reagent, <u>7</u>, were made with chloroform solutions and the chloroform resonance was used to provide a lock signal; some TMS was added to provide a chemical shift reference.

(b) An account of the modifications necessary for the measurement of  ${}^{1}$ H-( ${}^{13}$ C) INDOR spectra has been described elsewhere.<sup>2</sup>  ${}^{13}$ C chemical shifts are reported in p.p.m. relative to TMS.

(c) When applicable, analyses of the n.m.r. spectra were made with a modified version of the  $LAØCN3^*$  program and an I.B.M. 360-67 computer.

(d) Melting points were performed on a Thomas-Hoover capillary m.p. apparatus and are corrected for thermometer error.

(e) Deuterochloroform (99.8%) from Merck Sharp and Dohme, Montreal, was stored over Linde molecular sieve (4A), which had been

Modifications were performed by R.B. Malcolm of the Department of Chemistry, U.B.C.

heated in an oven at 110°C for 24 hours, to both dry it and remove traces of acid which decompose the lanthanide complex. Carbon tetrachloride (A.R. Grade) was distilled and stored over NaOH pellets prior to use. Ethanol-free chloroform was obtained by standing A.R. Grade chloroform over granular, self-indicating silica gel.

(f) A sample of the lanthanide reagent was vacuum sublimed immediately prior to an experiment. The lanthanide was dissolved in either deuterochloroform, chloroform, or carbon tetrachloride (<u>ca</u>. 0.04 g/ml). Aliquots of this standard solution were added via a 0.10 ml syringe to a solution of the carbohydrate (<u>ca</u>. 0.18 g/ml). After purification and/or sublimation, all further handling of the lanthanide reagent and carbohydrate was carried out in a glove bag flushed with dry nitrogen.

(g) The preparation of all solutions was conducted under dry nitrogen in a glove bag using apparatus that had been baked at 110°C immediately prior to use.

### Synthesis and Purification of Compounds

(a) The carbohydrate derivatives, <u>1</u>, <u>2</u>, and <u>3</u>, were stock samples which were recrystallized twice from  $CHCl_3$ -hexane 1:2 v/v. Crystals were then dried in vacuum at the temperature of boiling methylene chloride for 12-20 hours, immediately prior to use. M.p.s were determined as follows:

<u>1</u> 103-105°C <u>2</u> 73.5-74.8°C 3 57.5-58.5°C The n.m.r. parameters were in entire accord with the assigned structures.

(b) 2,2-Dimethyl-1-propanol (<u>neo-pentanol</u>), <u>8</u>, was purchased from Matheson Coleman and Bell and was purified by distillation from calcium hydride. The material had a b.p. of 114°C.

(c) Tris(dipivalomethanato)europium (III), 5, was prepared from europium oxide<sup>\*</sup> (99.99%) following the method of Eisentraut and Sievers.<sup>16</sup> Yield was greater than 95%. The material from the reaction was stored in a vacuum desiccator containing phosphorus pentoxide. A small sample was vacuum sublimed at 140°C at 0.1 mm Hg or lower immediately prior to an experiment. In the above synthesis, the europium oxide is dissolved in an excess of 15.4 M HNO<sub>3</sub> to prepare the hydrated europium(III) nitrate - Eu(NO<sub>3</sub>)·xH<sub>2</sub>O. Care must be taken at this stage to ensure all excess HNO<sub>3</sub> is removed with the help of a steam bath or preferably using a rotary evaporator. Any excess acid remaining at this step will cause a decomposition of the final product - Eu(dpm)<sub>3</sub>. The thulium reagent, <u>6</u>, the praseodymium reagent, <u>7</u>, and the gadolinium reagent, <u>9</u> were prepared by the same method, starting with the corresponding nitrate salt.<sup>\*</sup> 2,2,6,6-Tetramethyl-3,5-heptanedione (dpm) was purchased from Eastman Organic Chemicals.

(d)  $3-\underline{0}-Acetyl-1,2:5,6-di-\underline{0}-isopropylidene-\alpha-\underline{D}-allofuranose, 4,$ was prepared from 1,2:5,6-di- $\underline{0}$ -isopropylidene- $\alpha$ - $\underline{D}$ -allofuranose, 2, as described in the literature,<sup>92</sup> using excess acetic anhydride in dry pyridine. Product was recrystallized twice from ethanol-water mixture and then vacuum dried for 48 hours at the b.p. of methylene chloride.

\*

Obtained from Alfa Inorganics, Inc.

The yield was approximately 70% and had a m.p. of 73.5-74°C.

(e) 5-Hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene, <u>11</u>, was prepared from the hydrolysis of the adduct of vinyl acetate with hexachlorocyclopentadiene following the procedure of E.K. Fields.<sup>93</sup> This procedure was deviated from in that the alcohol adduct <u>11</u> was extracted from the water with CHCl<sub>3</sub> which was subsequently evaporated off under reduced pressure to give a syrup. This was then treated twice with decolourizing charcoal and the resulting crystals recrystallized from n-heptane. Product was further purified by vacuum sublimation immediately prior to use and had a m.p. of 153.5-154.0°C.

# <u>B</u>.

# General Methods

(a) All <sup>1</sup>H n.m.r. measurements were made with a Varian XL-100 operating in the frequency-swept mode with a probe temperature of 40.0°C. Tetramethylsilane (TMS) was used as the internal reference signal for the field-frequency lock for the experiments using deuterochloroform, deuterobenzene or carbon tetrachloride as solvents. Experiments with chloroform or benzene solutions used the chloroform resonance or the benzene resonance respectively to provide a lock signal; some TMS was added to provide a chemical shift reference.

(b) Deuterobenzene (99.8%) from Merck Sharp and Dohme, Montreal, and benzene (A.R. Grade) were stored over Linde molecular sieve (4A), which had been heated in an oven at 110°C for 24 hours prior to use. Other solvents were purified and/or dried as described in part A.

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(c) The preparation of all solutions was conducted under dry nitrogen in a glove bag using apparatus that had been baked at 110°C immediately prior to use.

(d) All plots of the experimental data were made with a Hewlett-Packard Calculator (model 9100B) and a Hewlett-Packard Calculator Plotter (model 9125A).

(e) <u>Method 1</u>. <u>Constant [S]</u>, Varying [L]

A series of standard solutions, each containing a known amount of the substrate (<u>ca</u>. 0.6, 0.2, 0.08, 0.04 M) was prepared. One particular standard solution was then selected and 1.0 ml of this solution was used to dissolve a known quantity of the lanthanide reagent (<u>ca</u>. 0.015 g, 0.02 M of  $Ln(dpm)_3$ ; <u>ca</u>. 0.190 g, 0.175 M of  $Ln(fod)_3$ ). The spectrum of this mixture then gave the maximum shift. Further spectra were run after each successive addition of a 0.10 ml aliquot of the standard substrate solution. In each case the observed shift decreased.

# (f) Method 2. Constant [L], Varying [S]

The lanthanide reagent (<u>ca</u>. 0.042 g, 0.012 M of  $Ln(dpm)_3$ ; <u>ca</u>. 0.070 g, 0.012 M of  $Eu(fod)_3$ ) was dissolved in 4.8 ml of solvent and 0.2 ml tetramethylsilane in a 5.0 ml volumetric flask. The substrate was separately dissolved in 5.0 ml of the same solvent. Aliquots (0.50 ml) of the lanthanide solution were then added to each of a series of 5-10 graduated 1.0 ml flasks. To each of these flasks was now added varying amounts of the stock solution of substrate; e.g., vial 1, 0.5 ml; vial 2, 0.4 ml; etc. The content of each flask was then made up to 1.0 ml by further addition of solvent. Each solution was then placed in a separate n.m.r. tube which was capped and stored in a thermostatted water bath prior to measurement.

(g) Appendix B, C and D contain a listing of the computer programs used to determine the complex conformation. Details, for the understanding and possible use of these programs, are provided in the form of comment statements which have been appropriately situated throughout the programs. A brief discussion of the necessary input data for each of these programs will be presented at the beginning of each Appendix.

## Synthesis and Purification of Compounds

(a) Tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III), <u>13</u>, was prepared from europium oxide (99.99%) following the method of Springer et al.<sup>94</sup> Yield was greater than 95%. The complex was recrystallized twice from methylene chloride and was thereafter stored in a vacuum desiccator containing phosphorus pentoxide. This is important because it has been reported<sup>17</sup> that the anhydrous fod complex absorbs one mol equiv of water when allowed to stand unprotected in a moist atmosphere. All further manipulations were carried out in a glove bag which had been flushed several times with dry nitrogen.

(b) <u>n</u>-Propylamine, <u>12</u>, from Eastman Organic Chemicals was purified by distillation from KOH pellets into a sealed receiver also containing KOH pellets. The material had a b.p. of  $49.0^{\circ}$ C.

(c) Bicyclo[2.2.1]heptan-2-one(norcamphor), <u>14</u>, from Aldrich Chemical Company was vacuum distilled at 120°C into a receiver containing KOH pellets. The material had a m.p. of 94-95°C.

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(d) <u>n</u>-Propanol, <u>15</u>, was purified by distillation from calcium hydride. The material had a b.p. of 98.7°C.

(e) Aniline (reagent grade), <u>16</u>, from British Drug Houses Ltd. was purified as follows.<sup>95</sup> 10.0 ml was distilled from a small amount of zinc dust and a 4.0 ml fraction collected from the middle: b.p. of 183°C.

(f) Pyridine, <u>17</u>, was purified by refluxing over KOH pellets for <u>ca</u>. 1 hour and then distilling into a sealed receiver also containing KOH pellets. The material had a b.p. of 114.2°C.

(g) 2,2-Dimethyl-3-butanone, <u>18</u>, from Aldrich Chemical Company was purified by distillation from  $MgSO_4$  into a sealed receiver also containing  $MgSO_4$ . The material had a b.p. of 106-107°C.

(h) The carbohydrate derivatives, <u>19</u>, <u>20</u>, and <u>21</u>, existed as pure stock samples in the laboratory. Crystals were dried in vacuum at the temperature of boiling methylene chloride for 12-20 hours, immediately prior to use. The n.m.r. parameters were in entire accord with the assigned structures.

 (i) Acenaphthenone, <u>22</u>, was a stock sample which was vacuum
 sublimed at 85°C at 0.3 mm Hg immediately prior to use: m.p. of 118-119.5°C.

(i) The dimethylaminocyclophosphonitriles, <u>23</u> to <u>27</u>, were obtained from N.L. Paddock and J.N. Wingfield, Department of Chemistry, U.B.C. The stable complex which was obtained by reacting  $Eu(fod)_3$ (1.0 mole equivalents) with 1.0 moles of  $N_9P_9(NMe_2)_{18}$  was prepared by the following method. 0.255 grams of  $Eu(fod)_3$  was added to a solution of 0.292 grams  $N_9P_9(NMe_2)_{18}$  in anhydrous carbon tetrachloride. The flask was sealed and the solution stirred at room temperature for 80 hours. Solvent was removed by vacuum distillation to give a white solid which melted to a paste at 60°C in a water bath. All attempts to purify the product by recrystallization and by eluting the product down an alumina column failed, giving only the pure nonamer, m.p. 232-234°C. The n.m.r. spectrum shown in Fig. 19C was thus recorded for the crude product.

## APPENDIX A

Calculation of  $r_i$  and  $\theta_i$  from R,  $\Omega$ , and  $\phi$ .

Referring to Figures 21A and 21B, it is convenient to deal with the following quantities:

r
i = distance vector between lanthanide atom and i'th proton of
 substrate;

 $\vec{R}$  = lanthanide-donor atom distance vector;

 $\hat{\vec{R}}$ ' = lanthanide - x-axis distance vector;

$$\theta_{i}$$
 = angle between  $\vec{R}$  and  $\vec{r}_{i}$ ;

- $\Omega$  = angle between  $\overline{R}$  and the x-axis;
- $\phi$  = angle between  $\vec{R}$ ' and y-axis (a measure of the angle of internal rotation of the lanthanide-donor bond axis about the bond axis from the donor atom to atom #2).

It is expedient to compute  $\cos^2 \theta_i$  directly from the dot product of  $\vec{R}$  and  $\vec{r_i}$ :

Eq [1] 
$$\cos^2 \theta_i = \{\frac{\vec{r}_i \cdot \vec{R}}{|\vec{r}_i| |\vec{R}|}\}$$

One can now write,

Eq [2] 
$$\frac{3\cos^2\theta_{i} - 1}{|\vec{r}_{i}|^3} = \frac{3(\vec{r}_{i} \cdot \vec{R})^2 - |\vec{R}|^2 |\vec{r}_{i}|^2}{|\vec{R}|^2 |\vec{r}_{i}|^5}$$

but  $\vec{r}_i = \vec{R} - \vec{r}_i'$ ,

and 
$$\vec{r_i'} = x_i \vec{i} + y_i \vec{j} + z_i \vec{k}$$
, where  $x_i, y_i, z_i$  are  
co-ordinates of the i'th  
proton,

$$\vec{R} = |\vec{R}| \cos \Omega \quad \vec{i} + |\vec{R}| \sin \Omega \cos \phi \quad \vec{j} + |\vec{R}| \sin \Omega \sin \phi \quad \vec{k}.$$

Substitution into Eq. [2] followed by some rearrangement gives the final result:

1

Eq. [3] 
$$\frac{3\cos^2\theta_{i} - 1}{|\vec{r}_{i}|^3} = \frac{2|\vec{R}|^2 - 4|\vec{R}|Q + 3Q^2 - |\vec{r}_{i}|^2}{(|\vec{r}_{i}|^2 + |\vec{R}|^2 - 2|\vec{R}|Q)^{5/2}},$$

where  $|\vec{r}_{i}|^{2} = x_{i}^{2} + y_{i}^{2} + z_{i}^{2}$ ,

and  $Q = x_i \cos \Omega + y_i \sin \Omega \cos \phi + z_i \sin \Omega \sin \phi$ .

## APPENDIX B

This computer program, COORD, written in Fortran was used to calculate the atomic cartesian co-ordinates for molecules given bond lengths, bond angles and dihedral angles. These values must be obtained from X-ray or microwave studies of the molecule or related molecules. Comment statements, appropriately spaced throughout the program explain the operational procedures of the program and the format required to read in the necessary data. The substrate atoms are numbered consecutively and if the calculated cartesian co-ordinates are required for input data to the geometry programs (Appendices C and D), atom #1 must be assigned to the donor atom.

С THIS PROGRAM AS STANDS WILL TAKE UP TO 24 ATOMS PER MOLECULE С С С С THIS PROGRAMME CALCULATES THE COORDINATES IN A 3 DIMENSIONAL С SPACE GIVEN THE BOND LENGTHS, BOND ANGLES, AND DIHEDRAL С THIS IS AN ADAPTATION OF PROGRAM COORD WRITTEN ORIGINALLY BY DEWAR С THE FIRST CARD HAS THE NAME OF THE MOLECULE (OR OTHER HEADING) С IN THE FIRST 36 COLUMNS С С С NOAT IS THE NUMBER OF ATOMS. R12 IS THE BOND DISTANCE FROM ATOM С 1 TO ATOM 2, R23 IS THE BOND DISTANCE FROM ATOM 2 TO 3, ETC. TH123 С IS THE 123 BOND ANGLE С C С С С С DIMENSION X (24), Y (24), Z (24), R (24, 24), NAME (9) CALL PLOTS С IKQ IS THE NUMBER OF MOLECULES FOR WHICH THE PROGRAM WILL CALCULATE С THE COORDINATES FOR IKQ=1DO 1111 LOVEU = 1.IKQ45 REAC 900 (NAME(I), I=1, 9)900 9A4) FORMAT ( WRITE(6,950) (NAME(I), I=1,9) 950 FORMAT (1H1, 9A4) READ (5,901) NOAT, R12, R23, TH123 901 12,2F7.4, P14.7) FORMAT ( WRITE (6,952) R12, R23, TH123, NOAT 952 FORMAT (7H R 12 = F7.4, 10H)R23 = F7.4, 10H TH123 = , 1PE10.3, 5X,,12) 117HNUMBER OF ATOMS= 3 THETA=TH123\*3.1415926536/180. CCOS=COS (THETA) SSIN=SIN (THETA) 4 DO 51 I=1,3X(I) = 0.0Y(I) = 0.051 Z(I) =0.0 X(2) = R12X(3) = R12 - R23 + CCOSY(3) = R23 \* SSINDO 5 I = 4, NOAT 5 X(I) = 10000.0WRITE (6,953) 953 NB NC ILAZY RCD FORMAT (88HO N A ND 1 THBCD PHABCD/) С С С ATOMS NA, NB, NC, HAVE KNOWN COORDINATES AND ARE NOT COLLINEAR. С THBCD IS THE BCD BOND ANGLE IN DEGREES AND PHABCD IS THE DIHEDRAL С ANGLE OF CD RELATIVE TO AB, MEASURED CLOCKWISE ALONG THE DIRECTION С ILAZY ALLOWS AUTOMATIC CALCULATION OF ANGLES IN NORMAL B TO C. С TETRAHEDRAL AND PLANAR SYSTEMS. 2LAZY = 0, 1, 2, 3, 4, 5; TETRAHECRAL С WITH DIHEDRAL ANGLES OF 0,60,120,180,240, AND 310 DEGREES

ILAZY= 6,7 ; PLANAR CIS, TRANS RESPECTIVELY.

С

RESPECTIVELY.

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C · ILAZY=8 : ATOMS B,C,D ARE COLLINEAR. ILAZY = 9 ; DATA WILL SUPPLY С. ANGLES. С DO 52 I=4, NOAT READ (5,902) NA, NB, NC, ND, ILAZY, RCD, THBCD, PHABCD 902 FORMAT (412, 2X, 11, F7.4, 2F14.7) С С CHECK TO SEE THAT COORDINATES OF ATOM NA, NB, AND NC HAVE BEEN С CALCULATED C 7 IF (X(NA) + X(NB) + X(NC) - 7000.0) 8, 50, 50 8 ILAZY, RCD, THBCD, PHABCD WRITE (6,954) NA, NB, NC, ND, 954 FORMAT (3X,12,3X,12,3X,12,3X,12, 18X, I1, 7X, F7.4, 8X, E14.7, 4X, 1E14.7IF (ILAZY - 8) 79, 78, 79 78 RBC=SQRT ((X (N C) -X (NE)) \*\*2+ (Y (NC) -Y (NB)) \*\*2+ (Z (NC) -Z (NB)) \*\*2) X(ND) = X(NC) + (X(NC) - X(NB)) \*RCD/RBCY(ND) = Y(NC) + (Y(NC) - Y(NB)) + RCD/RBCZ(ND) = Z(NC) + (Z(NC) - Z(NB)) \* RCD/RBCGO TO 52 С С С MOVE ATOM NC TO THE ORIGIN С 79 XA = X(NA) - X(NC)YA = Y(NA) - Y(NC)ZA = Z(NA) - Z(NC)XB = X(NB) - X(NC)YB = Y(NB) - Y(NC)ZB = Z(NB) - Z(NC)С С ROTATE ABOUT Z AXIS TO MAKE YE=0, XB IS POSITIVE. IF XYB IS TOO С SMALL, ROTATE FIRST 90 DEGREES ABOUT Y AXIS С XYB=SQRT(XB\*\*2+YB\*\*2)K = 1IF (XXB - 0.1) 9, 10, 10 9 K = 0XPA = ZAZPA = -XAXA = XPAZA = ZPAXPE = ZBZPE = -XBXB = XPBZB = ZPEXYB=SQR% (XB\*\*2+YB\*\*2) 10 COSTH = XB/XYBSINTH = YB/XYBXPA = XA\*COSTH + YA\*SINTH YPA = YA \* COSTH - XA \* SINTHС С ROTATE ABOUT Y AXIS TO MAKE ZE VANISH С 11 RBC=SQRT (XB\*\*2+YB\*\*2+2B\*\*2) SINFH = ZB/RBC COSPH=SQRT (1.-SINPH\*\*2) XQA = XPA\*COSPH + ZA\*SINPHZQA = ZA \* COSPH - XPA \* SINPH

С

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• .
С
      ROTATE ABOUT X AXIS TO MAKE ZA=0 , YA POSITIVE
12
      YZA=SQRT(YPA++2+ZQA++2)
      COSKH = YPA/YZA
      SINKH = ZQA/YZA
      IF (ILAZY - 1) 13, 14, 15
13
      COSD = 1.0
      SIND = 0
С
С
     COORDINATE A, (XQA,YZA,O): B, (RBC,O,O); C, (0,0,0); NONE ARE NEGATIVE
С
        COCRDINATES OF D NOW CALCULATED IN NEW FRAME
С
      GO TO 21
14
      COSD = 0.5
      SINC=0.5*SQRT(3.)
      GO TO 21
15
      IF (ILAZY - 3) 16, 17, 18
16
      COSD = -0.5
      SIND=0.5*SQRT (3.)
      GO TO 21
17
      COSD = -1.0
      SIND = 0
      GO TO 21
18
      IF (ILAZY - 5) 19, 20, 22
19
      COSD = -0.5
      SIND=-0.5*SQRT(3.)
      GO TO 21
20
      COSD = 0.5
      SIND=-0.5*SQRT(3.)
21
      COSA = -1.0/3.0
      SINA = (2./3.) * SQRT (2.)
      GO TO 29
22
      IF (ILAZY - 7) 23, 24, 26
23
      COSD \neq 1.0
      SINC = 0
      GO TO 25
24
      COSD = -1.0
      SIND = 0
25
      COSA = -0.5
      SINA=0.5 \neq SQRT(3.)
      GO TO 29
26
      IF (ILAZY - 9) 27, 28, 28
27
      CONTINUE
      GO TO 29
28
      THBCD=THECD*3.1415926536/180.
      PHABCD=PHABCD*3.1415926536/180.
      SINA=SIN (THBCD)
      COSA=COS (THBCD)
      SINC=SIN (PHABCD)
      COSD=COS (PHABCD)
29
      CONTINUE
      XD = RCD * COSA
      YD = RCD*SINA*COSD
      ZD = BCD + SINA + SIND
С
С
       TRANSFORM COORDINATES OF D BACK TO ORIGINAL SYSTEM
С
30
      YPD = YD*COSKH - ZD*SINKH
      ZPD = ZD*COSKH + YD*SINKH
      XPD = XD*COSPH - ZPD*SINPH
      ZQD = ZPD + COSPH + XD + SINPH
```

```
XQD = XPD * COSTH - YPD * SINTH
      YQD = YPD * COSTH + XPD * SINTH
      IF (K - 1) 31, 32, 31
31
      XRD = -ZOD
      ZRD = XQD
      XOD = XRD
      ZQD = ZRD
32
      X(ND) = XQD + X(NC)
      Y(ND) = YQD + Y(NC)
      Z(ND) = ZQD + Z(NC)
52
      CONTINUE
C
С
      PRINT 69
   69 FORMAT (///
                    94H THE ABOVE FEW LINES ARE JUST A REHASH OF THE INPU
     1T INFO. IN CASE ONE LACKS SELF-CONFIDENCE
                                                                32H
                                                                     NA=ATOM A
     2, N1= ATOM 1, ETC.
                            / 96H COORDINATES FOR ATOMS A, B, AND C ARE
     3 KNCWN, EACH CARD THEN SOVES FOR THE POSITION OF ATOM D
     LL.
        95H RCD= DISTANCE FROM ATOM C TO ATOM D : THBCD= ANGLE DEFINED
     5 BY ATOMS B,C,D: C BEING THE APEX:
                                                              50HPHABCD= DIHE
     6DRAL ANGLE OF THE ABC AND BCD PLANES
                                                         )
С
С
      WRITE (6, 950) (NAME (I), I=1,9
                                          )
      WRITE (6,955)
955
      FORMAT (78HONO. OF ATOM
                                                                  Y-COORDINAT
                                          X-COORDINATE
     1 E
                  Z-COORDINATE/)
      DO 41 I=1, NOAT
      WRITE (6,956) I, X (I), Y (I), Z (I)
956
      FORMAT (1H ,5X, 12, 15X, F10.7, 11X, F10.7, 11X, F10.7)
      PUNCH 881 , X(I) , Y(I) , Z(I)
  881 FORMAT (3 (1PE10.3))
41
      CONTINUE
      DO 88 I=1, NOAT
      DO 88 J=1, NOAT
88
      R(I,J) = SQRT((X(I) - X(J)) **2*(Y(I) - Y(J)) **2*(Z(I) - Z(J)) **2)
      WRITE (6, 950) (NAME (I), I=1, 9
                                          )
      WRITE (6,957)
957
      FORMAT (1H0, 21HINTERATOMIC DISTANCES, //)
С
С
      THE NEXT TWENTY OR SO STATEMENTS FORM A PRINT LOOP WHICH DOES NO
С
        MCRE THAN PRINT OUT THE ELEMENTS OR MATRIX R , THE INTERATOMIC
С
       DISTANCES MATRIX.
С
      NC= NUMBER OF COLUMNS IN PRINT OUT. PLEASE NOTE FORMAT111 BEFORE
С
       BECOMING ORIGINAL. LET'S LET NC = 10.
      NC = 10
      KK=0
      NCM1 = NC-1
      NICE =0
      DO 105 IZ=1, NOAT, NC
      JOY = IZ + NCM1
      IF (JOY.GT. NOAT) JOY=NOAT
       THE NEXT STATEMENT MAKES SURE YOU DON'T HAVE A DATA SET STRATIFIED
С
С
       BETWEEN TWO PAGES. (I.E. 52 LINES/PAGE MAX.)
      NICE = NICE+ NOAT
      IF (NICE-52) 106, 107, 107
  107 \text{ LIKE} = 0
      NICE = 0
      GO TO 108
  106 \text{ LIKE} = 1
```

- 180 -

```
- 181 -
  108 CONTINUE
      IF (LIKE+KK-1) 102,103,103
  101 FORMAT (1H1)
  102 PRINT 101
  103 PRINT 104 , (MUCK, MUCK=IZ, JOY)
  104 FORMAT (1H0,/10110)
  109 DO 112 IRS=1, NOAT
  112 PRINT111, IRS, (R(IRS,ICS), ICS=IZ, JOY)
  111 FORMAT (1H I2,2X,10(1PE10.3))
  105 CONTINUE
С
      CALL TRAIL (NOAT, X,Y,Z)
 1111 CONTINUE
      GO TO 665
50
      WRITE (6.958)
958
      FORMAT (1H0,38HCCORDS.OF 1 REFFRENCE ATOM UNAVAILABLE)
  665 CONTINUE
      CALL PLOTND
      STOP
      ENC
      SUBROUTINE TRAIL (NOAT, X,Y,Z)
С
С
       TRAIL PLOTS OUT THE POINTS IN 2: (WITH A 3D FLAVOR)
С
      NOAT IS THE NUMBER OF ATOMS TO BE PLOTTED
С
     X,Y,Z ARE THE COLUMN MATRICES CONTAINING THE ATOMIC COORDINATES
Ċ
     N IS THE NUMBER OF DIMENSIONS X,Y, AND Z ARE GIVEN IN THE MAIN
С
           HANDLE UP TO NOAT = 24
      CAN
С
      DIMENSION X(24), Y(24), Z(24), ZP(24), YP(24), HT(24)
      XMAXI = 0.
      XMINI = 0.
                       XMAXI, XMINI, NOAT)
      CALL PAT (X,
      OP = XMAXI - XMINI
      DO 79 MP= 1, NOAT
      ZP(MP) = -X(MP) * 0.5 + Z(HP)
      YP(MP) = -X(MP) * 0.5 + Y(MP)
   79 HT (MP) = (X (MP) - XMINI) /QP *0.56 + 0.14
      CALL SCALE (2P, NOAT, 10., YMIN, DY, 1)
      CALL SCALE (YP, NOAT, 10., XMIN, DX, 1)
      DO 779 MP=1, NOAT
      ZZZ = MP
  779 CALL SYMECL (YP (MP), ZP (MP), HT (MP), 01, 0., -1)
      CALL PLOT (12, 0, -3)
      RETURN
      END
      SUBROUTINE PAT (X, XMAXI, XHINI, NOAT)
С
С
      X IS A VECTOR OF NOAT DIMENSIONS OF WHICH THE LARGEST AND
С
     SMALLEST VALUES ARE TO BE FOUND. N IS THE DIMENSION OF THE TOTAL
С
    RESIDING SPACE OF WHICH NOAT MAY BE ONLY A SUBSPACE
С
    XMINI AND XMAXI WILL BE RETURNED AS THE MAXIMUM AND MINIMUM VALUES
С
       OF X
С
      DIMENSION X(24)
      XMAXI = X(1)
      DO 3 J=2, NOAT
      IF(XMAXI-X(J)) 2,2,3
    2 \times MAXI = X(J)
```

3 CONTINUE  

$$XMINI = X (1)$$
  
 $DO \ 4 \ J=2, NOAT$   
 $IF (XMINI-X (J)) \ 4,4,5$   
5  $XMINI = X (J)$   
4 CONTINUE  
RETURN  
END

۰.

`

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,

.

## APPENDIX C

This computer program was used to determine complex conformation for a rigidly locked complex (Eq. [3], Chapter III). Input data to this program includes: the initial value for the Eu-donor atom bond distance (R), bond angle ( $\Omega$ ), dihedral angle ( $\phi$ ), and the range over which these values are to be varied; the experimentally observed shift ratios; the cartesian co-ordinates for each atom considered. Numerous comment statements are appropriately spaced throughout the program to assist in explaining the specific computations carried out in this program.

```
- 184 -
       DIMENSION X (24), Y (24), Z (24), DX (24), DY (24), DZ (24), DIST (24)
                          , UNCER (6), RATIO (6), WT (6)
      1,DOT (24),SD (6)
       DIMENSION ZZ (24, 24), THEDAA (24), RR (24)
       DIMENSION NAME(6)
       PI = 3.141593
С
С
       THIS PROGRAM IS FOR A RIGIDLY LOCKED COMPLEX
С
       TAKE NOTE OF CO-ORDINATE CONVENTION
С
       READ 700, (NAME(I), I=1, 6)
       PRINT 701, (NAME(I), I=1,6)
  700 FORMAT (6A4)
  701 FORMAT (1H1, 6A4)
       READ 1, NUMHYD
     1 FORMAT(I1)
С
С
       NUJ = NUMHYD-1
С
       NUMHYD IS THE NUMBER OF HYDROGENS WHICH SHIFT RATIOS ARE TO BE
С
      CALCULATED THEORETICALLY AND FITTED TO EXPERIMENTAL VALUES
С
С
       READ 101, NTHEDA, NPHI, NRAD, DTHEDA, DPHI, DR
  101 \text{ FORMAT}(3(12), 3(E10.3))
С
С
С
       ALL INPUT ANGLES AND INCREMENTS ARE IN DEGREES
С
       DISTANCES I.E. RINT AND DR ARE IN ANGSTROMS
С
       NTHEDA = NUMBER OF INCREMENTS OF THEDA TO BE CONSIDERED (<21)
С
              = NUMBER OF INCREMENTS OF PHI
                                                TO BE CONSIDERED (<21)
       NPHI
C
              = NUMBER OF INCREMENTS OF BOND DISTANCES TO BE CONSIDERED
      NRAC
С
      DTHEDA = SIZE OF INCREMENT OF THEDA TO BE CONSIDERED
C
              = SIZE OF INCREMENT OF PHI
                                             TO BE CONSIDERED
      CPHI
C
              = SIZE OF INCREMENT OF BOND TO BE CONSIDERED
      DR
С
      NOTE: NTHEDA*DTHEDA-1= RANGE CF VALUES OF THEDA SCANNED, SAME FOR
С
      OTHER VALUES
С
С
      REAE 102, THEDAI, PHII, RINT
  102 FORMAT (3 (E10.3))
Ç
C
С
      THESE ARE THE INITIAL VALUES FOR THEDA, PHI AND BOND DISTANCE
С
      RESPECTIVELY
· C
      PRINT 337
  337 FORMAT (1H1, 9HVARIABLE ,5X13HINITIAL VALUE, 5X21HINCREMENTAL INCRE
            ,5X21HNUMBER OF INCREMENTS
      1ASE
                                         - 7)
      PRINT 338, RINT, DR, NRAD, THEDAI, DTHEDA, NTHEDA, PHII, DPHI, NPHI
  338 FORMAT (2X, 9HBOND DIST , 5XF5.2, 18XF5.3, 18X12 /
                   ,8XF6.1,2X3HDEG,15XF5.2, 3HDEG , 15XI3 /
      1 1X5HTHEDA
                   ,8XF6.1,2X3HDEG,15XF5.2, 3HDEG , 15XI3 /
     2 1X5HPHI
                                                                  )
      THECAI = THEDAI*PI/180.
      PHII = PHII*PI/180.
      DTHEDA = DTHEDA*PI/180.
      DPHI = DPHI*PI/180.
С
      PRINT 612
  612 FORMAT (//99HSTOP A MOMENT; DO THESE NUMBERS BELOW LOCK AT ALL FAMI
```

```
- 185 -
     1LIAR? IF NOT WE HAD BETTER OUIT HERE!
                                                                 )
С
С
С
С
Ç
      AA = 0.0
С
      AA IS A PARAMETER TO BE USED LATER ON IN NORMALIZING ERROR MEASURE
      DO 661 MM=1,NUJ
      READ 2,
                RATIO (MM), UNCER (MM), WT (MM)
      AA = RATIO(MM) * RATIO(MM) * WT(MM) + AA
      PRINT 2, RATIO (MM), UNCER (MM), WT (MM)
С
      WT DEFINES THE WEIGHTS ASSIGNED TO EACH RATIO FOR FINDING THE LEAST
C
      DISTANCE VALUES. N.B. SUM OF THE WEIGHTS = 1.
    2 FORMAT (3( E10.3))
  661 CONTINUE
С
С
      THE RATIOS ARE THE EXPERIMENTALLY DETERMINED
                                                      SHIFT RATIOS FOR ATOM
С
      ONE /ATOM 2: ATOM 1 / ATOM 3: ATOM 2 / ATOM 3 : IF NUMHYD = 3
С
      IN THAT ORDER *****???
С
C
      IF NUMHYD = 4 THEN RATIOS ARE 1/2; 1/3; 1/4; 2/
С
      UNCER GIVES THE UNCERTAINTIES IN EACH RESPECTIVE SHIFT RATIO. I.E.,
С
      IF THE CALCULATED RATIO IS WITHIN UNCER OF THE EXPERIMENTAL RATIO,
С
      THEN THE POINT WILL WARRANT FURTHER CONSIDERATION
С
С
С
С
      THIS STATEMENT READS IN THE VALUES OF THE X,Y, AND Z CO-ORDINATES
С
      FOR EACH ATOM (MUST BE COMPUTED ELSEWHERE, I.E. COORD ETC.)
      DO 3 I=1, NUMHYD
      READ 29, X(I), Y(I), Z(I)
      PRINT 29, X(I), Y(I), Z(I)
   29 FORMAT(3(
                E10.3))
    3 CONTINUE
С
C
      PRINT 333
                                  ,1X,12HDISTANCE-ANG ,5X,9HTHEDA-DEG ,6X
  333 FORMAT (1H1
     1, 3HPHI, 10X, 7HEPSILON
                                11)
С
С
      PHI = PHII
      DO 23 LP =1, NPHI
      HI = 180.*PHI /PI
      R = RINT
      DO 21 LR = 1, NRAD
      THEDA = THEDAI
      DO 22 LT=1,NTHEDA
      HEDA = 180.* THEDA/PI
           = R*COS (THEDA)
      XE
           = R*SIN (THEDA) * COS (PHI)
      YE
      ZE = R* SIN (THEDA) *SIN (PHI)
Ç
                  THE ATOM TO WHICH EU IS "BONDED" TO IS ASSUMED TO
      NOTE N.B.
С
       HAVE MOLECULAR COORDINATES (0,0,0). BE SURE YOUR DATA POINTS ARE
С
      RELATIVE TO THIS REFERENCE POINT
      DO 8 L=1,NUMHYD
С
С
С
      THIS NEXT PORTION GIVES THE POSITION VECTORS TO EACH ATOM WITH
```

```
С
        VECTORS HEAD SET AT THE EU ATOM
·C
        DX(L) = (XE)
                       - X(L))
                       - Y(L))
        DY(L) = (YE)
        DZ(L) = (ZE)
                       - Z(L))
 С
 С
        DIST GIVES THE ABSOLUTE VALUE FOR EACH OF THESE ATOMIC POSITION
 С
        VECTORS.
 С
        DOT GIVES THE SCALAR PRODUCT OF EACH POSITION VECTOR DOTTED WITH TH
 С
        EU-COMPLEX BOND VECTOR.
 С
        DIST(L) = SQRT(DX(L) * DX(L) + CY(L) * DY(L) + DZ(L) * DZ(L))
        DOT (L) = (XE *DX(L) + YE *DY(L) + ZE *DZ(L))/(DIST(L)*R)
     8 CONTINUE
        DO 108 KB=2, NUMHYD
        SD(KB-1) = (3.*DOT(1)*DOT(1) -1.) *DIST(KB) **3 /
       1 ((DIST(1) **3) * (3.*DOT(KB) *DOT(KB) -1.))
        SD(KB-1) = SD(KB-1) + SB
   108 CONTINUE
        EPS = 0.
        DO 62 IG=1, NUJ
    62 \text{ EPS} = WT(IG) * ((RATIO(IG) - SD(IG)) * 2) + EPS
        EPSQ = SQRT (EPS/AA)
        PRINT 33.
                          R, HEDA, HI, EPSQ
    33 FORMAT (
                          2X, F5.2, 10X, F6.1, 10XF6.1, 10X, 1PE10.3)
    67 CONTINUE
        ZZ(LR,LT) = EPSQ
        THEDAA(LT) = HEDA
    22 THEDA = THEDA+ DTHEDA
        RR(LR) = R
    21 R = R + DR
 С
 С
 С
        PLOTTING INSERTION
 С
 С
        CALL SCALE ( RR , LR, 10., XMIN, DX, 1)
        CALL SCALE (THEDAA, LT, 10., YBIN, DY, 1)
       CALL AXIS ( 0., 0., 12HBOND DIST. ,-10, 10., 0., XMIN, DX)
CALL AXIS ( 0., 0., 10HBOND ANGLE , 10, 10., 90., YMIN, DY)
        CALL NUMBER (2., 10.2, 0.14, HI, 0., -1)
        CALL SYMBOL (4., 10.2, 0.14, 17HCOMPOUND NAME
                                                               , 0., 17)
        PLOT THE CONTOURS
 С
        CN = 0.02
        CALL CNTOUR (RR, LR, THEDAA, LT, ZZ, 24, CN, 3., CN)
        CN = 0.04
        DO 200 I=1.7
        CALL CNTOUR (RR, LR, THEDAA, LT, ZZ, 24, CN, 3., CN )
   200 \text{ CN} = \text{CN} + 0.04
        CALL PLOT (12., 0., -3)
    23 \text{ PHI} = \text{PHI} + \text{DPHI}
        CALL PLOTND
        STOP
        END
```

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#### APPENDIX D

This computer program, also written in Fortran, was used to determine complex conformation when there is free internal rotation about the carbon-donor atom bond of the complex (Eq. [2], Chapter III). Input data to this program includes: the initial value for the Eu-donor atom bond distance (R), the bond angle ( $\Omega$ ), and the range over which these parameters are to be varied; the experimentally observed shift ratios; the cartesian co-ordinates for each atom considered. To assist in the use and understanding of this program, several comment statements are appropriately situated throughout the program.

```
- 188 -
      EXTERNAL
                       CO2AVE
      COMMON X (24), Y (24), Z (24), R, THEDA, N, ETA
      DIMENSION AVE (24), UNCER (10), RATIO (10), SD (10), WT (10)
      DIMENSION ZZ (24,24), THEDAA (24), RR (24)
      DIMENSION NAME(6)
      READ 700, (NAME(I) , I=1,6)
      PRINT 701 , (NAME(I) , I=1,6)
  700 FORMAT (6A4)
  701 FORMAT (1H1, 6A4)
С
C
      THIS PROGRAM IS FOR FREE OR ESSENTIALLY FREE INTERNAL ROTATION
С
      BE SURE TO TAKE NOTE OF CO-ORDINATE AND ROTATION CONVENTIONS
С
      PI = 3.141593
С
      CALL PLOTS
      READ 1, NUMHYD
    1 FORMAT(I1)
      NUMHYD IS THE NUMBER OF HYDROGENS WHICH SHIFT RATIOS ARE TO BE
С
С
      CALCULATED THEORETICALLY AND FITTED TO EXPERIMENTAL VALUES
      NUJ = NUMHYD - 1
С
      READ 101, NTHEDA, NETA, NRAD, DTHEDA, DETA, DR
  101 FORMAT( 3(12) , 3(E10.3))
      ALL INPUT ANGLES AND INCREMENTS ARE IN DEGREES
С
С
      DISTANCES I.E. RINT AND DR ARE IN ANGSTROMS
С
      NTHEDA = NUMBER OF INCREMENTS OF THEDA TO BE CONSIDERED (<21)
С
             = NUMBER OF INCREMENTS OF BOND DISTANCES TO BE CONSIDERED
      NRAD
С
      DTHEDA = SIZE OF INCREMENT OF THEDA TO BE CONSIDERED
С
             = SIZE OF INCREMENT OF BOND TO BE CONSIDERED
      DR
С
      NOTE: NTHEDA*DTHEDA-1= RANGE OF VALUES OF THEDA SCANNED, SAME FOR
С
      OTHER VALUES
С
      READ 102, THEDAI, ETAI, RINT
C
      THESE ARE THE INITIAL VALUES FOR THEDA, PHI AND BOND DISTANCE
С
      RESPECTIVELY
  102 \text{ FORMAT}(3(E10.3))
С
      PRINT 337
  337 FORMAT (1H1, 9HVARIABLE ,5X13HINITIAL VALUE, 5X21HINCREMENTAL INCRE
           .5X21HNUMBER OF INCREMENTS
     1ASE
                                        - / )
      PRINT 338, RINT, DR, NRAD, THEDAI, DTHEDA, NTHEDA
  338 FORMAT (2X, 9HBOND DIST , 5XF5. 2, 18XF5. 3, 18XI2 /
     1 1X5HTHEDA ,8XF6.1,2X3HDEG,15XF5.2, 3HDEG , 15XI3 /
                                                                 )
      THEDAI = THEDAI*PI/180.
      CTHFDA = DTHEDA*PI/180.
      ETAI = ETAI * PI / 180.
      DETA = DETA*PI/180.
С
      PRINT 612
  612 FORMAT (//99HSTOP & MOMENT; DO THESE NUMBERS BELOW LOOK AT ALL FAMI
     1LIAR? IF NOT WE HAD BETTER QUIT HERE!
                                                                       )
С
С
С
С
С
      R = RINT
```

AA = 0.0

```
- 189 -
```

```
С
      AA IS A PARAMETER TO BE USED LATER ON IN NORMALIZING ERROR MEASURE
      DO 661 MM=1,NUJ
      READ 2,
                 RATIO (MM), UNCER (MM), WT (MM)
      WT DEFINES THE WEIGHTS ASSIGNED TO EACH RATIO FOR FINDING THE LEAST
С
С
      DISTANCE VALUES. N.B. SUM OF THE WEIGHTS = 1.
      AA = RATIO(MM) * RATIO(MM) * WT(MM) + AA
      PRINT 2, RATIO (MM), UNCER (MM), WT (MM)
    2 FORMAT (3 ( E10.3))
  661 CONTINUE
С
С
      THE RATIOS ARE THE EXPERIMENTALLY DETERMINED SHIFT RATIOS FOR ATOM:
С
      ONE /ATOM 2; ATOM 1 / ATOM 3; ETC.
С
      IN THAT ORDER !!!!!????
С
С
      IF NUMHYD = 6 THEN RATIOS ARE 1/2; 1/3; 1/4; 1/5; 1/6.
С
      UNCER GIVES THE UNCERTAINTIES IN EACH RESPECTIVE SHIFT RATIO I.E.,
С
      IF THE CALCULATED RATIO IS WITHIN UNCER OF THE EXPERIMENTAL RATIO,
С
      THEN THE POINT WILL WARRANT FURTHER CONSIDERATION
С
С
С
     THIS STATEMENT READS IN THE VALUES OF THE X,Y, AND Z CO-ORDINATES FO
С
      EACH ATOM (MUST BE COMPUTED ELSEWHERE, I.E. COORD ETC.)
      DO 3 I=1, NUMHYD
      READ 29, X(I), Y(I), Z(I)
      PRINT 29, X(I), Y(I), Z(I)
   29 FORMAT(3( E10.3))
    3 CONTINUE
С
С
      PRINT 333
  333 FORMAT (1H1
                                  ,1X,12HDISTANCE-ANG ,5X,9HTHEDA-DEG ,6X
     1 .,
                   ,7HEPSILON
             16 X
                                11)
С
С
      DO 21 LR = 1, NRAD
      THEDA = THEDAI
      DO 22 LT=1, NTHEDA
      HEDA = 180.* THEDA/PI
С
С
С
      ETA = ETAI
      DO 23 LN =1, NETA
      TA= ETA*180./PI
С
С
      STEP TO CARRY OUT THE NUMERICAL INTEGRATION
С
      A IS THE LOWER BOUND OF INTEGRATICN, B THE UPPER
С
      PLEASE USE NORMALIZED WEIGTING FUNCTIONS W.R.T. PHI
      DO 72 N=1, NUMHYD
      A=0.
      B= 2.*PI
   72 AVE(N)
             = FGAU08 (A, B, CO2AVE) / (B-A)
С
      8 POINT GAUSS-LEGENDRE QUADRATURE WAS USED TO CARRY OUT NUMERICAL
С
      INTEGRATION
С
      STANDARD SUBROUTINE U.B.C.
С
      PRINT 73, (AVE(LS), LS= 1, NUMHYD)
  73
      FORMAT (10(1X, 1PE11.4))
С
```

С

```
DO 108 KB=2, NUMHYD
    SD(KB-1) = AVE(1) / AVE(KB)
108 CONTINUE
    EPS = 0.
    DO 553 IG=1,NUJ
    EPS = WT(IG) * ((RATIO(IG) - SD(IG)) **2) + EPS
553 CONTINUE
    EPSQ = SQRT (EPS/AA)
                      R, HEDA, TA, EPSQ
    PRINT 33,
 33 FORMAT (
                      2X, F5. 2, 2 (10X, F6. 1),
                                                        10X, 1PE10.3)
 67 CONTINUE
    ZZ(LR,LT) = EPSQ
23
    ETA = ETA + DETA
    THEDAA (LT) = HEDA
 22 THELA = THEDA+ DTHELA
    RR(LR) = R
 21 R = R + DR
   PLOTTING INSERTION
    CALL SCALE( RR , LR, 10., XMIN, DX, 1)
    CALL SCALE (THEDAA, LT, 10., YMIN, DY, 1)
    CALL AXIS ( 0., 0., 10HBOND DIST. ,-10, 10., 0., XMIN, DX)
    CALL AXIS ( 0., 0., 10 HBOND ANGLE , 10, 10., 90., YMIN, DY)
    CALL SYMBOL (4., 10.2, 0.14, 17HCOMPOUND NAME , 0., 17)
PLOT THE CONTOURS, CNTOUR IS A STANDARD SUBROUTINE AT U.B.C.
    CN = 0.05
    DO 200 I=1,6
    CALL CNTOUR (RR, LR, THEDAA, LT, ZZ, 24, CN, 3., CN )
200 \text{ CN} = \text{CN} + 0.05
    CALL PLOTND
    STOP
    END
    FUNCTION CO2AVE (PHI)
    COMMON X (24), Y (24), Z (24), R, THEDA, N, ETA
    PI = 3.141593
             (R*R + X(N) * X(N) + Y(N) * Y(N) + Z(N) * Z(N) - 2.*R *
    0
        Ξ
   1 (X (N) *COS (THEDA) + SIN (THEDA) * (Y (N) *COS (PHI) + Z (N) *SIN (PHI)))
    CO2AVE= (3.*(R-(X(N)*COS(THEDA) + SIN(THEDA) *(Y(N) *COS(PHI)))
   1 + Z(N) * SIN(PHI))) **2 -Q)/
   2 (Q * * (2.5))
    TO DO A GAUSSIAN WEIGHT ABOUT PHI NOUGHT, SIMPLY ADD A GAUSSIAN
    WEIGHT FACTOR, EQ(4), TIMES THE QUANTITY ABOVE
    RETURN
    END
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- 190 -

C C C

C C

С

C C

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