16518

NATIONAL LIBRARY
OTTAWA

BIBLIOTHÈQUE NATIONALE
OTTAWA

NAME OF AUTHOR.... Helmut. Beierbeck.....
TITLE OF THESIS... Some Applications of Lanthanide Shift.....
..... Reagents in NMR Spectroscopy of Organic...
..... Compounds.....
UNIVERSITY..... Carleton.....
DEGREE FOR WHICH THESIS WAS PRESENTED.... Ph.D.....
YEAR THIS DEGREE GRANTED..... 1973.....

Permission is hereby granted to THE NATIONAL LIBRARY
OF CANADA to microfilm this thesis and to lend or sell copies
of the film.

The author reserves other publication rights, and
neither the thesis nor extensive extracts from it may be
printed or otherwise reproduced without the author's
written permission.

(Signed).....

H. Beierbeck

PERMANENT ADDRESS:

DEPT. CHEM.
UNIV. SHERBROOKE
SHERBROOKE, QUE.

DATED... *1/3/73* ...19

SOME APPLICATIONS OF LANTHANIDE SHIFT REAGENTS
IN NMR SPECTROSCOPY OF ORGANIC COMPOUNDS

by

Helmut Beierbeck, M.Sc.

A Thesis submitted to the Faculty of Graduate
Studies in partial fulfilment of the require-
ments for the degree of Doctor of Philosophy

Department of Chemistry

Carleton University

Ottawa, Ontario

September, 1972

The undersigned hereby recommend to
the Faculty of Graduate Studies acceptance
of this thesis, submitted by Helmut Beierbeck
M.Sc., in partial fulfilment of the require-
ments for the degree of Doctor of Philosophy

Thesis Supervisor

Chairman, Department of Chemistry

External Examiner

Carleton University
May 18, 1973

ABSTRACT

The examination of the interaction of the lanthanide shift reagents with organic substrates, their effect on the proton nmr spectra of these substrates and their possible uses for structure elucidations in organic chemistry form the subject of this thesis.

The introductory chapter gives a brief discussion of the properties and applications of the lanthanide shift reagents and an outline of the objectives of this thesis.

In chapter 2 it is shown that for monofunctional organic substrates the ratios of the lanthanide induced shifts are independent of the shift reagent concentration, provided that only 1:1 shift reagent-substrate adducts are formed. In this case the linear parts in plots of chemical shifts vs shift reagent/substrate concentration ratios can be improved by plotting the observed shifts against coordinates which are proportional to the sums of the shifts in each spectrum. This is possible because the concentration ratios are exactly the same for all substrate nuclei.

In chapter 3 it is shown that this possibility to improve shift reagent plots is not restricted to the linear parts, because it is generally true that the concentration ratios are the same for all substrate nuclei. By including the experimental points from the nonlinear parts in plots of chemical shifts vs sums of shifts nonlinear plots are converted to linear plots.

It is not always straightforward to trace the signals of a given nucleus through a series of shift reagent spectra, if the signals cannot be identified by their appearance. In chapter 4

an algorithm is described which is suitable for a computerized signal sorting routine. It consists of plotting the chemical shifts against the sums of the shifts in each spectrum and connecting all points from the last spectrum in turn with each of the points from the first spectrum. Those combinations are the correct ones and those experimental points between the first and last set belong to the same nucleus which give the lowest standard deviation.

In chapter 5 a simple test for the presence of shift reagent-substrate complexes containing more than one substrate molecule is described. It is shown that 1:2 complexes have been formed whenever the initial slopes in chemical shift vs shift reagent-substrate concentration ratios are found to be larger than the observed induced shifts for shift reagent-substrate ratios greater than three.

In chapter 6 it is shown that the ratios of the slopes in plots of chemical shifts vs sums of chemical shifts are independent of the solvent and the substrate concentrations, but slightly temperature dependent.

Chapter 7 is a summary and discussion of the results described in chapters 2 - 6.

In chapter 8 an algorithm is described for fitting the pseudocontact shielding equation to the experimental lanthanide induced shifts. A Taylor series expansion in the proportionality constant and three metal coordinates is carried out to permit an iterative linear least squares optimization of these parameters.

In chapter 9 an algorithm is described for the determination

of equilibrium constants and bound shifts, in cases where only shift reagent-substrate complexes of 1:1 stoichiometry are formed. The full expression for the induced shifts as function of the bound shifts and the equilibrium constant is expanded in a Taylor series in the two parameters, which are then optimized iteratively by the linear least squares method.

ACKNOWLEDGEMENTS

I would like to thank Prof. ApSimon for his interest in and support of this work and Dr. Fruchier for a very fruitful collaboration during the last twelve months.

Thanks are also due to Mr. McCarville for running most of the 100 MHz nmr spectra.

TABLE OF CONTENTS

	<u>Page</u>
TITLE PAGE.....	i
STATEMENT OF FACULTY APPROVAL.....	ii
ABSTRACT.....	iii
ACKNOWLEDGEMENTS.....	vi
TABLE OF CONTENTS.....	vii
LIST OF TABLES.....	viii
LIST OF FIGURES.....	x
1. INTRODUCTION.....	1
2. DETERMINATION OF ACCURATE BOUND SHIFTS FROM THE SLO- PES IN THE LINEAR PARTS OF δ_{ij} vs $[L_o]/[S_o]$ PLOTS....	11
3. CONVERSION OF NONLINEAR SHIFT REAGENT PLOTS TO LINEAR PLOTS.....	18
4. AUTOMATIC SORTING OF SIGNALS IN SHIFT REAGENT SPECTRA	24
5. ON THE STOICHIOMETRY OF SHIFT REAGENT-SUBSTRATE ADDUCTS.....	29
6. VARIATION OF THE RATIOS OF THE BOUND SHIFTS WITH CHANGES IN EXPERIMENTAL CONDITIONS.....	36
7. SUMMARY AND DISCUSSION OF THE RESULTS DESCRIBED IN THE FOREGOING CHAPTERS.....	42
8. STRUCTURE ELUCIDATION WITH THE USE OF THE PSEUDO- CONTACT EQUATION.....	46
9. DETERMINATION OF EQUILIBRIUM CONSTANTS FOR $L + S \rightleftharpoons LS$ EQUILIBRIA.....	54
EXPERIMENTAL.....	60
APPENDIX 1. MATHEMATICAL DERIVATIONS OF EXPRESSIONS FOR THE COEFFICIENTS IN EQUATION (11) OF CHAPTER 8 AND EQUATION (18) IN CHAPTER 9....	62
APPENDIX 2. COMPUTER PROGRAMS.....	67
REFERENCES.....	103

LIST OF TABLES

<u>Table</u>	<u>Page</u>
1. Slope ratios for the methyl group signals of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$	22
2. Intercepts for the methyl group signals of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$	22
3. Standard deviations for the lines calculated in step two of the sorting routine.....	25
4. Ratios of induced shifts and approximate bound shifts for the methyl group protons of borneol complexed to $\text{Pr}(\text{fod})_3$	33
5. Variation of slopes and slope ratios for the methyl group signals of β -amyrin with change of solvent.....	37
6. Variation of slopes and slope ratios for the methyl group signals of β -amyrin with change in absolute concentration of substrate.....	37
7. Variation of slopes and slope ratios for the methyl group signals of β -amyrin with change in temperature.....	38
8. Slopes and slope ratios for the methyl group signals of β -amyrin and germanicol.....	39
9. Slopes and slope ratios in shift reagent plots for the chemical shifts of the C-18 and C-19 methyl groups of various keto and thioketal androstanes, in the presence of $\text{Pr}(\text{fod})_3$	40
10. Carbon and hydrogen coordinates for borneol and calculated induced shifts for the ring and methyl group protons.....	49
11. Iterative approach to the best values for C, x, y, and z, with the coordinates and calculated induced shifts in table 10.....	50

12. Iterative approach to the best values for C, x, y, and z for the system borneol/Pr(fod) ₃	51
13. Experimental induced shifts and differences between calculated and experimental induced shifts for the system borneol/Pr(fod) ₃	51
14. Simulated experimental $[L_0]/[S_0]$ ratios and δ_{ij} used in the illustration of the derivation of K and $\Sigma\Delta_i$	57
15. Iterative derivation of the best values for K and $\Sigma\Delta_i$ with the data in table 14.....	57

LIST OF FIGURES

<u>Figure</u>	<u>Page</u>
1. 100 MHz spectrum of cholesterol, before and after addition of $\text{Eu(dpm)}_3 \cdot 2\text{py}$	1
2. 100 MHz spectrum of <i>t</i> -butylcyclohexanol with and without Eu(dpm)_3	2
3. Lanthanide induced shifts for some of the methyl groups of β -amyrin, plotted against experimental $[\text{L}_0]/[\text{S}_0]$ ratios.....	13
4. Lanthanide induced shifts for some of the methyl groups of β -amyrin, plotted against corrected $[\text{L}_0]/[\text{S}_0]$ ratios.....	14
5. Plot of chemical shifts <u>vs</u> $[\text{L}_0]/[\text{S}_0]$ for the methyl groups of β -amyrin in the presence of Pr(fod)_3	19
6. Plot of chemical shifts <u>vs</u> $[\text{LS}]/[\text{S}_0]$ for the methyl groups of β -amyrin in the presence of Pr(fod)_3	20
7. Illustration of step two of the sorting routine with the methyl group shifts of β -amyrin in the presence of Pr(fod)_3	26
8. Plot of ratios of approximate to theoretical bound shifts <u>vs</u> equilibrium constants for the equilibrium $\text{L} + \text{S} \rightleftharpoons \text{LS}_1$	31
9. Plot of induced shifts <u>vs</u> shift reagent/substrate ratios for the methyl protons of borneol in the presence of Pr(fod)_3	35
10. Initial and optimized lanthanide metal locations relative to the substrate for the system borneol- Pr(fod)_3	52
11. Experimental induced shifts and theoretical curves based on the $\text{L} + \text{S} \rightleftharpoons \text{LS}$ model, for the system borneol- Pr(fod)_3	58

CHAPTER 1. INTRODUCTION

The proton nmr spectra of all but the simplest organic compounds are complex and usually the majority of the signals cannot be identified and analysed. The spectrum of the steroid cholesterol, shown in Fig. 1, is a typical example.

Fig. 1. 100 MHz spectrum of cholesterol, before and after addition of $\text{Eu(dpm)}_3 \cdot 2\text{py}$. Taken from ref. (1).

In 1969 Hinckley (1) published the proton nmr spectrum of cholesterol in a solution containing a lanthanide complex, $\text{Eu(dpm)}_3 \cdot 2\text{py}$. This spectrum shown in Fig.1 and especially the spectra in Fig. 2, taken from the paper by Demarco and coworkers (2) explain the excitement following the discovery of the first "shift reagent".

Fig.2. 100 MHz nmr spectra of *t*-butylcyclohexanol with and without Eu(dpm)_3 , taken from ref. (2).

In the meantime close to 200 papers have reported the use of shift reagents in structure elucidation work.

Shift reagents are paramagnetic lanthanide complexes, the most widely used of which are the chelates of Eu^{3+} and Pr^{3+} with dpm (2,2,6,6-tetramethylheptane-3,5-dione) and fod (1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) ligands. These chelates can further complex with substrates having functional groups with lone pair electrons (5), such as alcohols, ketones, amines etc. In fact, the first shift reagent was the dipyridine adduct of $\text{Eu}(\text{dpm})_3$ (1).

Complexation to the paramagnetic chelates induces shifts in the nmr spectra of the substrates which in some cases are several times larger than the total previously known range of chemical shifts. The unpaired 4f electrons of the metal ion affect the screening of the substrate nuclei in one of two ways (3,4). Firstly, spin delocalization or polarization via the molecular orbitals of the substrate may transfer net spin density from the metal to the substrate nuclei. If there is a finite probability of finding an unpaired electron at the nucleus, this gives rise to a so-called contact shift (3,4). It appears that this shielding mechanism is of minor importance in the lanthanide series because the 4f electrons are effectively shielded from interaction with the lone pair electrons of the substrate by the overlying $6s^2$ and $6p^6$ shells (5). The second shielding effect, the so-called dipolar or pseudocontact mechanism, consists of the modification of the effective magnetic field at the nucleus by the magnetic moment of the central ion (3,4). The Russell-Saunders states of the central ion, which in the lanthanide series

are practically unaffected by crystal fields (5) are associated with angular momentum characterized by the quantum number J (6). The combination of electronic charge and angular momentum gives rise to a magnetic moment. In the external magnetic field the $(2J + 1)$ fold degeneracy of the electronic states is lifted and levels of slightly different energies are obtained with different magnetic moment components along the field direction. The resultant magnetic moment is the vector sum of the moments of the different energy levels. If the complex has effectively axial symmetry, as it is usually assumed for the lanthanide shift reagents, the shift increment caused by the magnetic moment of the central ion is given by (3,7)

$$\Delta_i = \frac{-\beta^2 S(S+1)(g_{\parallel} + 2g_{\perp})(g_{\parallel} - g_{\perp})}{27kT} \frac{(3\cos^2\theta_i - 1)}{R_i^3} \quad (1)$$

β is the Bohr magneton, S is the total electron spin, $g_{\parallel}$ and $g_{\perp}$ are the components of the g tensor parallel and perpendicular to the principal axis of the complex, respectively. R_i is the vector from the metal to the i 'th nucleus and θ_i is the angle between the principal axis of the complex and the vector R_i . This shielding mechanism has been shown (10,11,23,26) to be the predominant one for the lanthanide shift reagents.

Large shielding or deshielding effects by paramagnetic complexes are not unique to the lanthanide series and similar effects with transition metal complexes have been known and studied for a number of years (3,4). What is unique to the shift

reagents, however, is the fact that the displaced signals are hardly broadened. The electronic magnetic moments are several orders of magnitude larger than the nuclear moments because the magnetic moments are inversely proportional to the masses of the spinning particles (4). With electronic and nuclear relaxation times of comparable magnitude paramagnetic species provide powerful means of relaxation shortening the nuclear lifetimes in any given state to such an extent that, in accordance with the uncertainty principle, the lines become too broad for high resolution nmr. Only if the electronic relaxation times are fast on the nmr time scale is it possible to observe narrow lines. The electronic relaxation times are short for the lanthanide shift reagents because the spacing of the energy levels of a given state is small compared to kT and electronic transitions between these levels are fast (4).

At room temperature the nmr spectra of the substrate in the presence of lanthanide shift reagents show only one set of signals (Fig. 1 and 2), indicating that the association-dissociation between substrate and shift reagent is fast on the nmr time scale. Consequently the observed chemical shifts are averages of the shifts in the uncomplexed and complexed states, weighted according to the fractions of the times that the substrate is uncomplexed and complexed, respectively. If $[L_0]$ and $[S_0]$ represent the total concentrations of shift reagent and substrate, $[S]$, $[LS_1]$, $[LS_2]$ etc the concentrations of uncomplexed and complexed substrate, and Δ_{0i} , Δ_{1i} , Δ_{2i} etc the chemical shifts for the i 'th

substrate nucleus after the j'th addition of shift reagent the observed shifts δ_{ij} are given by

$$\delta_{ij} = [S]/[S_0] \Delta_{0i} + [LS_1]/[S_0] \Delta_{1i} + [LS_2]/[S_0] \Delta_{2i} + \dots \quad (2)$$

Usually Δ_{0i} is set equal to zero and the chemical shifts in the uncomplexed state become the reference points for the lanthanide induced shifts.

In a typical shift reagent experiment a stock solution of the lanthanide complex in an nmr solvent, usually $CDCl_3$ or CCl_4 , is prepared and aliquots of this solution are added to the substrate solution in the nmr tube. Since water complexes more strongly with the lanthanide chelates than the organic substrates its presence reduces the effectiveness of the shift reagent. The shift reagents are conveniently purified by sublimation prior to use. The chemical shifts of the substrate nuclei are redetermined after every addition of shift reagent. They are then plotted against the corresponding shift reagent-substrate ratios.

It has usually been assumed that only 1:1 shift reagent-substrate adducts are formed in which case only the second term in equation (2) remains. Provided that the experiment is restricted to low $[L_0]/[S_0]$ ratios the shift reagent is practically completely complexed by the substrate which is present in excess, and the fractions $[LS]/[S_0]$ are practically equal to the fractions $[L_0]/[S_0]$. In this case the bound shifts Δ_{1i} are given by the slopes in the plots of chemical shifts vs $[L_0]/[S_0]$ ratios (13-24) or by the induced shifts obtained by extrapolation to $[L_0]/[S_0]$

ratios of unity (25-27). The chemical shifts obtained by extrapolation to $[L_o]/[S_o]$ ratios of unity differ from the observed shifts for experimental $[L_o]/[S_o] = 1$ ratios which have also been equated with the bound shifts (9-12). The validity of the results obtained in this fashion now appear questionable, however, since in more recent papers evidence for the formation of complexes of the composition LS_2 was presented (8,29-31).

The bound shifts are used to characterize substrates of known structure and, more importantly, to confirm proposed structures with the aid of the pseudocontact equation. The first factor in equation (1) is characteristic of the lanthanide metal whereas the second factor is a function of the geometry of the substrate-shift reagent adduct. Detailed structural information about the substrate can be extracted from the lanthanide induced shifts by correlating them with the geometric quantities in equation (1). In order to obtain valid results it is necessary that the induced shifts are indeed entirely due to the dipolar shielding mechanism and that the complex is axially symmetric. It is usually also assumed that the principal axis of the complex points toward the complexing heteroatom of the substrate. These assumptions would appear to be justified by the successful correlation between induced shifts and geometric quantities in equation (1), both in 1H and ^{13}C nmr spectroscopy (10,11,23,26).

The lanthanide induced shifts and the bound shifts are the shift reagent parameters of main interest because of the struc-

tural information that they contain, but there have also been some attempts to determine the equilibrium constants for the interaction between shift reagent and substrate. Usually it was assumed that only 1:1 adducts are formed (30,32,34), but there is one report of the determination of both equilibrium constants for the equilibria $L + S \rightleftharpoons LS_1 + S \rightleftharpoons LS_2$ (31).

The literature on lanthanide shift reagents, beginning with Hinckley's first paper, has been reviewed in a recent article which is believed to be complete up to the end of 1971 (33).

The accurate determination and the use of lanthanide induced shifts to gain structural information and insight into the chemistry of the interaction between shift reagent and substrate form the subject of this thesis.

In chapter 2 it is shown that for monofunctional organic substrates the ratios of the lanthanide induced shifts are independent of the shift reagent concentration, provided that only 1:1 shift reagent-substrate adducts are formed. In this case the linear parts in plots of chemical shifts vs shift reagent/substrate concentration ratios can be improved by plotting the observed shifts against coordinates which are proportional to the sums of the shifts in each spectrum. This is possible because the concentration ratios are exactly the same for all substrate nuclei.

In chapter 3 it is shown that this possibility to improve shift reagent plots is not restricted to the linear parts, because it is generally true that the concentration ratios are the same

for all substrate nuclei. By including the experimental points from the nonlinear parts in plots of chemical shifts vs sums of shifts nonlinear plots can be converted to linear plots.

It is not always straightforward to trace the signals of a given nucleus through a series of shift reagent spectra, if the signals cannot be identified by their appearance. In chapter 4 an algorithm is described which is suitable for a computerized signal sorting routine. It consists of plotting the chemical shifts against the sums of the shifts in each spectrum and connecting all points from the last spectrum in turn with each of the points from the first spectrum. Those combinations are the correct ones and those experimental points between the first and last set belong to the same nucleus which give the lowest standard deviation.

In chapter 5 a simple test for the presence of shift reagent-substrate complexes containing more than one substrate molecule is described. It is shown that 1:2 complexes have been formed whenever the initial slopes in chemical shift vs shift reagent/substrate concentration ratios are found to be larger than the observed induced shifts for shift reagent/substrate ratios greater than three.

In chapter 6 it is shown that the ratios of the slopes in plots of chemical shifts vs sums of chemical shifts are independent of the solvent and the substrate concentration, but slightly temperature dependent.

Chapter 7 is a summary and discussion of the results described in chapters 2 - 6.

In chapter 8 an algorithm is described for fitting the pseudocontact shielding equation to the experimental lanthanide induced shifts. A Taylor series expansion in the proportionality constant and three metal coordinates is carried out to permit an iterative linear least squares optimization of these parameters.

In chapter 9 an algorithm is described for the determination of equilibrium constants and bound shifts, in cases where only shift reagent-substrate complexes of 1:1 stoichiometry are formed. The full expression for the induced shifts as function of the bound shifts and the equilibrium constant is expanded in a Taylor series in the two parameters, which are then optimized iteratively by the linear least squares method.

CHAPTER 2. DETERMINATION OF ACCURATE BOUND SHIFTS FROM THE SLOPES IN THE LINEAR PARTS OF δ_{ij} vs $[L_o]/[S_o]$ PLOTS (36).

It was shown in the introduction that the lanthanide induced shifts for monofunctional organic substrates forming 1:1 shift reagent adducts are given by

$$\delta_{ij} = [LS]/[S_o] \Delta_i \quad (3)$$

At low concentrations of shift reagent $[LS] \approx [L_o]$ and the induced shifts δ_{ij} become approximately equal to

$$\delta_{ij} = [L_o]/[S_o] \Delta_i \quad (4)$$

The δ_{ij} are the lanthanide induced shifts for the i 'th substrate nucleus in the j 'th spectrum. $[L_o]$, $[S_o]$ and $[LS]$ are the total concentrations of shift reagent and substrate and the concentration of bound substrate respectively. The Δ_i are the bound shifts, ie the shift differences between complexed and uncomplexed state of the substrate, for the i 'th substrate nucleus. The distinguishing subscript 1, used in the introductory chapter, has been dropped in $[LS_1]$ and Δ_{1i} since only 1:1 adducts are considered here.

According to equation (4) Δ_i estimates are obtained by plotting the induced shifts δ_{ij} against the experimental molar ratios $[L_o]/[S_o]$. The slopes in these plots (13 - 24) or the induced shifts estimated by extrapolation to a value $[L_o]/[S_o] = 1$ in these plots (25 - 27) are equal to the Δ_i .

It is difficult to determine the concentrations of shift reagent and substrate with a precision comparable to that of the

chemical shifts. This, however, only affects the precision of the slopes but not that of the slope ratios. Since the concentrations $[L_0]$ and $[S_0]$ have to be exactly the same for all nuclei all experimental points from a given spectrum have to fall on the same vertical line. It is this fact which eliminates the need to know the concentrations as the following considerations show.

Consider an array of points defined by the intercepts of a series of lines with arbitrary slopes and a series of vertical lines at arbitrary horizontal positions. Suppose that the vertical lines, and all points on them, have been displaced horizontally, but not vertically, by different and unknown amounts. With the condition that all points have to fall on straight lines the original plot can be regenerated except for an unknown scale factor along the horizontal axis. This scale factor affects the slopes but not the slope ratios. Thus, without a knowledge of the horizontal coordinates a perfect plot and the correct slope ratios are obtained.

The same has to be true for the plots of δ_{ij} vs $[L_0]/[S_0]$ if the true curves are straight lines in the range of the experimental points. Conversely, the correction of the horizontal coordinates is justified and the true curves are straight lines if all experimental points are less than 1 Hz, the estimated experimental error for the chemical shifts, from the lines and if the slope ratios remain unchanged.

Fig. 3 and 4 show plots of chemical shifts against $[L_0]/[S_0]$

Fig. 3. Lanthanide induced shifts for some of the methyl groups of β -amyrin, plotted against experimental $[L]/[S]$ ratios.

Fig. 4. Lanthanide induced shifts for some of the methyl groups of β -amyrin, plotted against corrected $[L_0]/[S_0]$ ratios.

ratios for the methyl groups of β -amyrin, omitting those at C-23 and C-24, before and after adjustment of the experimental data.

In this and in all other cases where the adjusting procedure, outlined below, was applied improved plots were obtained with the same slope ratios, to the decimal place beyond the last significant figure for the slopes. Furthermore, it became much easier to assign the signals in regions of extensive line crossings.

The shift reagent coordinates $[L_0]/[S_0]$ are adjusted in the following manner. Suppose there are m signals per spectrum and spectra for n different ratios $[L_0]/[S_0]$. The experimental molar ratios c_1 and c_n , for the first and last run, are kept constant and the others are chosen such that the sum of the deviations of the experimental shifts from the lines is a minimum. Since the chemical shift δ_{ij} (for the i 'th proton in the j 'th spectrum) should fall on the straight line drawn through δ_{i1} and δ_{in} (the shifts for proton i in the first and n 'th spectrum) we have to have

$$(c_j - c_1)/(c_n - c_1) = (\delta_{ij} - \delta_{i1})/(\delta_{in} - \delta_{i1}) \quad (5)$$

and therefore the corrected shift reagent coordinate c_j is given by

$$c_j = (c_n - c_1)(\delta_{ij} - \delta_{i1})/(\delta_{in} - \delta_{i1}) + c_1 \quad (6)$$

This relation holds for all protons, i.e. all values of i . However, because of the errors in the chemical shifts slightly different values for c_j would be obtained. Instead of averaging these values, equation (5) is summed over all i , giving after rearrangement

$$c_j = (c_n - c_1)(\sum_i \delta_{ij} - \sum_i \delta_{i1})/(\sum_i \delta_{in} - \sum_i \delta_{i1}) + c_1 \quad (7)$$

c_j is now the molar ratio for which the sum of the deviations for the m experimental shifts in the j 'th spectrum is a minimum. Equation (7) has the advantage that it is not necessary to know whether there is signal crossover, i.e. corrected molar ratios are obtained prior to plotting.

Since the experimental molar ratios c_1 and c_n , which are kept constant, are presumably not accurate, the whole plot may be displaced from the origin and the intercepts will in general not agree with the experimental shifts in the spectrum of the pure substrate. Therefore the same procedure is used to bring these shifts in line with the rest. Thus, the "corrected" molar ratio for zero concentration of shift reagent will in general be different from zero as a consequence of the arbitrary choice of the fixed points c_1 and c_n . It can be brought back to zero by displacing the whole plot.

Thus there is a simple graphical method for eliminating the experimental errors in the $[L_0]/[S_0]$ concentration ratios. It affords intercepts which are in excellent agreement with the chemical shifts in the absence of shift reagent (Fig. 4). This degree of accuracy is difficult to obtain in plots of induced shifts vs experimental $[L_0]/[S_0]$ concentration ratios, even in very careful work, because the presence of even traces of water will lower the effective concentration of shift reagent. In addition the sorting of the signals in regions of line crossings is greatly facilitated. Thus the method yields highly accurate results from routine measurements.

CHAPTER: 3. CONVERSION OF NONLINEAR SHIFT REAGENT PLOTS TO LINEAR PLOTS (37).

In the preceding chapter it was shown that the ratios of the slopes in the linear part of the shift reagent plots are independent of the shift reagent/substrate concentration ratios. As the $[L_0]/[S_0]$ ratios increase the plots of chemical shifts vs $[L_0]/[S_0]$ become nonlinear (Fig.5). However, since the lanthanide induced shifts are equal to the product of the fractions $[LS]/[S_0]$ of the complexed substrate and the induced shifts Δ_i in the complexed state there exists another variable, $[LS]/[S_0]$, such that the chemical shifts are a linear function of this variable for any value of $[L_0]/[S_0]$. Since the $[LS]/[S_0]$ are also the same for all nuclei in any given sample, regardless of the amount of added shift reagent, it is again possible to obtain accurate slope ratios and intercepts without any knowledge of the values of $[LS]/[S_0]$. As before the chemical shifts are simply plotted against coordinates c_j which are proportional to the sums of the shifts in each spectrum. If the absolute values of the bound shifts are known these values can be normalized to the actual values for the fractions $[LS]/[S_0]$ of complexed substrate. The slope ratios are equal to the ratios of the limiting shifts and the same values must be obtained from the linear part of the δ_{ij} vs $[L_0]/[S_0]$ plot and from the linear δ_{ij} vs $[LS]/[S_0]$ plot.

Figures 5 and 6 illustrate this conversion for the methyl

Fig. 5. Plot of chemical shifts vs $[L_0]/[S_0]$ for the methyl groups of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$.

Fig. 6. Plot of chemical shifts vs $[LS]/[S]$ for the methyl groups of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$. It is assumed that the last points represent bound shifts.

group signals of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$. The assumption that the shifts in the last spectrum represent the limiting shifts is certainly incorrect in this case. However, this does not affect the following results. Table 1 shows that within experimental error the slope ratios are the same whether the range of $[\text{L}_0]/[\text{S}_0]$ ratios is 0.5, 1.0 or 1.5. Similarly the intercepts vary little and are in good agreement with the experimental shifts in the spectrum of β -amyrin alone (table 2).

This extension of the linearity of the shift reagent plots should be useful for working with ring protons, since their signals are usually hidden in the methylene envelope for small values of $[\text{L}_0]/[\text{S}_0]$. In order to obtain the intercepts in this case it is necessary to "calibrate" the plots with signals, such as methyl group shifts, which can be seen in the spectrum of the pure substrate. That in this case accurate intercepts can still be obtained can be demonstrated with the methyl group signals of β -amyrin. Thus, it was assumed that the signals for the methyl groups 23 and 24 were observed in every spectrum including the "zero" spectrum, but that for the remaining six methyl groups only the signals in the range $0.5 \leq [\text{LS}]/[\text{S}_0] \leq 1.0$ were available. First, the shifts for methyls 23 and 24 were used to obtain corrected shift reagent coordinates in the usual way. Then the remaining signals were plotted against these corrected values. As tables 1 and 2 show, slope ratios and intercepts for methyls 25-30 agree well with the values obtained previously.

Table 1. Slope ratios for the methyl group signals of β -amyrin^a in the presence of $\text{Pr}(\text{fod})_3$.

Range of $[\text{L}_0]/[\text{S}_0]$ Me	0-0.5	0-1.0	0-1.5	0.5-1.0 ^b
	slope ratios ^c			
30	8.6	7.0	6.4	6.4
29	23.2	20.4	19.8	18.1
28	63.7	59.4	59.0	57.1
27	81.2	81.7	81.4	80.0
26	169.4	167.7	166.9	167.2
25	415.9	414.4	413.0	412.2
24	964.1	970.4	973.5	970.4
23	1000.0	1000.0	1000.0	1000.0

- a. formula and numbering system on page 115, spectra 17-20, 22-23, 25
- b. only the chemical shifts for methyl groups 23 and 24 were used to derive relative $[\text{LS}]/[\text{S}_0]$ values.
- c. all slopes are normalized to a slope of 1000.0 for methyl group 23

Table 2. Intercepts for the methyl group signals of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$.

Range of $[\text{L}_0]/[\text{S}_0]$ Me	0-0.5	0-1.0	0-1.5	0.5-1.0
exp ^a	intercepts			
30	87.5	87.8	87.4	87.2
29	87.5	88.3	87.5	87.2
28	83.0	84.0	82.8	82.7
27	113.5	113.6	113.6	113.5
26	97.0	97.3	97.0	96.7
25	94.0	93.3	93.0	92.5
24	100.0	99.1	101.6	102.9
23	79.0	78.1	78.6	78.7

- a. chemical shifts in the absence of shift reagent

Thus by plotting the chemical shifts against coordinates, which are proportional to the sums of the shifts in each spectrum, linear plots are obtained over any range of $[L_o]/[S_o]$ ratios. These linear plots are free from any experimental errors which occur in the determination of the concentrations of shift reagent and substrate. The method is the graphical analogue to the numerical method of Kelsey (28) who found a linear correlation between the induced shifts regardless of the nonlinearity of the δ_{ij} vs $[L_o]/[S_o]$ plots. The fact that it is unnecessary to restrict the shift reagent experiment to low $[L_o]/[S_o]$ values has obvious advantages. A wider range of $[L_o]/[S_o]$ ratios gives better spectral dispersion and higher numerical accuracy. Signals which are still hidden at low shift reagent concentrations emerge at higher $[L_o]/[S_o]$ ratios and the corresponding slopes and intercepts are accessible in this way.

CHAPTER 4. AUTOMATIC SORTING OF SIGNALS IN SHIFT REAGENT SPECTRA (38).

Sometimes it can be difficult to trace the signal of a given nucleus through a series of spectra, especially if the number of signals is great and if the lines cross in the studied range of molar ratios of shift reagent and substrate, as in noise decoupled ^{13}C spectra of substrates containing a large number of carbon atoms. The correlation between the chemical shifts and the improved shift reagent coordinates is good enough to permit the automatic sorting of the signals, for instance by the algorithm described in this chapter.

Suppose the chemical shifts of m nuclei or groups of magnetically equivalent nuclei are measured in the absence of shift reagent and for n different shift reagent concentrations. Let the chemical shifts in the shift reagent spectra be arranged as a matrix Δ of dimensions $m \times n$ in which the signals in the i 'th spectrum are found in the i 'th column. This matrix has to be rearranged in such a way that all signals for any given nucleus are in one row. The chemical shifts in the spectrum without shift reagent then have to be matched with the data in the shift reagent matrix.

In the first step corrected shift reagent coordinates are derived as outlined in the preceding chapters.

In the second step the signals in the shift reagent spectra are sorted out. Lines are drawn from δ_{1n} (the first signal in the n 'th spectrum) to each of the m points δ_{i1} from the first

spectrum (see Fig. 7) and the m slopes are calculated. For each of the m lines every column of points is searched for that signal which is closest to the line and the standard deviation of these points is calculated for each line (see table 3). That combination $(\delta_{i1}, \delta_{1n})$ is taken to be the correct one for which the standard deviation is a minimum. The slope is recalculated using all n points which are then removed from the matrix Δ and form a row in the new matrix Δ' .

Table 3. Standard deviations for the lines calculated in step 2. The indices i and k are those for the signals in the first (row) and last (column) spectrum, from low to high field.

$k \backslash i$	1	2	3	4	5	6	7	8
1	6.3	5.6	<u>0.3</u>					
2	<u>0.2</u>							
3	0.6	<u>0.6</u>						
4	1.9	2.7	6.7	1.1	<u>0.7</u>			
5	2.8	3.5	6.0	<u>0.5</u>				
6	5.3	5.8	7.1	9.0	15.3	<u>0.4</u>		
7	13.2	13.8	14.5	16.2	24.7	26.5	<u>0.5</u>	
8	14.5	16.0	18.0	21.1	30.5	34.2	9.5	<u>0.6</u>

This procedure is repeated with the reduced matrix Δ until all signals are sorted out and the new matrix Δ' is completed in which all signals for any nucleus are in one row. If it is not already the case, the rows are ordered according to increasing slopes.

Fig. 7. Illustration of step two with the methyl group shifts of β -amyrin in the presence of $\text{Pr}(\text{fod})_3$ (shifts upfield from TMS are negative).

In the third step the m chemical shifts in the spectrum before addition of shift reagent are matched with the m slopes. First, the correction procedure for the shift reagent coordinates is applied to the zero position. In general, the best zero position after correction will not be exactly at the coordinate origin, and it is brought back to zero by displacing the whole plot. Then the intercepts are calculated and the experimental shifts are ordered accordingly.

Spectra in which not all signals can be observed are excluded and the slopes of the best lines are calculated with the shifts in the remaining spectra. If the experimental shift reagent coordinates are accurate enough to permit the assignment of some of the signals, these signals can be used to obtain improved shift reagent coordinates. The remaining signals can then be sorted out as in step 3.

The method is illustrated with the chemical shifts for the eight ($m = 8$) methyl groups of β -amyrin, in the presence of $\text{Pr}(\text{fod})_3$. In Fig. 7 most of the signals upfield from TMS have been omitted. The figure illustrates the first stage in step 2, the combination of the downfield methyl signal in the last shift reagent spectrum with each of the methyl group signals in the first shift reagent spectrum. For each of the eight lines indicated in the figure the intermediate points closest to each line are determined and their standard deviations from each of the lines are calculated. The deviations for the eight lines in Fig. 7 are given in column one ($i = 1$) of table 3. The value of

0.2 (underlined) is the lowest and therefore the second signal in the first spectrum and the first signal in the last spectrum belong to the same methyl group. These two signals and the intermediate ones which were found to be closest to the corresponding line are now removed and the procedure is repeated with the remaining points. Thus the second lowest downfield signal in the last shift reagent spectrum would next be connected with each of the remaining seven points from the first spectrum. It can be easily seen that the third signal from the top would be the correct match, as indicated by underlining the value of 0.6 in row three ($k = 3$) of column two ($i = 2$) in table 3.

CHAPTER 5. ON THE STOICHIOMETRY OF SHIFT REAGENT-SUBSTRATE ADDUCTS (39).

Diadducts between shift reagents and substrates are known in the crystalline state (eg the original shift reagent $\text{Eu(dpm)}_3 \cdot 2\text{py}$ (1)) and in solution at low temperatures (8), but it has usually been assumed that only complexes of 1:1 stoichiometry are formed at ambient temperatures. However, there is recent evidence for the formation of LS_2 and possibly larger complexes in solution at room temperature (29-32). Two tests have been suggested to verify the assumption that 1:1 adducts are formed. Plots of induced shifts δ_{ij} vs $[\text{L}_0]/([\text{L}_0] + [\text{S}_0])$, with $([\text{L}_0] + [\text{S}_0])$ being kept constant, are expected to show a maximum at 0.5 if 1:1 adducts are formed, and maxima at lower values for complexes containing more than one substrate molecule (29). Alternatively straight line plots of $[\text{S}_0]$ vs $1/\delta_{ij}$ are evidence for 1:1 species provided that the equilibrium constant is not too large (32). However, it has been shown (31) that the second test is rather insensitive.

In this section a simple test for the presence of complexes containing more than one substrate molecule is described and the implications of changes in composition for the determination of relative bound shifts are examined. It is assumed that only LS_1 and/or LS_2 species can be formed in which case the δ_{ij} are given by

$$\delta_{ij} = ([LS_1]/[S_0])_j \Delta_{1i} + 2 ([LS_2]/[S_0])_j \Delta_{2i} \quad (8)$$

Consider the δ_{ij} vs $[L_0]/[S_0]$ plot for a substrate forming only LS_1 species. For small $[L_0]/[S_0]$ ratios $[LS_1] \approx [L_0]$ and the slopes Δ_{1i}' of the curves in the linear part of the plot are approximately equal to the bound shifts Δ_{1i} . For large $[L_0]/[S_0]$ ratios $[LS_1] \approx [S_0]$ and the observed shifts Δ_{1i}'' approach the Δ_{1i} asymptotically. Both Δ_{1i}' and Δ_{1i}'' are only approximations of the true bound shifts Δ_{1i} but, as Fig. 8 shows, the Δ_{1i}'' are the better approximations. This means that the experimental points for small $[L_0]/[S_0]$ must lie below lines with slopes equal to the induced shifts for high $[L_0]/[S_0]$ ratios.

The appearance of the δ_{ij} vs $[L_0]/[S_0]$ plot changes as LS_2 adducts are formed. The same amount of shift reagent binds twice as much substrate in LS_2 complexes and therefore the fraction of bound substrate can be up to twice as high as in the case of LS_1 adducts. Since the induced shifts are proportional to the fractions of bound substrate, the experimental initial slopes can be up to twice as large as the maximum slopes in the 1:1 model.

Thus there is a simple test for the presence of LS_2 species. Straight lines through the origin are constructed with slopes equal to the induced shifts observed for high $[L_0]/[S_0]$ ratios. If the experimental points lie below these lines only LS_1 complexes have been formed. Of course, it is not possible to decide in this way whether LS_2 adducts have been formed exclusively or in addition to LS_1 species.

Fig. 8. Plot of ratios of approximate to theoretical bound shifts vs equilibrium constants for the equilibrium $L + S \rightleftharpoons LS$. The substrate concentration is 0.1 moles/liter. Solid lines: the $\Delta(\text{appr})$ are the theoretical induced shifts for the $[L_0]/[S_0]$ ratios indicated in the insert. Dashed line: the $\Delta(\text{appr})$ are the theoretical initial slopes.

However, if one is only interested in bound shifts, the question whether or not there is a mixture of complexes may not have to be answered. According to equation (8) the induced shifts are proportional to the bound shifts Δ_{1i} and Δ_{2i} respectively if only LS_1 or only LS_2 adducts are formed. If a mixture of LS_1 and LS_2 is obtained, the induced shifts can still be proportional to a set of bound shifts, provided that the Δ_{1i} and Δ_{2i} are equal.

$$\frac{\delta_{ij}}{\delta_{nj}} = \frac{([LS_1]/[S_o])_j \Delta_{1i} + 2 ([LS_2]/[S_o])_j \Delta_{2i}}{([LS_1]/[S_o])_j \Delta_{1n} + 2 ([LS_2]/[S_o])_j \Delta_{2n}}$$

$$= \Delta_i/\Delta_n, \text{ if } \Delta_{1i} = \Delta_{2i} \equiv \Delta_i \quad (9)$$

In other words, if the ratios of the induced shifts are found to be independent of the shift reagent concentration, the induced shifts are proportional to a set of bound shifts. For the purpose of structure elucidation the question whether they are proportional to the Δ_{1i} or the Δ_{2i} , ie whether only LS_1 or only LS_2 are formed, or whether the Δ_{1i} and Δ_{2i} are equal is of secondary importance. This simple relation between induced and bound shifts only breaks down if more than one **species** is formed and the bound shifts in the various adducts differ. In this case the ratios of the induced shifts are expected to be a function of the shift reagent concentration and a multiparameter fit to the experimental data is required for the determination of bound shifts.

Table 4. Ratios of induced shifts and approximate bound shifts for the methyl group protons of borneol^a complexed to $\text{Pr}(\text{fod})_3$ ^b.

	8 ^c	9 ^c	10
$[L_o]/[S_o]$	ratios of induced shifts		
0.1	43.4	46.3	100.0
0.2	43.5	45.9	100.0
0.4	43.4	45.8	100.0
0.6	43.5	45.9	100.0
0.8	43.5	45.9	100.0
1.0	43.5	46.0	100.0
2.0	43.5	46.1	100.0
3.0	43.4	46.2	100.0
4.0	43.4	46.1	100.0
5.0	43.4	46.1	100.0
	approximate bound shifts		
Δ_i^{d}	563.3	593.9	1302.8
Δ_i^{e}	369.5	393.0	852.0

a. borneol numbering system

- b. to a 0.1 m solution of borneol in CDCl_3 aliquots of a 0.5 m stock solution of $\text{Pr}(\text{fod})_3$ were added. The chemical shifts were obtained on an XL 100 nmr spectrometer operating at 32.5°C
- c. the assignments may have to be reversed
- d. initial slopes of the curves in Fig.9
- e. observed induced shifts for $[L_o]/[S_o]=5$

To test these theoretical considerations the system $\text{Pr}(\text{fod})_3$ -borneol was studied. Fig. 9 is a plot of the induced shifts of the borneol methyl protons as a function of the shift reagent/substrate concentration ratio. Also indicated are the dividing lines between the 1:1 and 1:2 stoichiometries. It is clear that the experimental data are inconsistent with the 1:1 model and that LS_2 adducts must have been formed. Furthermore, the ratios of the induced shifts, given in table 4, are found to be independent of the shift reagent concentration in the range $0 \leq [\text{L}_0]/[\text{S}_0] \leq 5$. Thus we can conclude that in this case induced shifts are directly proportional to the bound shifts. The fact that the ratios of the induced shifts are independent of the shift reagent concentration also justifies the tacit assumption that internal standards compensate for the bulk magnetic susceptibility changes caused by the addition of shift reagent.

From the results for borneol and other compounds studied in this laboratory it appears that even if a substrate can form complexes of different stoichiometries the induced shifts will generally be found to be proportional to a set of bound shifts, presumably because the bound shifts in the different complexes are the same. It is clear, however, that this must be established for every individual case, ie the ratios of the induced shifts have to be independent of the shift reagent concentration.

Fig. 9. Plot of induced shifts vs shift reagent/substrate ratios for the methyl protons of borneol in the presence of $\text{Pr}(\text{fod})_3$.

CHAPTER 6. VARIATION OF THE RATIOS OF THE BOUND SHIFTS
WITH CHANGES IN EXPERIMENTAL CONDITIONS (40).

It has been shown in the preceding chapters that the ratios of the induced shifts and therefore the ratios of the bound shifts are independent of the shift reagent concentrations. In this chapter the influence of the change of solvent, substrate concentration and temperature on the ratios of the bound shifts are considered. Since the bound shifts are a function of the geometry of the shift reagent-substrate adduct, only changes in this geometry should affect the relative bound shifts. Therefore the ratios of the induced shifts are not expected to be a function of solvent and concentration and this is indeed borne out by the data in tables 5 and 6. However, there is a slight but systematic variation of the ratios of the induced shifts with change in temperature (table 7), presumably due to changes in the adduct structure.

Because of their insensitivity to variations in the experimental conditions the ratios of the bound shifts are the parameters of choice for the characterization of substrates. Since it is expected that compounds with the same structural units carrying the complexing functionality will form adducts of the same geometry, it was interesting to see whether this is reflected in the ratios of the bound shifts. The partial structures in β -amyrin and germanicol, carrying the methyl groups 23-27, are practically the same. These methyl groups should

Table 5. Variation of slopes and slope ratios for the methyl group signals of β -amyrin with change of solvent. Shift reagent is $\text{Pr}(\text{fod})_3$, maximum $[\text{L}_0]/[\text{S}_0]$ is 0.5

Me	CDCl_3			benzene		
	slopes	ratios	errors	slopes	ratios	errors
30	11.6	7.5	0.6	14.1	6.9	1.3
29	33.2	21.5	1.4	42.4	20.9	2.6
28	95.2	61.1	1.4	129.1	63.8	1.6
27	129.1	83.0	1.2	174.8	86.1	1.8
26	262.1	168.4	1.9	349.7	172.3	0.8
25	649.5	417.3	1.7	850.2	418.9	1.0
24	1503.9	966.3	1.9	1956.3	963.8	0.9
23	1556.2	1000.0	-	2029.8	1000.0	-

Table 6. Variation of slopes and slope ratios for the methyl group signals of β -amyrin with changes in absolute concentration of substrate. Solvent is CDCl_3 , shift reagent $\text{Pr}(\text{fod})_3$, maximum $[\text{L}_0]/[\text{S}_0]$ ratio is 0.5.

conc.	0.100		0.068		0.051	
Me	slopes	ratios	slopes	ratios	slopes	ratios
30	11.6	7.5	10.8	7.6	9.5	7.3
29	33.2	21.5	29.3	20.7	26.8	20.4
28	95.2	61.1	85.0	60.2	79.2	60.4
27	129.1	83.0	118.1	83.5	109.5	83.5
26	262.1	168.4	238.5	168.9	222.4	169.8
25	649.5	417.3	590.3	418.0	546.4	417.2
24	1503.9	966.3	1368.2	968.8	1266.3	967.1
23	1566.2	1000.0	1412.1	1000.0	1309.4	1000.0

Table 7. Variation of slopes and slope ratios for the methyl group signals of β -amyrin with change in temperature. Shift reagent is $\text{Pr}(\text{fod})_3$, solvent is CDCl_3 , maximum $[\text{L}_0]/[\text{S}_0]$ is 0.5

temp. $^{\circ}\text{C}$	45		32		15		0	
Me	slopes	ratios	slopes	ratios	slopes	ratios	slopes	ratios
30	10.6	7.5	11.6	7.5	4.0	1.9	11.6	5.7
29	31.3	22.1	33.2	21.5	35.2	18.6	46.9	23.3
28	86.5	60.6	95.2	61.1	111.4	59.2	116.6	58.2
27	119.6	83.8	129.1	83.0	142.0	75.4	146.8	73.1
26	238.8	167.4	262.1	168.4	308.7	164.1	326.4	162.9
25	592.9	415.5	649.5	417.3	774.1	411.5	817.9	408.2
24	1392.1	975.5	1503.9	966.3	1774.5	943.5	1871.0	933.6
23	1427.0	1000.0	1556.2	1000.0	1880.3	1000.0	2004.2	1000.0

therefore have the same geometric relation to the chelate and consequently the same relative bound shifts. As table 8 shows this is indeed the case. It is also apparent that the relative bound shifts are sensitive enough to configurational and conformational changes to reflect structural differences 10 Å or more from the complexing functionality.

Table 8. Slopes and slope ratios for the methyl group signals of β -amyrin and germanicol. Shift reagent is $\text{Pr}(\text{fod})_3$, solvent is CDCl_3 , maximum $[\text{L}_0]/[\text{S}_0]$ is 0.5.

Me	β -amyrin			germanicol		
	slopes	ratios	errors	slopes	ratios	errors
30	11.6	7.5	0.6	12.3	9.4	1.4
29	33.2	21.5	1.4	24.2	18.5	2.2
28	95.2	61.1	1.4	65.8	50.2	1.6
27	129.1	83.0	1.2	108.1	82.5	1.8
26	262.1	168.4	1.9	225.4	172.0	2.0
25	649.5	417.3	1.7	545.3	415.9	4.2
24	1503.9	966.3	1.9	1263.4	963.6	4.4
23	1566.2	1000.0	-	1311.2	1000.0	-

Table 9. Slopes and slope ratios in shift reagent plots for the chemical shifts of the C-18 and C-19 methyl groups of various keto and thioketal androstanes, in the presence of $\text{Pr}(\text{fod})_3$.

androstane derivative	shifts without $\text{Pr}(\text{fod})_3$		slope ratios	
	C-18	C-19	C-18	C-19
1-keto	69.2	114.4	23.6	100.0
2-keto	69.5	74.7	13.1	100.0
3-keto	72.7	101.9	23.4	100.0
4-keto	71.0	75.3	16.4	100.0
6-keto	71.6	74.4	16.7	100.0
7-keto	69.2	105.5	88.2	100.0
11-keto	66.4	101.3	65.3	100.0
12-keto	101.1	87.2	100.0	34.3
16-keto	88.0	83.0	100.0	22.5
17-keto	85.4	80.7	100.0	20.8
17-keto- 3-thioketal	86.0	84.0	100.0	21.2
11-keto, 3,17-dithioketal	87.0	103.0	59.8	100.0

steroid numbering system:

Similarly it is found that blocking of one functional group in a bifunctional molecule gives an effectively mono-

functional compound with the same relative bound shifts as the actual monofunctional substrate, provided that the blocking group is not too close to the complexing site. For instance a comparison of the slope ratios for the methyl groups of 3-keto androstane, 17-keto androstane and the monothioketal derivative of 3,17-diketo androstane (table 9) shows that the keto group in position 3 was thioketalized. Agreement between the slope ratios for the methyl groups of 11-keto androstane and its 3,17-dithioketal derivative was not as good, possibly due to conformational changes or steric interactions between the shift reagent ligands and the thioketal groups, causing a change in the adduct geometry.

CHAPTER 7. SUMMARY AND DISCUSSION OF THE RESULTS DESCRIBED
IN THE FOREGOING CHAPTERS.

It is clear from the foregoing that there is no need to know the absolute values of the bound shifts. The ratios of the bound shifts contain exactly the same structural information, can be obtained very accurately from routine measurements, and are in fact more useful for comparison purposes. The bound shifts are proportional to the geometric quantities in equation (1) describing the position of each of the substrate nuclei in the coordinate system of the chelate.

$$\Delta_i = C (1-3\cos^2\theta_i)/R_i^3 \quad (1)$$

Since the proportionality constant in equation (1) is the same for all nuclei in a given substrate the ratios of the bound shifts are proportional to the geometric factors. Furthermore, this proportionality constant, and therefore the absolute values of the bound shifts, are temperature dependent (see full equation (1) on page 4) and cannot be used for a direct comparison of results obtained with instruments operating at different temperatures. A change in temperature may also change the geometry of the adduct and therefore not even relative bound shifts obtained at different temperatures may be strictly comparable.

The determination of relative bound shifts is simple if only one kind of adduct is formed or if the bound shifts in adducts of all compositions are equal.

$$\delta_{ij} = \{([\text{LS}_1] + 2 [\text{LS}_2] + \dots)/[\text{S}_0]\}_j \Delta_i \quad (10)$$

This proportionality holds whenever there is a linear correlation between the induced shifts for the different substrate nuclei. This has indeed been observed for the compounds studied in this laboratory. The simple relation between induced and bound shifts only breaks down if there is no linear correlation between the induced shifts. In this case the induced shifts are weighted averages of several sets of bound shifts and a multiparameter fit to the experimental data would be required to obtain structural parameters (31).

The direct correlation between the induced shifts, however, is not the most convenient way to obtain relative bound shifts. It is not always possible to measure the chemical shifts in the absence of shift reagent and to assign the signals unambiguously in every spectrum. It is simpler to generate an intermediate plot of chemical shifts against shift reagent coordinates which are proportional to the sums of the shifts in each spectrum. In this case complete linearity of the curves over a wide range of $[\text{L}_0]/[\text{S}_0]$ ratios is necessary to assure proportionality between induced and bound shifts. If it should be impossible to obtain straight line plots this is an indication that complexes of different composition with different bound shifts are formed.

If chemical shifts at sufficiently high shift reagent concentrations are measured and the hypothetical shift reagent coordinates are normalized to the interval $[0,1]$, these coor-

ordinates represent the total fractions of bound substrate,

$$([LS_1] + 2 [LS_2] + \dots)/[S_0].$$

If the plots are indeed linear the bound shifts are directly proportional to the slopes of the best lines through the experimental points. In addition to elimination the need to know the chemical shifts before addition of shift reagent, these plots facilitate the sorting of signals and provide a graphical check of the experimental data. If some of the chemical shifts can be measured in the absence of shift reagent these plots also provide excellent estimates for the chemical shifts of the other nuclei.

It is clear that it is completely unnecessary to restrict the experiment to the linear part of shift reagent plots, as it is usually done. It is best to collect experimental data over a wide range of $[L_0]/[S_0]$ ratios to obtain maximum spectral dispersion and maximum accuracy. The same relative bound shifts must be obtained from the correlation between the induced shifts themselves, from the slopes of linear plots of chemical shifts vs shift-derived shift reagent coordinates and from linear plots of chemical shifts vs experimental $[L_0]/[S_0]$ ratios at low shift reagent concentrations. The elimination of the comparatively inaccurate experimental $[L_0]/[S_0]$ ratios from the calculations does not give more accurate relative bound shifts. The independence of the ratios of the induced shifts from the shift reagent concentrations is an implicit property of the experimental data and it is unnecessary to introduce it explicitly. The

generation of intermediate linearized shift reagent plots or the direct correlation between the induced shifts merely gives smaller and more realistic error estimates. Thus it is clear that the different methods used in the literature - the determination of slopes in the linear parts of experimental shift reagent plots (13-24), the determination of induced shifts at fixed $[L_0]/[S_0]$ ratios of unity (9-12), their extrapolation to $[L_0]/[S_0]$ ratios of unity (25-27) etc - all have to give sets of structural parameters which are proportional to each other and to results obtained with the methods described here. If they are normalized, for instance by assigning a value of 100.0 or 1000.0 to the shift for the fastest moving signal, all these methods should in principle give the same results. Of course, their accuracy increases with the magnitude of the induced shifts, ie with the range of $[L_0]/[S_0]$ ratios, and with the number of spectra obtained at different shift reagent concentrations.

CHAPTER 8. STRUCTURE ELUCIDATION WITH THE USE OF THE PSEUDOCONTACT EQUATION.

In the preceding chapters our approach to the determination of accurate values for the relative bound shifts were outlined. These parameters are of interest because they are characteristic quantities for every substrate. Since their sign and magnitude is a function of the substrate structure, a proposed structure can be supported by fitting the theoretical shielding equation to the experimental data, for instance by the method outlined in this chapter.

It is generally assumed, and has been verified (10,11,23,26) by the successful prediction of experimental induced shifts with the pseudocontact equation that lanthanide induced shifts are predominantly or entirely due to a dipolar shielding mechanism. The method by which the pseudocontact equation was fitted to the experimental data was not specified in ref. (11) and (26). The results in ref. (23) were obtained by a nonlinear regression technique, and those reported in ref. (10) were obtained by continuous variation of spherical polar coordinates of the metal atom to locate its best position.

For a complex having effectively axial symmetry the pseudo-contact contribution to the chemical shift is given by equation (1)

$$\Delta_i = C (1-3\cos^2\theta_i)/R_i^3 \quad (1)$$

The form of the proportionality constant C is of no interest

here. However, C is one of the data fitting variables. R_i is the vector from the metal to the i 'th nucleus and θ_i is the angle between the principal axis of the chelate and the vector R_i . If it is assumed that the principal axis of the chelate points toward the complexing heteroatom there are four variables: the proportionality constant C and the metal coordinates x , y , and z .

Since the Δ_i are nonlinear functions of the three variables x , y , and z it is not possible to carry out a linear least squares fit with equation (1) in its present form. To bring it into a form suitable for linear least squares analysis Δ_i is expanded in a Taylor series in the variables C , x , y , and z , truncating after the linear terms. The necessary derivations are outlined in appendix 1.

$$\begin{aligned} \Delta_i' = (\Delta_i)_1 + (\partial\Delta_i/\partial C)_1\Delta C + (\partial\Delta_i/\partial x)_1\Delta x + (\partial\Delta_i/\partial y)_1\Delta y \\ + (\partial\Delta_i/\partial z)_1\Delta z \end{aligned} \quad (11)$$

The subscript 1 in equation (11) indicates that Δ_i and the partial derivatives are evaluated with the parameters derived in the 1'th cycle of the iteration.

At the beginning of the iterations it must be possible to assign a sufficient number of signals to nuclei in the proposed compound. Signals whose assignment is doubtful and those which cannot be assigned are excluded until the parameters have been optimized.

The substrate structure is defined in terms of Cartesian coordinates. Starting values for the lanthanide metal coordinates

are conveniently obtained by specifying a substrate nucleus which, together with the heteroatom on the substrate, defines a vector pointing to a likely metal position. For instance, the point on the vector $C(7) - O$, $3\text{\AA}$ from oxygen, served as starting point in the case of borneol.

The optimization of the parameters begins by evaluating the coefficients in equation (11) with the starting values for C , x , y , and z . Least squares optimization of the variables ΔC , Δx , Δy , and Δz in equation (11) gives a new set of values for the parameters C , x , y , and z . The coefficients in equation (11) are reevaluated with the new parameters and the next set of C , x , y , and z is obtained. The calculations are terminated when the ΔC , Δx , Δy , and Δz drop below preset limits.

A program was written based on the described algorithm and tested with a problem for which the exact solution was known. The substrate was borneol and its cartesian coordinates, used in the calculations, are given in table 10. The proportionality constant C and the x , y , and z coordinates chosen for this test case are given in the last row of table 11. The predicted shifts calculated for this value for C and with the geometric quantities based on the borneol coordinates in table 10 and the metal coordinates in the last row of table 11, are given in the last column of table 10. These calculated induced shifts represented the "experimental" induced shifts in the test case. The starting values for C , x , y , and z are indicated in the first row of table 11. x , y , and z were arrived at, as

Table 10. Carbon and hydrogen coordinates for borneol and calculated induced shifts for the ring and methyl group protons^a.

atom	coordinates			Δ_i^b
	x	y	z	
C-1	1.158	0.000	0.000	
C-2	0.776	1.220	-0.886	
C-3	-0.776	1.220	-0.886	
C-4	-1.158	0.000	0.000	
C-5	-0.776	-1.220	-0.886	
C-6	0.776	-1.220	-0.886	
C-7	0.000	0.000	1.043	
Me-10	2.828	0.000	0.906	18.7
O-2n	1.258	1.096	-2.226	
H-3n	-1.152	1.123	-1.931	42.0
H-4	-2.138	0.000	0.532	13.0
H-5n	-1.152	-1.123	-1.931	24.4
H-6n	1.152	-1.123	-1.931	47.5
Me-8	0.000	1.537	2.161	11.0
H-2x	1.152	2.184	-0.472	60.4
H-3x	-1.152	2.184	-0.472	21.1
H-5x	-1.152	-2.184	-0.472	14.9
H-6x	1.152	-2.184	-0.472	20.7
Me-9	0.000	-1.537	2.161	10.8

- a. the carbon and ring proton coordinates are those given in ref. (35) for bornane. The methyl protons are represented by the centers of the circles of rotation of the hydrogens. For the determination of the methyl and oxygen positions standard bond lengths and angles were assumed.
- b. calculated with the parameters given in the last row of table 11.

Table 11. Iterative approach to the best values for C, x, y, and z, with the coordinates and calculated shifts in table 10.

cycle	C	x	y	z	RMS
0 ^a	-3.00	2.064	3.244	-4.087	1.06
1	-2.77	2.018	2.967	-4.002	0.14
2	-2.80	2.004	2.992	-4.003	0.02
3	-2.80	2.004	2.991	-4.003	0.02
b	-2.80	2.000	3.000	-4.000	

a. initial estimates

b. values with which the induced shifts were calculated

mentioned earlier, by going $3\text{\AA}$ from oxygen along the vector pointing from C(7) to oxygen. The convergence to the correct parameters is illustrated in table 11.

The program was then used to predict induced shifts and to optimize C and the lanthanide metal location with experimental induced shifts for the system borneol-Pr(fod)₃. The borneol coordinates used were those in table 10, the experimental induced shifts, taken from reference (26), and the differences between prediction and experiment are found in table 13. Table 12 indicates the starting parameters and Fig. 10 shows the initial and optimized lanthanide metal positions.

The choice of the starting parameters is not critical. Convergence to the best values is rapid even if the initial lanthanide location is $2\text{\AA}$ or more from the best position. Typically

Table 12. Iterative approach to the best values for C, x, y, and z for the system borneol/ $\text{Fr}(\text{fod})_3^{\text{a}}$. The coordinates are given in table 10, the experimental shifts in table 13.

cycle	C	x	y	z	R^{c}	RMS
0 ^b	-3.00	2.064	3.244	-4.087	2.954	6.83
1	-2.43	1.256	3.197	-4.565	3.144	1.44
2	-2.40	1.153	2.922	-4.576	2.978	0.90
3	-2.43	1.077	2.885	-4.618	2.992	0.89
4	-2.43	1.082	2.878	-4.616	2.986	0.89

a. the experimental induced shifts were taken from ref. (26)

b. initial estimates

c. distance between hydroxyl oxygen and metal atom.

Table 13. Experimental induced shifts and differences between calculated and experimental induced shifts for the system borneol/ $\text{Pr}(\text{fod})_3$.

atom	$\Delta_i(\text{obs})$	$\Delta_i(\text{calc}) - \Delta_i(\text{obs})$		
		ref. (26)	all Δ_i	H-2x excl.
Me-10	17.8	-1.3	-1.7	-1.8
H-3n	34.2	-4.0	0.1	0.1
H-4	10.1	0.3	-1.2	-1.2
H-5n	16.0	0.1	1.2	1.0
H-6n	35.6	3.1	0.4	0.4
Me-8	8.0	0.1	1.4	1.5
H-2x	45.0	4.0	-0.2	-1.0
H-3x	16.6	-0.8	-0.5	-0.3
H-5x	10.5	0.5	-0.1	-0.3
H-6x	15.7	0.3	0.1	-0.1
Me-9	7.8	0.1	0.6	0.5

Fig. 10. Initial ($\square$) and optimized (Δ) lanthanide metal locations relative to the substrate for the system borneol- $\text{Pr}(\text{fod})_3$.

five or six iterations are necessary, requiring only fractions of a minute of computer time.

It appears that the induced shifts even for nuclei close to the coordinating site are accounted for satisfactorily by the pseudocontact shielding mechanism. However, ^{13}C nmr studies of the same system (11), borneol- $\text{Pr}(\text{fod})_3$, indicate that there may be contact contributions to the induced shifts of nuclei close to the coordinating site. Thus, there was an 18% difference between predicted and observed induced shifts for the hydroxyl carbon of borneol (11). Clearly further investigations are necessary to decide whether large discrepancies

between predicted and observed induced shifts are indeed due to contact contributions or to unjustified approximations such as the assumption that the principal axis of the complex points to the complexing functionality.

CHAPTER 9. DETERMINATION OF EQUILIBRIUM CONSTANTS FOR
 $L + S \rightleftharpoons LS$ EQUILIBRIA.

Although it may be quite common that mixtures of shift reagent-substrate adducts of different compositions are formed it was nevertheless interesting to develop a reliable method for the determination of equilibrium constants for the simplest case

Within this model defined by equation (12) the equilibrium constant and the induced shifts are given by

$$K = [LS] / ([L_0] - [LS])([S_0] - [LS]) \quad (13)$$

and

$$\delta_{ij} = ([LS]/[S_0])_j \Delta_i \quad (14)$$

Two slightly different approximate relations between the δ_{ij} and K and Δ_i have been derived, based on two different simplifications of equation (13), both valid in the region $[S_0] \gg [L_0]$. If the term $[LS]^2$ in the denominator of equation (13) is neglected, the combination of equation (13) in its simplified form and equation (14) gives (32)

$$[S_0] = [L_0] \Delta_i / \delta_{ij} - (1/K + [L_0]) \quad (15)$$

If instead the approximation $([S_0] - [LS]) \approx [S_0]$ is made in the denominator of equation (13), the combination of equation (13)

in its abbreviated form and equation (14) gives (30)

$$1/\delta_{ij} = 1/\Delta_i [L_o][S_o] + 1/\Delta_i [L_o] K \quad (16)$$

Thus Δ_i and K are obtained from the slopes and intercepts of linear $[S_o]$ vs $1/\delta_{ij}$ and $1/\delta_{ij}$ vs $[S_o]$ plots respectively.

It was also shown (34) that concentration variation experiments at constant $[L_o]/[S_o] = 1$ give linear plots of δ_{ij} vs $\sqrt{\delta_{ij}/[S_o]}$, with slopes equal to $-\sqrt{\Delta_i/K}$ and intercepts equal to Δ_i .

The approach outlined below is similar to that in ref. (31) and does not introduce any approximations within the model defined by equation (12). The full equation (13) is solved for $[LS]$ and the expression for $[LS]$ is substituted into equation (14), giving

$$\delta_{ij} = (K[S_o] + K[L_o] + 1 - \sqrt{(K[S_o] + K[L_o] + 1)^2 - 4K^2[S_o][L_o]}) \Delta_i / 2K[S_o] \quad (17)$$

Since δ_{ij} is a nonlinear function of K , equation (17) cannot be used for a linear least squares fit to the experimental data. Therefore δ_{ij} is expanded in a Taylor series in Δ_i and K , truncating after the linear terms.

$$\delta_{ij}' = (\delta_{ij})_1 + (\partial\delta_{ij}/\partial\Delta_i)_1 \Delta\Delta_i + (\partial\delta_{ij}/\partial K)_1 \Delta K \quad (18)$$

The subscript 1 indicates that δ_{ij} and the partial derivatives are evaluated with the parameters derived in the i 'th cycle of the iteration. The necessary derivations are outlined in appendix 1. With this approximate equation for δ_{ij}' an iterative least squares fit could be carried out for every nucleus, for which chemical shift data are available. Presumably, slightly

different values for K would be obtained, which could be averaged to obtain a best value. Instead, the sum of the induced shifts in each spectrum is used and minimization gives directly the best values for K and for the sum of the bound shifts. If absolute values for the individual Δ_i are desired, they can be obtained by scaling relative bound shifts such that their sum equals the sum of the bound shifts obtained by the iterative least squares fit. By working with the sum of the shifts one uses again the fact that the shift reagent coordinates are exactly the same for all substrate nuclei in a given sample.

The method is illustrated with the data in table 14. The δ_{ij} and $[L_0]/[S_0]$ in the first four columns are the exact solutions for a hypothetical system with an equilibrium constant $K = 500$ and with the bound shifts indicated in the same table. As table 15 shows the correct values for K and Δ_i are obtained after only a few iterations. The simulation of data with experimental errors, by addition of random numbers to the δ_{ij} and $[L_0]/[S_0]$, affords a more realistic test of the method. One set of such simulated experimental data is given in columns five to eight in table 14 and the iterative approach to the best values for K and Δ_i is shown in table 15. Series of calculations with data to which random errors in the range $-1 \leq \Delta\delta_{ij} \leq 1$ [Hz] and $-5 \leq \Delta V_L \leq 5$ [μ l of 0.5 M shift reagent stock solution] were added generally gave equilibrium constants and sums of bound shifts which were within 10% and 1% respectively of the correct solutions.

Table 14. Simulated experimental $[L_o]/[S_o]$ ratios and δ_{ij} used in the illustration of the derivation of K and $\Sigma\Delta_i$.

$[L_o]/[S_o]$	exact solution			with random errors ^a		
	δ_{i1}	δ_{i2}	δ_{i3}	δ_{i1}	δ_{i2}	δ_{i3}
0.2	39.0	117.0	195.0	42.2	126.0	209.8
0.4	77.3	231.8	386.4	72.6	216.4	361.6
0.6	114.1	342.2	570.3	119.8	357.2	595.1
0.8	147.1	441.3	735.5	150.8	452.2	752.8
1.0	171.3	514.0	856.6	168.5	507.3	847.4
1.5	190.9	572.7	954.5	192.1	574.2	956.8
2.0	194.7	584.1	973.4	194.7	583.1	973.9
3.0	196.9	590.6	984.4	196.8	590.4	983.9
4.0	197.6	592.9	988.2	198.0	591.9	988.4
5.0	198.0	594.1	990.1	198.6	594.6	989.8
Δ_i	200.0	600.0	1000.0	200.0	600.0	1000.0

a. the induced shifts are calculated with equation (17) after random errors were added to $[L_o]$ and $[S_o]$. Then random errors were added to the δ_{ij} .

Table 15. Iterative derivation of the best values for K and Δ_i with the data in table 14.

cycle	exact solution			with random errors		
	RMS	K	$\Sigma\Delta_i$	RMS	K	$\Sigma\Delta_i$
0 ^a	7.89	750.0	1782.2	11.32	750.0	1802.3
1	4.44	418.5	1798.8	9.88	457.5	1800.4
2	0.50	490.4	1799.7	9.28	530.3	1799.3
3	0.01	499.9	1800.0	9.27	534.7	1800.4
4	0.00	500.0	1800.0	9.27	534.4	1800.4

a. initial estimates

Fig. 11. Experimental induced shifts and theoretical curves based on the $L + S \rightleftharpoons LS$ model, for the system borneol/ $\text{Pr}(\text{fod})_3$.

The system borneol/ $\text{Pr}(\text{fod})_3$ was the only case for which an attempt was made to derive values for the equilibrium constant. However, as mentioned earlier, it was found that LS_2 species are formed in this case, possibly in addition to LS adducts. The iterative least squares fit to the experimental data gave reasonable values for the bound shifts, which are close to the observed shifts for $[\text{L}_0]/[\text{S}_0]$ ratios of 5. The values for K ranged from 500 to 700 liter/mole and presumably have no significance since the physical model is inadequate. The failure of the model in this case is illustrated in Fig. 11 by the lack of agreement between the experimental and theoretical curves.

Although the present substrate-shift reagent combination borneol/ $\text{Pr}(\text{fod})_3$ was definitely shown to form 2:1 adducts it is conceivable that other shift reagents and substrates, especially bulky ones, form only 1:1 adducts. For these cases the present method provides a quick and reliable way to determine equilibrium constants and bound shifts.

EXPERIMENTAL

Compounds used in these studies. The organic substrates used in the shift reagent studies were available in the laboratory from other projects. The shift reagents $\text{Eu}(\text{fod})_3$ and $\text{Pr}(\text{fod})_3$ were purchased from Norell Chemical Co. and used without further purification.

Sample preparations. In the standard procedure 0.1 molar solutions of the substrates in CDCl_3 were prepared. 0.5 ml of the sample solutions were transferred with a 0.5 ml syringe to the nmr tube. The shift reagents were kept in the desiccator. Prior to every run a sufficient amount of shift reagent was weighted out and dissolved in CDCl_3 to obtain a 0.5 molar stock solution. No special precautions were taken during weighing and solution preparation to exclude moisture, but the task was carried out as quickly as possible. Depending on the desired range of $[\text{L}_0]/[\text{S}_0]$ concentration ratios a 0.05 or 0.1 ml syringe was filled with the shift reagent solution. This filled syringe was kept in a desiccator. Aliquots of the shift reagent solution were added from the syringe to the nmr tube.

A different sample preparation procedure was used in the temperature and concentration variation studies. 0.5 ml of a 0.1 molar substrate solution were added to ten different nmr tubes. To each of the tubes a different amount of shift reagent stock solution was added to obtain a series of solutions with $[\text{L}_0]/[\text{S}_0]$ ratios ranging from 0.05 to 0.5. The tubes were then

sealed, without degassing, and the temperature variation studies were carried out. After completion the tubes were opened and solvent was added in two steps for the concentration variation studies.

Nmr spectra. All nmr spectra were obtained on a Varian XL 100/12 nmr spectrometer operating at 32.5 °C, with the exception of the temperature variation studies. ^2H of CDCl_3 was the internal lock signal. The nmr spectra were recorded at a sweep width of 1000 Hz and a sweep rate of 500 sec. One trace was recorded. The chemical shifts were read, by interpolation, at the center of the signal at half height. Errors in reading off the chemical shifts are estimated to be of the order of 1 Hz, which also was the order of magnitude of the deviations of the experimental points from the least squares lines in the corrected shift reagent plots.

The chemical shifts for β -amyrin plotted in Figures 3 and 4 and in Figures 5 and 6 and the chemical shifts for borneol were determined by the author. The nmr spectra in the temperature and concentration variation series and the nmr spectra of the steroids were obtained by Mr. McCarville.

Data analysis and computations. All calculations were performed on the XDS Sigma 6 and XDS Sigma 9 computers at Carleton University, with programs written in Fortran IV. Details on the programs are found in appendix 2.

APPENDIX 1. MATHEMATICAL DERIVATIONS OF EXPRESSIONS FOR THE COEFFICIENTS IN EQUATIONS (11) OF CHAPTER 8 AND EQUATION (18) IN CHAPTER 9.

In the first part of this appendix the mathematical derivations necessary for the iterative least squares fit of the pseudo-contact equation to the experimental induced shifts are given (see also chapter 8). First the expression for the bound shifts in terms of the proportionality constant and the lanthanide shift reagent metal location is given. Next the set of linear equations for the least squares minimization is expressed in terms of the partial derivatives with respect to the four variables. Then these partial derivatives are evaluated in terms of the substrate coordinates and the parameters to be optimized.

In the second part of this appendix the necessary derivations for the iterative least squares derivation of equilibrium constants and bound shifts are given (see also chapter 9). First the expression for the induced shifts is expanded in the equilibrium constant and the bound shifts (equation (18) in chapter 9). Then the set of linear equations of the least squares minimization is given in terms of the partial derivatives with respect to the equilibrium constant and the bound shift. Finally the partial derivatives are evaluated in terms of the shift reagent and substrate concentrations and the parameters to be optimized.

Derivation of expressions for the coefficients in equation (11), chapter 8, for the iterative least squares fit of the pseudocontact equation to the experimental induced shifts.

Δ_i is expanded in a Taylor series in C , x , y , and z , truncating after the linear terms (equation (11) in chapter 8)

$$\begin{aligned}\Delta_i' &= (\Delta_i)_1 + (\partial\Delta_i/\partial C)_1 \Delta C + (\partial\Delta_i/\partial x)_1 \Delta x + (\partial\Delta_i/\partial y)_1 \Delta y \\ &\quad + (\partial\Delta_i/\partial z)_1 \Delta z \\ &= c_{i0} + \sum_j c_{ij} x_j, \quad j = 1, \dots, 4\end{aligned}$$

The sum of the squares of the differences between calculated and experimental induced shifts is minimized with respect to the four variables $x_1 - x_4$, and a set of linear equations for the best changes in the parameters, ΔC , Δx , Δy , and Δz , is obtained.

$$\frac{\partial \sum_i [\Delta_i' - \Delta_i]^2}{\partial x_k} = \frac{\partial \sum_i [c_{i0} + \sum_j c_{ij} x_j - \Delta_i]^2}{\partial x_k} = 0, \quad k = 1, \dots, 4$$

$$\sum_{ij} c_{ij} c_{ik} x_j = \sum_j c_{ik} (\Delta_i - c_{i0}), \quad k = 1, \dots, 4$$

In the following derivations of expressions for the coefficients $c_{i1} - c_{i4}$ the symbols correspond to those in the computer program in appendix 2. b_{11} is the first derivative of a_{11} with respect to each of the x_k etc. $\delta_{k1} = 0$, if $k \neq 1$ and $\delta_{k1} = 1$ if $k = 1$.

u_i, v_i, w_i proton coordinates

u_m, v_m, w_m metal coordinates

u_0, v_0, w_0 heteroatom coordinates

$$a_{11} = u_i - u_m, a_{12} = v_i - v_m, a_{13} = w_i - w_m$$

$$a_{14} = u_0 - u_m, a_{15} = v_0 - v_m, a_{16} = w_0 - w_m$$

$$a_{18} = \sqrt{a_{14}^2 + a_{15}^2 + a_{16}^2}$$

$$a_{31} = \sqrt{a_{11}^2 + a_{12}^2 + a_{13}^2}$$

$$a_{32} = a_{11}a_{14} + a_{12}a_{15} + a_{13}a_{16}$$

$$a_{34} = a_{32}/a_{31}$$

$$a_{43} = 1 - 3a_{34}^2$$

$$a_{45} = Ca_{43}$$

$$a_{46} = a_{45}/a_{31}^3 \quad (\text{pseudocontact equation})$$

$$b_{11} = -\delta_{k1}, b_{12} = -\delta_{k2}, b_{13} = -\delta_{k3}$$

$$b_{17} = -(\delta_{k1}a_{14} + \delta_{k2}a_{15} + \delta_{k3}a_{16})$$

$$b_{14} = -(\delta_{k1} + a_{14}b_{17})/a_{18}$$

$$b_{15} = -(\delta_{k2} + a_{15}b_{17})/a_{18}$$

$$b_{16} = -(\delta_{k3} + a_{16}b_{17})/a_{18}$$

$$b_{31} = (a_{11}b_{11} + a_{12}b_{12} + a_{13}b_{13})/a_{31}$$

$$b_{32} = a_{11}b_{14} + b_{11}a_{14} + a_{12}b_{15} + b_{12}a_{15} + a_{13}b_{16} + b_{13}a_{16}$$

$$b_{34} = a_{34}(b_{32}/a_{32} - b_{31}/a_{31})$$

$$b_{43} = -6a_{34}b_{34}$$

$$b_{45} = Cb_{43} + \delta_{k4}a_{43}$$

$$c_{1i} = a_{46}(b_{45}/a_{45} - 3b_{31}/a_{31}), \quad i = 1, \dots, 4$$

Derivation of expressions for the coefficients in equation (18), chapter 9, for the iterative least squares optimization of K and $\sum_i \Delta_i$.

Suppose the chemical shifts for m nuclei are measured for n different concentrations of shift reagent. For each of the n spectra the experimental shifts of all m nuclei are summed to obtain a new set of data, $se_j = \sum_i \Delta_{ij}$. By fitting the theoretical expression (equation (17), chapter 9) for the sum sc_j of the shifts to the experimental sums se_j of the induced shifts one obtains directly the best value for K , but only the sum of the bound shifts for the m nuclei $sb = \sum_i \Delta_i$.

$$sc_j = \left\{ K[L_0] + [S_0] + 1 - \sqrt{(K[L_0] + K[S_0] + 1)^2 - 4K^2[S_0][L_0]} \right\} \sum_i \Delta_i / (2K[S_0])$$

sc_j is expanded in a Taylor series in K and $\sum_i \Delta_i$, truncating after the linear terms (equation (18), chapter 9)

$$\begin{aligned} sc_j' &= (sc_j)_1 + (\partial sc_j / \partial K)_1 \Delta K + (\partial sc_j / \partial sb)_1 \Delta sb \\ &= c_{j0} + \sum_l c_{jl} x_l, \quad l = 1, 2 \end{aligned}$$

The sum of the squares of the differences between calculated and experimental sums is minimized with respect to the two variables x_1 and x_2 , and a set of linear equations for the best changes in the parameters, ΔK and $\Delta \sum_i \Delta_i$, is obtained.

$$\frac{\partial \sum_j [sc_j' - se_j]^2}{\partial x_k} = \frac{\partial \sum_j [c_{j0} + \sum_l c_{jl} x_l - se_j]^2}{\partial x_k} = 0$$

$$\sum_j \sum_k c_{jk} x_k = \sum_j (sc_j - c_{j0}), \quad k = 1, 2$$

Derivation of expressions for the coefficients c_{j1} and c_{j2} .

$$as = K[S_o] + K[L_o] + 1$$

$$ap = 4K^2[S_o][L_o]$$

$$ar = \sqrt{as^2 - ap}$$

$$ad = sb/(2[S_o]K)$$

$$at = ad(as - ar) \quad (\text{expression for } sc_j)$$

$$ac = at[S_o]/sb$$

$$c_{j1} = ad ([S_o] + [L_o] - 2ac) ar + ap/K - as ([S_o] + [L_o])/ar$$

$$c_{j2} = at/sb$$

APPENDIX 2. COMPUTER PROGRAMS.

"Slope Ratios for Lanthanide Shift Reagents". The present version of this program was written by Dr. A. Fruchier. Given lanthanide induced shifts, shift reagent and substrate concentrations the program calculates the correlation between the induced shifts. The program contains a subroutine, based on the algorithm described in chapter 4, for the automatic sorting of signals. Intermediate output useful for plotting purposes is optional. A listing of a sample data deck is provided at the end of the program, together with the corresponding output.

"Iterative Least Squares Fit of the Pseudocontact Equation to Lanthanide Induced Shifts". Given the substrate coordinates, a set of induced shifts and starting values for the proportionality constant and the lanthanide metal coordinates the program derives the best lanthanide metal position and proportionality constant and predicts induced shifts. A sample listing of data cards is provided at the end of the program, followed by the corresponding results.

"Calculation of Equilibrium Constants for Equilibria $L + S \rightleftharpoons LS$ and Sums of Bound Shifts". The program reads in lanthanide induced shifts and the corresponding $[L_0]/[S_0]$ concentration ratios as well as starting estimates for the equilibrium constants and bound shifts. The program optimizes the equilibrium constant and the bound shifts. Sample input and output are provided at the end of the program.

```

1: C SLOPE RATIOS FOR LANTHANIDE SHIFT REAGENTS (NAME OF THE PROGRAMME
2: C RN TAPE # 1580 : RATIO2)
3: C *****
4: C *****
5: C DATA CARDS :
6: C *****
7: C *****
8: C - M0,M1,M2,M3,M4,M5,M6 (712) :
9: C M0 MUST BE NONZERO.
10: C M0 IS LESS THAN 10 IF VARIOUS VOLUMES OF SHIFT REAGENT SOLUTION
11: C ARE ADDED TO THE SUBSTRATE SOLUTION.
12: C M0 IS LARGER THAN 10 AND LOWER THAN 50 IF SHIFT REAGENT IS
13: C ADDED OTHERWISE.
14: C M0 IS GREATER THAN 50 IF THE MOLAR RATIOS SUBSTRATE/LSR ARE NOT
15: C AVAILABLE.
16: C M1 : NUMBER OF SOLUTIONS WITH LSR.
17: C M2 : NUMBER OF SIGNALS.
18: C M3 : MUST BE NONZERO IF AN AUTOMATIC SORTING OF THE CHEMICAL
19: C SHIFTS MUST BE RUN. IF M3 IS LESS THAN 10, INTERMEDIATE
20: C RESULTS ARE PRINTED AND PUNCHED FOR CONTROL FROM THE
21: C SUBROUTINE OF AUTOMATIC SORTING.
22: C M4 : MUST BE NONZERO IF PUNCHED OUTPUT ARE NEEDED FOR PLOTTING
23: C PROGRAM.
24: C M5 : IS NON ZERO IF THE CHEMICAL SHIFTS ARE TO BE TRANSFORMED
25: C IN INDUCED CHEMICAL SHIFTS.
26: C M6 : IF M6 IS NONZERO, THE REGRESSION SUBROUTINE GIVES MORE
27: C INFORMATION ON EACH LINE.
28: C - ANGRM (F10.0) :
29: C ANGRM : NORMALISATION FACTOR FOR SLOPE RATIOS.
30: C - MTITLE : TITLE OF THE EXPERIMENT (2044).
31: C - NAME(J),J=1,M2 : NAME OF EACH SIGNAL IN THE SPECTRUM (A4).
32: C - CS-HIFT(J),J=1,M2 : EXPERIMENTAL CHEMICAL SHIFTS IN THE SPECTRUM
33: C OF THE ZERO SOLUTION (7F10.0).
34: C IF M0 IS MORE THAN 10, THE NEXT CARD IS OMITTED :
35: C - CZEROL,WEIGHT,VZERO,CMOLW (4F10.0) :
36: C CZEROL : CONCENTRATION (IN MOLE/LITER) OF THE LSR SOLUTION.
37: C WEIGHT : WEIGHT (IN GRAM) OF SUBSTRATE DISSOLVED IN VZERO ML
38: C OF SOLVENT.
39: C VZERO : INITIAL VOLUME OF THE SOLUTION.
40: C CMOLW : MOLECULAR WEIGHT OF SUBSTRATE.
41: C - M1 CARDS OF FOLLOWING TYPE :
42: C - IF M0 IS LOWER THAN 50 : C,(X(J),J=1,M2) FORMAT 7F10.0.

```

```

43: C      - IF M0 IS LARGER THAN 50 : X(J),J=1,M2  FORMAT 7F10.0.
44: C      C : MOLAR RATIO LSR/SUBSTRATE IF M0 IS GREATER THAN 10.
45: C      C : VOLUMES OF SHIFT REAGENT SOLUTION IF M0 IS LESS THAN 10.
46: C      X : EXPERIMENTAL CHEMICAL SHIFTS.
47: C      - FIRST CARD OF THE NEXT PROBLEM OR BLANK CARD.
48: C
49: C *****
50: C
51: C      IMPLICIT REAL*8(A-H,B-Z)
52: C      COMMON KP1,KP2,KP3
53: C      DIMENSION X(50,50),MTITLE(20),NAME(50),C(50),DH(50),A1(50),A2(50),
54: C      CR1(50),B2(50),E1(50),E2(50),F1(50),F2(50),CX(50),CY(50),CSHIFT(50)
55: C      C,V(50),L1(50,50),A1(50)
56: C      KP1=105 ; KP2=108 ; KP3=106 ; PRUB1=0.25D=01
57: C      1000 READ(KP1,101) M0,M1,M2,M3,M4,M5,M6
58: C      IF(M0.EQ.0) WRITE(KP2,300) ; STOP
59: C      READ(KP1,103) ANORM
60: C      N1=M2+1 ; N2=M1+1
61: C      READ(KP1,200) MTITLE
62: C      READ(KP1,200) (NAME(J),J=1,M2)
63: C      WRITE(KP2,201) MTITLE
64: C      READ(KP1,103) (CSHIFT(J),J=1,M2)
65: C      IF(M0.GT.50) M4=0 ; GO TO 19
66: C      IF(M0.GT.9) GO TO 1
67: C      READ(KP1,103) CZEROL,WEIGHT,VZER0,CHBLW
68: C      CZER0S=1000.0*WEIGHT/(VZER0*CHBLW) ; R1=CZER0L/(CZER0S*VZER0)
69: C      WRITE(KP2,112) CZEROL,CZERES
70: C      1 DO 4 I=1,M1
71: C      READ(KP1,103) C(I),(X(I,J),J=1,M2)
72: C      IF(M0.LE.9) C(I)=C(I)*R1
73: C      4 CONTINUE
74: C      GO TO 20
75: C      19 DO 21 I=1,M1
76: C      21 READ(KP1,103) (X(I,J),J=1,M2)
77: C      20 IF(M3.NE.0) CALL INTERP(CSHIFT,X,C,M1,M2,M3,M0)
78: C      IF(M4.EQ.0) GO TO 978
79: C      WRITE(KP3,200) MTITLE
80: C      WRITE(KP3,301) (CSHIFT(J),J=1,M2)
81: C      DO 989 J=1,M2
82: C      989 WRITE(KP3,301) (X(I,J),I=1,M1)
83: C      978 M10=M1/10.0+0.91 ; IE=1
84: C      DO 500 IC=1,M10

```



```

85:      ID=MINO(IC*10,M1)
86:      IF(IC.NE.1) WRITE(KP2,300)
87:      WRITE(KP2,202) ; WRITE(KP2,118) (C(I),I=IE,ID)
88:      DO 5 J=1,M2
89:      5 WRITE(KP2,105) J,NAME(J),(X(I,J),I=IE,ID)
90:      IE=IE+10
91:      500 CONTINUE
92:      DO 970 J=1,M2
93:      DO 970 I=1,M1
94:      L(I,J)=0
95:      IF(X(I,J).EQ.0.0) L(I,J)=1
96:      970 CONTINUE
97:      IF(M5.EQ.0) GO TO 971
98:      DO 972 J=1,M2
99:      DO 974 I=1,M1
100:      X(I,J)=DABS(X(I,J)-CSHIFT(J))
101:      974 CONTINUE
102:      CSHIFT(J)=0.0
103:      972 CONTINUE
104:      IF(M2.GT.50) GO TO 987
105:      971 IF(M6.NE.0.AND.M5.EQ.0) WRITE(KP2,108)
106:      IF(M6.NE.0.AND.M5.NE.0) WRITE(KP2,1108)
107:      DO 2 J=1,M2
108:      NT=0
109:      DO 3 I=1,M1
110:      K=I-NT
111:      IF(L(I,J).NE.0) GO TO 14
112:      CY(K)=X(I,J)
113:      CX(K)=C(I)
114:      GO TO 12
115:      14 NT=NT+1; K=K-1
116:      12 IF(I.EQ.M1) N3=K
117:      3 CONTINUE
118:      IF(M6.NE.0) WRITE(KP2,107) J
119:      CALL CORR(CY,CX,PROB1,SLOPE,AINT,ESL0P,EINT,N3,M6)
120:      R1(J)=AINT ; A1(J)=SLOPE ; E1(J)=ESL0P ; F1(J)=EINT
121:      2 CONTINUE
122:      CALL ORDER (X,CSHIFT,A1,B1,E1,F1,L,M1,M2)
123:      IF(M0.GT.50) GO TO 986
124:      IF(M4.EQ.0) GO TO 987
125:      WRITE(KP3,301) (A1(J),J=1,M2)
126:      WRITE(KP3,301) (B1(J),J=1,M2)

```

```

127: V(I)=0.0
128: DO 984 I=2,N2
129: 984 V(I)=C(I-1)
130: WRITE(KP3,301) (V(J),J=1,N2)
131: IF(M6.NE.0.AND.M5.EQ.0) WRITE(KP2,109)
132: IF(M6.NE.0.AND.M5.NE.0) WRITE(KP2,1109)
133: IF(M0.GT.50) GO TO 973
134: DO 7 I=1,M1
135: SUMY=0.0 ; SUMB=0.0 ; SUMA=0.0
136: DO 6 J=1,M2
137: IF(L(I,J).NE.0) GO TO 6
138: SUMY=SUMY+X(I,J) ; SUMA=SUMA+A1(J) ; SUMB=SUMB+B1(J)
139: 6 CONTINUE
140: DH(I)=(SUMY-SUMB)/SUMA
141: 7 CONTINUE
142: SUMY=0.0 ; SUMB=0.0 ; SUMA=0.0
143: DO 8 J=1,M2
144: IF(M5.NE.0) GO TO 81
145: IF(CSHIFT(J).EQ.0.0) GO TO 8
146: SUMY=SUMY+CSHIFT(J)
147: 81 SUMA=SUMA+A1(J) ; SUMB=SUMB+B1(J)
148: 8 CONTINUE
149: DH0=(SUMY-SUMB)/SUMA
150: DO 9 J=1,M2
151: NT=0
152: DO 10 I=1,M1
153: K=I-NT
154: IF(L(I,J).NE.0) GO TO 13
155: CY(K)=X(I,J)
156: CX(K)=DH(I)-DH0
157: GO TO 11
158: 13 NT=NT+1 ; K=K+1
159: 11 IF(1.EQ.M1) N3=K
160: 10 CONTINUE
161: IF(M6.NE.0) WRITE(KP2,107) J
162: CALL CORR(CY,CX,PROB1,SLOPE,AINT,ESLOP,EINT,N3,M6)
163: H2(J)=AINT ; F2(J)=EINT ; A1(J)=SLOPE
164: 9 CONTINUE
165: IF(M4.EQ.0) GO TO 986
166: WRITE(KP3,301) (A(J),J=1,M2)
167: WRITE(KP3,301) (B2(J),J=1,M2)
168: V(I)=0.0

```

```

1169:      DB 985 I=2,N2
1170:      V(I)=DH(I=1)
1171:      WRITE(KP3,301) (V(J),J=1,N2)
1172:      IF(M6.NE.0.AND.M5.EQ.0) WRITE(KP2,110)
1173:      IF(M6.NE.0.AND.M5.NE.0) WRITE(KP2,1110)
1174:      DO 15 J=1,N1
1175:      NT=0
1176:      DO 16 I=1,M1
1177:      K=I-NT
1178:      IF(L(I,M2).NE.0.OR.L(I,J).NE.0) GO TO 17
1179:      CX(K)=X(I,M2) ; CY(K)=X(I,J)
1180:      GO TO 18
1181:      17 NT=NT+1 ; K=K+1
1182:      18 IF(I.EQ.M1) N3=K
1183:      16 CONTINUE
1184:      IF(M6.NE.0) WRITE(KP2,111) J,M2
1185:      CALL CORR(CY,CX,PROB1,SLOPE,AINT,ESLAP,EINT,N3,M6)
1186:      A2(J)=SLOPE*ANORM ; E2(J)=ESLAP*ANORM
1187:      15 CONTINUE
1188:      WRITE(KP2,201) MTITLE ; WRITE(KP2,302)
1189:      IF(MO.GT.50) GO TO 22
1190:      DO 977 J=1,N1
1191:      977 WRITE(KP2,303) J,NAME(J),CSHIFT(J),B1(J),F1(J),B2(J),F2(J),A1(J),E
1192:      C1(J),A2(J),E2(J)
1193:      WRITE(KP2,304) M2,NAME(M2),CSHIFT(M2),B1(M2),F1(M2),B2(M2),F2(M2),
1194:      CA1(M2),E1(M2),ANORM
1195:      GO TO 24
1196:      22 DO 23 J=1,N1
1197:      23 WRITE(KP2,305) J,NAME(J),CSHIFT(J),B1(J),F1(J),A2(J),E2(J)
1198:      WRITE(KP2,306) M2,NAME(M2),CSHIFT(M2),B1(M2),F1(M2),ANORM
1199:      24 IF(M5.NE.0) WRITE(KP2,116)
1200:      IF(M5.EQ.0) WRITE(KP2,1116)
1201:      IF(MO.LE.50) WRITE(KP2,102) DH0
1202:      IF(MO.GT.50) WRITE(KP2,307)
1203:      GO TO 1000
1204:      101 FORMAT(40I2)
1205:      102 FORMAT(8X,'ADJUSTED ZERO POSITION',F8.4)
1206:      103 FORMAT(7F10.0)
1207:      105 FORMAT(8X,12,3X,A4,2X,10F8.1)
1208:      107 FORMAT(11LINE N0.1,13/1X,11(1H*1)/)
1209:      108 FORMAT(11CYRRELATION BETWEEN CHEMICAL SHIFTS (Y) AND EXPERIMENTAL
1210:      CNOLE EQUIVALENTS OF LSR (X),1X,84(1H*1)/)

```

```

211: 1108.FORMAT('CORRELATION BETWEEN INDUCED CHEMICAL SHIFTS (Y) AND EXPER
212: CIMENTAL MOLE EQUIVALENTS OF LSR (X)'/1X,92(1H*))/)
213: 109.FORMAT('CORRELATION BETWEEN CHEMICAL SHIFTS (Y) AND CORRECTED MOL
214: CE EQUIVALENTS OF LSR (X)'/1X,81(1H*))/)
215: 1109.FORMAT('CORRELATION BETWEEN INDUCED CHEMICAL SHIFTS (Y) AND CORRE
216: CTED MOLE EQUIVALENTS OF LSR (X)'/1X,89(1H*))/)
217: 110.FORMAT('CORRELATION BETWEEN THE CHEMICAL SHIFTS'/1X,39(1H*))/)
218: 1110.FORMAT('CORRELATION BETWEEN THE INDUCED CHEMICAL SHIFTS'/1X,48(1H
219: C*)//)
220: 111.FORMAT('LINE NO.',13,' VS LINE NO.',13/1X,23(1H*))/)
221: 112.FORMAT('X',CONCENTRATION OF THE LANTHANIDE SHIFT-REAGENT SOLUTION
222: C:'/F8.5,1 MOLE/LITER'/8X,'CONCENTRATION OF THE SUBSTRATE SOLUTION
223: C:'/F8.5,1 MOLE/LITER'/)
224: 116.FORMAT('8X'E' : EXPERIMENTAL INDUCED CHEMICAL SHIFTS IN THE FRE
225: CF SUBSTRATE SPECTRUM'/8X'11 : VALUES OF E CALCULATED BY REGRESSIO
226: CN ANALYSIS FROM INDUCED CHEMICAL SHIFTS'/14X'AND EXPERIMENTAL MOLA
227: CR RATIOS'/8X'D11 : ESTIMATED ERRORS ON 11'/8X'12 : VALUES OF E CA
228: LCULATED AS 11 BUT WITH EXPERIMENTAL MOLAR RATIOS REPLACED BY CORR
229: COINATES'/14X'PROPORTIONAL TO THE SUM OF SHIFTS'/8X'D12 : ESTIMATED
230: C ERRORS ON 12'/8X'5 : SLOPES OBTAINED IN THE CALCULATION OF 11'/
231: CRX'D5 : ESTIMATED ERRORS ON SLOPES'/8X'R : RELATIVE BOUND SHIFT
232: CS CALCULATED BY REGRESSION ANALYSIS FROM THE EXPERIMENTAL INDUCED
233: C/14X'SHIFTS'/8X'DR : ESTIMATED ERRORS ON R'//)
234: 1116.FORMAT('8X'E' : EXPERIMENTAL CHEMICAL SHIFTS IN THE FREE SUBSTR
235: CATE SPECTRUM'/8X'11 : VALUES OF E CALCULATED BY REGRESSION ANALYS
236: CIS FROM CHEMICAL SHIFTS AND EXPERIMENTAL'/14X'MOLAR RATIOS'/8X'D11
237: C : ESTIMATED ERRORS ON 11'/8X'12 : VALUES OF E CALCULATED AS 11 B
238: CUT WITH EXPERIMENTAL MOLAR RATIOS REPLACED BY COORDINATES'/14X'PRO
239: PORTIONAL TO THE SUM OF SHIFTS'/8X'D12 : ESTIMATED ERRORS ON 12'/8
240: CX'5 : SLOPES OBTAINED IN THE CALCULATION OF 11'/8X'D5 : ESTIMAT
241: CED ERRORS ON SLOPES'/8X'R : RELATIVE BOUND SHIFTS CALCULATED BY
242: CREGRESSION ANALYSIS FROM THE EXPERIMENTAL SHIFTS'/8X'DR : ESTIMAT
243: CED ERRORS ON R'//)
244: 118.FORMAT('3X',NAME,'2X,10F8.3//)
245: 200.FORMAT(20A4)
246: 201.FORMAT(1H1,7X,20A4//8X,80(1H*))/)
247: 202.FORMAT('2X,1EXPERIMENTAL SHIFTS'/2X,19(1H=))/)
248: 300.FORMAT(1H1)
249: 301.FORMAT(8F10.4)
250: 302.FORMAT('8X',J5X,NAME'9X'E'8X'11'5X'D11'7X'12'5X'D12'8X'9'8X'D5'8X'
251: CR'8X'DR'//)
252: 303.FORMAT(7X,12,5X,A4,F11.1,F10.1,F7.1,F10.1,F7.1,F11.1,F8.1,F12.1,F9

```

```

253:      C.1)
254:      304 FORMAT(7X,I2,5X,A4,F11.1,F10.1,F7.1,F10.1,F7.1,F11.1,F8.1,F12.1,5X
255:      C.1.1)
256:      305 FORMAT(7X,I2,5X,A4,F11.1,17X,F10.1,F7.1,19X,F10.1,F9.1)
257:      306 FORMAT(7X,I2,5X,A4,F11.1,17X,F10.1,F7.1,19X,F10.1,17X,1.1)
258:      307 FORMAT(8X,61(1H*))//8X'SUBSTRATE AND SHIFT-REAGENT CONCENTRATIONS
259:      CHAVE NOT BEEN USED')
260:      END

```

```

1: SUBROUTINE CORR(Y,X,PROBI,SLOPE,AINT,ESLOP,EINT,N,M)
2: COMMON KP1,KP2
3: IMPLICIT REAL*8 (A-H,O-Z)
4: DIMENSION Y(50),X(50),YCALC(50),DIF(50),YMIN(50),YMAX(50)
5: A=0.0 ; B=0.0 ; AA=0.0 ; BB=0.0 ; AB=0.0
6: AM=N ; NDEG=N-2 ; ANDEG=NDEG ; STUDF=TFISH(NDEG,PROBI)
7: DO 1 I=1,N
8:   A=A+X(I) ; B=B+Y(I) ; AA=AA+X(I)*X(I)
9:   BB=BB+Y(I)*Y(I) ; AB=AB+X(I)*Y(I)
10: 1 CONTINUE
11: T1=AB*AB=A*B
12: T2=AB*AA=A*A
13: T3=AB*BB=B*B
14: SLOPE=T1/T2
15: AINT=(B-SLOPE*A)/AN
16: CORE=T1/DSQRT(T2*T3)
17: SSMEAN=T3/AN
18: SSDREG=T1*T1/(AN*T2)
19: SSAREG=SSMEAN-SSDREG
20: R2=100.0*SSDREG/SSMEAN
21: T4=SSAREG/(ANDEG*T2)
22: ESLOP=CSQRT(T4*AN)
23: EEINT=DSQRT(T4*AA)
24: AM=A/AN
25: T5=SSAREG/(AN*ANDEG)
26: T6=AM*T4
27: RMS=0.0
28: DO 2 I=1,N
29:   YCALC(I)=SLOPE*X(I)+AINT
30:   DIF(I)=YCALC(I)-Y(I)
31:   RMS=RMS+DIF(I)**2
32:   FSEY=STUDF*DSQRT(T5+T6*(X(I)-AM)**2)
33:   YMIN(I)=YCALC(I)-ESEY
34:   YMAX(I)=YCALC(I)+ESEY
35: 2 CONTINUE
36: RMS=DSQRT(RMS/AN)
37: FSL0P=EEESLOP*STUDF
38: EINT=EEINT*STUDF
39: IF (M.EQ.0) RETURN
40: WRITE(KP2,100) STUDF,R2,SLOPE,ESLOP,AINT,EINT,RMS,CORE
41: WRITE(KP2,200)
42: DO 3 I=1,N

```

```

43:      3 WRITE(KP2,300) X(I),Y(I),YCALC(I),DIF(I),YMIN(I),YMAX(I)
44:      RETURN
45:      100 FORMAT(' STUDENT-FISHER COEFFICIENT',F10.3,' PROPORTION OF TOTAL V
46:      CARIATION ABOUT THE MEAN EXPLAINED BY THE REGRESSION',F10.3,' SLOPE
47:      C',D15.6,' ERROR',D15.6,' INTERCEPT',D15.6,' ERROR',D15.6,' S
48:      CTANDARD DEVIATION',D15.6,' CORRELATION COEFFICIENT',F10.4)
49:      200 FORMAT('///12X,'X',13X,'Y',11X,'Y(CALC)',10X,'DIFF',11X,'YMIN',11X
50:      C,'YMAX'///)
51:      300 FORMAT(6F15.4)
52:      END

```

```

1: SUBROUTINE INTERP(W,X,CCOR,M1,M2,M11,M0)
2: COMMON KP1,KP2,KP3
3: IMPLICIT REAL*8 (A-H,O-Z)
4: DIMENSION W(50),X(50,50),C(50),CCOR(50),SUM(50),A(50,50),B(50,50),
5: C0(50),DRIN(50,50),RMS(50),SLAPE(50),AINT(50),N(50,50)
6: IF(M0.GT.50) C(M1)=1.0 ; C(1)=0.0
7: J1=1
8: DO 2 I=1,M1
9: SUM(I)=0.0
10: DO 30 J=J1,M2
11: 30 SUM(I)=SUM(I)+X(I,J)
12: 2 CONTINUE
13: S=0.0
14: DO 1 J=J1,M2
15: 1 S=S+W(J)
16: CO=(C(M1)-C(1))*(S-SUM(1))/(SUM(M1)-SUM(1))+C(1)
17: IF(M11.LE.9) WRITE(KP2,300) CO
18: DO 3 I=1,M1
19: 3 CCOR(I)=(C(M1)-C(1))*(SUM(I)-SUM(1))/(SUM(M1)-SUM(1))+C(1)-CO
20: IF(M11.GT.9) GO TO 46
21: WRITE(KP3,600)(W(J),J=1,M2)
22: DO 45 J=1,M2
23: 45 WRITE(KP3,600)(X(I,J),I=1,M1)
24: V=0.0
25: WRITE(KP3,600) V,(CCOR(I),I=1,M1)
26: WRITE(KP2,400) (CCOR(I),I=1,M1)
27: 46 M3=N1-1 ; M4=M2-1 ; M5=N1-2
28: DO 4 I=1,M1
29: DO 5 J=1,M4
30: F=X(I,J) ; JP=J+1 ; NOTE=0
31: DO 6 K=JP,M2
32: IF(F.LT.X(I,K)) F=X(I,K) ; NOTE=K
33: 6 CONTINUE
34: IF(NOTE.EQ.0) GO TO 5
35: FM=X(I,J) ; X(I,J)=X(I,NOTE) ; X(I,NOTE)=FM
36: 5 CONTINUE
37: 4 CONTINUE
38: IF(M11.GT.9) GO TO 12
39: WRITE(KP2,200)
40: DO 31 J=1,M2
41: 31 WRITE(KP2,100)(X(I,J),I=1,M1)
42: WRITE(KP2,99)(CCOR(I),I=1,M1)

```



```

43:      WRITE(KP2,200)
44:      12 DO 9 J=1,M2
45:      JP=J+1 ; IF (M11,LE,9) WRITE(KP2,200)
46:      DO 14 L=J,M2
47:      A(J,L)=X(M1,J)-X(1,L)/(CCOR(M1)-CCOR(1))
48:      B(J,L)=X(M1,J)-A(J,L)*CCOR(M1)
49:      IF (J.EQ,M2) SLOPE(M2)=A(J,L) ; AINT(M2)=B(J,L) ; GO TO 9
50:      DO 8 I=2,M3
51:      FO=A(J,L)*CCOR(I)+B(J,L)
52:      DO 10 K=J,M2
53:      D(K)=(FO-X(I,K))*2
54:      10 CONTINUE
55:      DMIN(I,L)=D(J) ; N(I,L)=J
56:      DO 11 K=JP,M2
57:      IF (D(K).LT,DMIN(I,L)) DMIN(I,L)=D(K) ; N(I,L)=K
58:      11 CONTINUE
59:      8 CONTINUE
60:      RMS(L)=O.O
61:      DO 13 K=2,M3
62:      RMS(L)=RMS(L)+DMIN(K,L)
63:      13 CONTINUE
64:      RMS(L)=DSQRT(RMS(L)/M5)
65:      IF ( M11,LE,9) WRITE(KP2,101) J,L,A(J,L),L,RMS(L)
66:      14 CONTINUE
67:      R=RMS(J) ; N0TE=J
68:      DO 7 L=JP,M2
69:      IF (R.GT,RMS(L)) R=RMS(L) ; N0TE=L
70:      7 CONTINUE
71:      SLOPE(J)=A(J,N0TE) ; AINT(J)=B(J,N0TE)
72:      IF (M11,LE,9) WRITE(KP2,200);WRITE(KP2,102) N0TE,J,SLOPE(J),AINT(J)
73:      IF (N0TE.EQ,J) GO TO 140
74:      FM=X(1,J) ; X(1,J)=X(1,N0TE) ; X(1,N0TE)=FM
75:      140 DO 130 L=2,M3
76:      IF (N(L,N0TE).EQ,J) GO TO 130
77:      FM=X(1,J) ; X(1,J)=X(1,N(L,N0TE)) ; X(L,N(L,N0TE))=FM
78:      130 CONTINUE
79:      IF (M11.GT,9) GO TO 9
80:      WRITE(KP2,200)
81:      DO 90 JJ=J,M2
82:      90 WRITE(KP2,100)(X(I,JJ),I=1,M1)
83:      9 CONTINUE
84:      DO 17 J=1,M4

```

```

85:      DO 18 K=J,M2
86:        18 D(K)=DABS(AINT(J)-W(K))
87:        DMUN=D(J) ; NOTE=J ; JP=J+1
88:      DO 19 K=JP,M2
89:        IF(D(K).LT.DMUN) DMUN=D(K) ; NOTE=K
90:      19 CONTINUE
91:      IF(NOTE.EQ.J) GO TO 17
92:      FW=W(NOTE) ; W(NOTE)=W(J) ; W(J)=FW
93:      17 CONTINUE
94:      WRITE(KP2,700)
95:      IF(M1.GT.9) RETURN
96:      WRITE(KP2,200)
97:      DO 32 J=1,M2
98:        32 WRITE(KP2,500) J,SLOPE(J),AINT(J),W(J)
99:      RETURN
100:      99 FORMAT(10F10.4)
101:      100 FORMAT(10F10.4)
102:      101 FORMAT(' A(',I1,I1) =',F8.1,5X,'RMS(',I1,I1) =',F8.4)
103:      102 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
104:      103 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
105:      104 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
106:      105 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
107:      106 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
108:      107 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
109:      108 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
110:      109 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
111:      110 FORMAT('10NOTE =',I2,5X,'SLOPE(',I1,I1) =',F8.1,5X,'INTERCEPT =',F8.
111:      END

```

```

1: SUBROUTINE ORDER (X,W,SLOPE,AINT,E1,F1,L,M1,M2)
2: IMPLICIT REAL*8 (A-H,O-Z)
3: DIMENSION X(50,50),W(50),SLOPE(50),AINT(50),E1(50),F1(50),L(50,50)
4: C)
5: M4=M2-1
6: DO 20 J=1,M4
7: F=DABS(SLOPE(J)) ; JP=J+1 ; NOTE=0
8: DO 15 K=JP,M2
9: IF(F*GT,DABS(SLOPE(K))) F=DABS(SLOPE(K)) ; NOTE=K
10: 15 CONTINUE
11: IF(NOTE.EQ.0) GO TO 20
12: FM=SLOPE(J) ; SLOPE(J)=SLOPE(NOTE) ; SLOPE(NOTE)=FM
13: FM=AINT(J) ; AINT(J)=AINT(NOTE) ; AINT(NOTE)=FM
14: FM=W(J) ; W(J)=W(NOTE) ; W(NOTE)=FM
15: FM=E1(J) ; E1(J)=E1(NOTE) ; E1(NOTE)=FM
16: FM=F1(J) ; F1(J)=F1(NOTE) ; F1(NOTE)=FM
17: DO 16 I=1,M1
18: IM=L(I,J) ; L(I,J)=L(I,NOTE) ; L(I,NOTE)=IM
19: FM=X(I,J) ; X(I,J)=X(I,NOTE) ; X(I,NOTE)=FM
20: 16 CONTINUE
21: 20 CONTINUE
22: RETURN
23: END

```

```

1: FUNCTION TFISH(NFRD,PROB1).
2: DIMENSION U(8)
3: IMPLICIT REAL*8(A-H,O-Z)
4: DATA PI/3.1415926535898/
5: DATA U/12.706,4.303,3.182,2.776,2.571,1.98,1.97,1.96/
6: TF(PROB1.NE.0.025) GO TO 1
7: IF(NFRD.GE.500) TFISH=U(8) ; RETURN
8: IF(NFRD.GE.200) TFISH=U(7) ; RETURN
9: IF(NFRD.GT.75) TFISH=U(6) ; RETURN
10: IF(NFRD.LT.6) TFISH=U(NFRD) ; RETURN
11: 1 PRO=1.0-PROB1 ; AFRD=NFRD ; A2=(AFRD+1.0)/2.0
12: ANUM=GAMMA(A2) ; DNOM=GAMMA(AFRD/2.0)
13: A1=ANUM/((DSORT(PI*AFRD))*DNOM)
14: P=0.0 ; N=24 ; B0=1.0 ; B1=0.0 ; B2=0.0
15: 5 1=B2 ; 12=B1*B0
16: A=WINT(N,NFRD,B1,B2,A1,A2)
17: PP=P+A*0.5
18: IF(PP.LT.(PRO-1.0D-6)) GO TO 2
19: IF(PP.GT.(PRO+1.0D-6)) GO TO 4
20: TFISH=B2 ; RETURN
21: 2 P=P+A ; GO TO 5
22: 4 R0=R0/10.0 ; N=N/2 ; B2=B1
23: IF(N.LT.2) N=2
24: GO TO 5
25: END

```

```

1:  FUNCTION WINT (N1,NF,A,B,C,D)
2:  IMPLICIT REAL*8(A-H,O-Z)
3:  N1=2*N1 ; N2=N1+1 ; AN=N1 ; EVEN=0.0 ; ODD=0.0 ; H=(B-A)/AN ; T=A
4:  DO 1 I=1,N2
5:  Y=DLOG(C) - D*DLOG(1.0+T*T/NF) ; Y=DEXP(Y)
6:  IF(I.EQ.1) E=Y ; GO TO 1
7:  IF(I.EQ.N2) F=Y ; GO TO 1
8:  IF(2*(I/2).EQ.(2+I)/2) EVEN=EVEN+Y ; GO TO 1
9:  ODD=ODD+Y
10:  1 T=T+H
11:  WINT=(E+F+4.0*EVEN+2.0*ODD)*H/3.0
12:  RETURN
13:  END

```

```

1:  FUNCTION GAMMA(ALPHA)
2:  IMPLICIT REAL*8(A-H,B-Z)
3:  DIMENSION Z(15),W(15)
4:  DATA Z/0.933078120170-1,0.492691740302000,0.1215595412071001,
5:  C 0.2269949526204001,0.3667622721751001,0.5425336627414001,
6:  C 0.7565916226613001,0.10120228568019002,0.13130282482176002,
7:  C 0.15654407708330002,0.20776478899449002,2.5623894226729001,
8:  C 0.31407519159754002,0.38530683306486002,4.8026085572686001/
9:  DATA W/0.21823485940000,0.342210177929000,0.263027577942000,
10: C 0.126425818106000,0.4020686492100-1,0.8563877803610-2,
11: C 0.1212436147210-2,0.1116743923440-3,0.6459926762020-5,
12: C 0.2226316907100-6,0.4227430384980-8,0.3921897267040-10,
13: C 0.1456515264070-12,0.1483027051110-15,0.1600594906210-19/
14:  A1=ALPHA-1.0 ; T=0.0
15:  DO 1 I=1,15
16:  A=DLG(K(I))+A1*DLG(Z(I)) ; A=DEXP(A) ; T=T+A
17:  1 CONTINUE
18:  GAMMA=T
19:  RETURN
20:  END

```


BORNEOL (8) / COCL3 (TMS) / PR(FOD)3

AUTOMATIC SORTING OF SIGNALS HAS BEEN RUN

EXPERIMENTAL SHIFTS

	NAME	.025	.050	.075	.100	.125	.150	.175	.200	.225	.250
1		-53.2	-18.3	15.2	49.4	79.6	113.4	142.8	171.6	199.9	239.6
2		-71.8	-55.7	-40.5	-24.7	-11.3	4.4	17.9	30.8	43.6	61.2
3		-73.2	-58.3	-43.5	-28.6	-15.8	.6	12.1	24.6	36.8	53.8

BORNEOL (8) / CDCL3 (TMS) / PR(F00)3

J	NAME	E	I1	O11	I2	O12	S	DS	R	DR
1		-87.0	-85.3	2.5	-87.2	.6	553.9	16.4	43.46	.44
2		-87.0	-84.3	2.4	-86.3	.2	579.9	15.3	45.49	.19
3		-85.2	-81.3	5.1	-85.6	.6	1274.8	32.6	100.00	

E : EXPERIMENTAL CHEMICAL SHIFTS
 I1 : CHEMICAL SHIFTS CALCULATED BY REGRESSION ANALYSIS FROM CHEMICAL SHIFTS AND
 EXPERIMENTAL MOLAR RATIOS
 O11 : ESTIMATED ERRORS ON I1
 I2 : CHEMICAL SHIFTS CALCULATED AS I1 BUT WITH CORRECTED MOLAR RATIOS
 O12 : ESTIMATED ERRORS ON I2
 S : SLOPES OBTAINED IN THE CALCULATION OF I1
 DS : ESTIMATED ERRORS ON SLOPES
 R : RATIOS OF SLOPES CALCULATED BY REGRESSION ANALYSIS FROM THE EXPERIMENTAL CHEMICAL
 SHIFTS
 DR : ESTIMATED ERRORS ON RATIOS

ADJUSTED ZERO POSITION =.0034

```

1. C      ITERATIVE LEAST SQUARES FIT OF THE PSEUDOCONTACT EQUATION TO LANTHANIDE
2. C      INDUCED SHIFTS
3. C      *****
4. C      *****
5. C      N1      NUMBER OF CARBON ATOMS IN THE SUBSTRATE MOLECULE
6. C      C(I,J,K)  COORDINATES FOR THE SUBSTRATE NUCLEI
7. C      I: NUMBER OF THE CARBON ATOM
8. C      J: CARBON(I), ALPHA(2), AND BETA(3) SUBSTITUENT
9. C      K: X(1), Y(2), AND Z(3) COORDINATES
10. C      P(I,J)=P(3,1) INITIAL GUESSES FOR THE X,Y AND Z COORDINATES OF THE
11. C      LANTHANIDE ION, ARRIVED AT BY GOING 3A FROM OXYGEN,
12. C      NITROGEN ETC, ALONG A VECTOR POINTING FROM SOME SUBSTRATE
13. C      NUCLEUS J3,J4 TO THE FUNCTIONAL GROUP J1,J2
14. C      A14=A16  COMPONENTS OF THE PRINCIPAL AXIS POINTING FROM THE METAL
15. C      A11=A13, A31  ATOM TOWARD OXYGEN, NITROGEN ETC
16. C      COMPONENTS AND LENGTH OF THE VECTOR POINTING FROM THE METAL
17. C      ATOM TO THE I'ITH NUCLEUS
18. C      A34  COSINE OF THE ANGLE BETWEEN PRINCIPAL AXIS AND THE VECTOR
19. C      POINTING TO THE I'ITH NUCLEUS
20. C      A46  PSEUDOCONTACT EQUATION
21. C      SE(I,J)  EXPERIMENTAL INDUCED SHIFTS FOR SUBSTITUENT J, ALPHA(2)
22. C      OR BETA(3), ON THE I'ITH CARBON
23. C      SC(I,J)  INDUCED SHIFTS CALCULATED WITH THE OPTIMIZED PARAMETERS
24. C      DI(I,J)  DIFFERENCES BETWEEN CALCULATED AND OBSERVED SHIFTS
25. C      N12(I,J)  0: THERE IS NO ALPHA(J=2) OR NO BETA(J=3) HYDROGEN ON THE
26. C      I'ITH CARBON ATOM
27. C      1: THE OBSERVED SHIFT FOR HYDROGEN I,J IS INCLUDED IN
28. C      THE CALCULATIONS
29. C      2: THE OBSERVED SHIFT FOR HYDROGEN I,J IS EXCLUDED FROM
30. C      THE CALCULATIONS
31. C      B11...  FIRST DERIVATIVES OF THE CORRESPONDING A11... WITH RESPECT
32. C      TO THE FOUR PARAMETERS X,Y,Z,CONSTANT (P(1,M)=P(4,M))
33. C      X(K,L)  COEFFICIENTS OF THE LINEAR EQUATIONS FOR THE CHANGES IN
34. C      THE PARAMETERS
35. C      P(1,M)=P(4,M)  VALUES FOR THE PARAMETERS AFTER THE M'ITH ITERATION
36. C      RMS(M)  ROOT MEAN SQUARE ERROR AFTER THE M'ITH CYCLE
37. C      SOLVD  SUBROUTINE TO SOLVE THE LINEAR EQUATIONS, SUPPLIED BY
38. C      THE COMPUTER CENTER
39. C      *****
40. C      *****
41. C      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
42. C      COMMON C(40,3,3),SE(40,3),SC(40,3),DI(40,3),P(4,40),N11(40,3),

```


83. CSX, 'ERROR', /)
86. 221 FORMAT(I16,5X,3F10.2,A1,4X,3F10.2,A1)
87. 222 FORMAT(I16,40X,3F10.2,A1)
88. CALL EXIT
89. END

```

1. SUBROUTINE PARA
2. IMPLICIT DOUBLE PRECISION (A-H,O-Z)
3. COMMON C(40,3,3),SE(40,3),SC(40,3),DI(40,3),P(4,40),N1(40,3),
4. CN12(40,3),N13(40),J1,J2,J3,J4,N1,N2,N3
5. DIMENSION X(4,5),B46(6),O(6,6),S(40)
6. DO 6 I=1,6
7. DO 6 J=1,6
8. J(I,J)=0.
9. IF(I.EQ.J) D(I,J)=1.
10. 6 CONTINUE
11. M=1; S(1)=0.
12. C31=C(J1,J2,1)=C(J3,J4,1); C32=C(J1,J2,2)=C(J3,J4,2)
13. C33=C(J1,J2,3)=C(J3,J4,3); R3=DSORT(C31**2+C32**2+C33**2)
14. P(1,M)=C(J1,J2,1)*3.*C31/R3; P(2,M)=C(J1,J2,2)*3.*C32/R3
15. P(3,M)=C(J1,J2,3)*3.*C33/R3
16. 10 CONTINUE
17. DO 5 K=1,7
18. DO 5 L=1,5
19. 5 X(K,L)=0.
20. C41=C(J1,J2,1)=P(1,M); C82=C(J1,J2,2)=P(2,M)
21. C43=C(J1,J2,3)=P(3,M); R8=DSORT(C81**2+C82**2+C83**2)
22. A14=C41/R8; A15=C82/R8; A16=C83/R8; A41=P(4,M)
23. NM=0
24. DO 1 I=1,N1
25. DO 1 J=2,3
26. IF(N12(I,J).EQ.0) SC(I,J)=0.; N11(I,J)=N3; GO TO 1
27. IF(N12(I,J).EQ.1) N11(I,J)=N3; NM=NM+1
28. IF(N12(I,J).EQ.2) N11(I,J)=N2
29. A11=C(I,J,1)=P(1,M); A12=C(I,J,2)=P(2,M); A13=C(I,J,3)=P(3,M)
30. A31=DSORT(A11**2+A12**2+A13**2); A32=A11*A1+A12*A15+A13*A16
31. A3=A32/A31; A43=1.-3.*A3**2; A45=1000.*A41*A43; A46=A45/A31**3
32. SC(I,J)=A46; A47=SE(I,J); DI(I,J)=A46*A47
33. IF(N12(I,J).NE.1) GO TO 1
34. S(M)=5(M)+DI(I,J)**2
35. DO 2 K=1,4
36. B11=-D(K,1); B12=-D(K,2); B13=-D(K,3); B41=D(K,4)
37. BR8=-D(K,1)*A14+D(K,2)*A15+D(K,3)*A16
38. B14=-D(K,1)+A14*BR8/R8; B15=-D(K,2)+A15*BR8/R8
39. B16=-D(K,3)+A16*BR8/R8
40. B31=(A11+311+A12+B12+A13*B13)/A31
41. B32=A11*B1+B11+A14*A12+B12+A15+A13*B16+B13*A16
42. B34=A3+(B32/A32-B31/A31); B43=-6.*A34*B34

```

```

43.      B*5=1000.*(A+1*B+3+B*1*A+3); B*6(K)=A+6*(B+5/A+5-3.*B31/A31)
44.      2 CONTINUE
45.      DO 3 K=1,4
46.      DO 4 L=1,4
47.      4 X(K,L)=X(K,L)+B*6(K)*B*6(L)
48.      3 X(K,5)=X(K,5)+DI(I,J)*B*6(K)
49.      1 CONTINUE
50.      S(M)=DSORT(S(M)/NM)
51.      PRINT 102,M,P(4,M),(P(J,M),J=1,3),R8,S(M)
52.      IF(M.EQ.1) GO TO 7
53.      IF(DABS(S(M)-S(M-1)).LT.0.001.OR.M.GT.20) RETURN
54.      7 CONTINUE
55.      CALL SOLVD(X,4,4,5,0.,DET,TEST)
56.      IF(TEST.NE.0.) PRINT 201
57.      M=M+1; S(M)=0.
58.      DO 9 I=1,4
59.      9 P(I,M)=P(I,M-1)+X(I,5)
60.      30 TO 10
61.      102 FORMAT(120,F10.2,3F10.3,F10.3,F10.2)
62.      201 FORMAT(/10X,'SINGULAR MATRIX')
63.      RETURN
64.      END

```


ITERATIVE LEAST SQUARES FIT OF THE PSEUDOCONTACT EQUATION TO
 LANTHANIDE INDUCED SHIFTS
 SUBSTRATE: BORNEOL SHIFT REAGENT: PR(DPM)3
 EXP. SHIFTS: J.BRIGGS, F.A.HART AND G.P.MOSS, CHEM.COMM. 1506 (1970)
 COORD'S: J.F.CHIANG, C.F.WILCOX AND S.H.BAUER, JACS 90, 3149 (1968)

COORDINATES

I	CARBON	ALPHA SUBST			BETA SUBST		
1	1.158	.000	.000	.906	.000	.000	.000
2	.776	1.220	-.886	1.258	1.096	-2.226	1.152
3	-.776	1.220	-.886	-1.152	1.123	-1.931	-1.152
4	-1.158	.000	.000	-2.138	.000	.632	.000
5	-.776	-1.220	-.886	-1.152	-1.123	-1.931	-1.152
6	.776	-1.220	-.886	1.152	-1.123	-1.931	1.152
7	.000	.000	1.043	.000	1.937	2.161	.000

OPTIMIZATION OF PARAMETERS

L	K	X	Y	Z	R	RMS
1	-3.00	1.379	2.420	-4.915	3.000	5.23
2	-2.38	1.011	2.806	-4.696	3.013	1.01
3	-2.42	1.061	2.802	-4.682	2.997	.92
4	-2.42	1.036	2.801	-4.683	2.998	.92

CHEMICAL SHIFTS

I	CALC	EXP	ERROR	CALC	EXP	ERROR
1	16.02	17.80	-1.78			
2				44.00	45.00	-1.00*
3	34.19	34.20	-.01	16.31	16.60	-.29
4	8.90	10.10	-1.20			
5	16.95	16.00	.95	10.24	10.50	-.26
6	35.98	35.60	.38	15.59	15.70	-.11
7	9.52	8.00	1.52	8.34	7.80	.54

* EXCLUDED FROM LEAST SQUARES ANALYSIS

```

1. C
2. C
3. C
4. C
5. C
6. C
7. C
8. C
9. C
10. C
11. C
12. C
13. C
14. C
15. C
16. C
17. C
18. C
19. C
20. C
21. C
22. C
23. C
24. C
25. C
26. C
27. C
28. C
29. C
30. C
31. C
32. C
33. C
34. C
35. C
36. C
37. C
38. C
39. C
40. C
41. C
42. C

CALCULATION OF EQUILIBRIUM CONSTANTS FOR EQUILIBRIA L + S = LS
AND SUMS OF BOUND SHIFTS
*****
N1 NUMBER OF ALIQUOTS OF SHIFT REAGENT ADDED, INCL. CL(I)=0.
N2 NUMBER OF SIGNALS PER SPECTRUM
Y(I,J) EXP. CHEM. SHIFT FOR THE J'ITH PROTON IN THE I'ITH SPECTRUM
CSO CONCENTRATION OF SUBSTRATE BEFORE ADDITION OF SHIFT REAGENT
CLO CONCENTRATION OF SHIFT REAGENT STOCK SOLUTION
VO INITIAL VOLUME OF SUBSTRATE SOLUTION IN THE NMR TUBE
V(I) TOTAL VOLUME OF SHIFT REAGENT STOCK SOLUTION ADDED
CV(I) TOTAL VOLUME OF SOLUTION IN THE NMR TUBE
CS(I) CONCENTRATION OF SUBSTRATE IN THE I'ITH SOLUTION
CL(I) SHIFT REAGENT CONCENTRATION IN THE I'ITH SOLUTION
CK ESTIMATE FOR THE EQUILIBRIUM CONSTANT AFTER THE L'ITH
ITERATION
CDS ESTIMATE FOR THE SUM OF THE BOUND SHIFTS AFTER THE L'ITH
ITERATION
CD(J) ESTIMATE FOR THE BOUND SHIFT OF THE J'ITH PROTON AFTER
THE L'ITH ITERATION
RMS(L) ROOT MEAN SQUARE DEVIATION AFTER THE L'ITH ITERATION
*****
IMPLICIT DOUBLE PRECISION (A-H,O-Z)
DIMENSION V(30),Y(30,10),CV(30),CS(30),CL(30),B(2),R(30),X(30),
CSR(30),RMS(30),CD(30),A(30),SY(30),TMS(30),SL(10),N1(20)
30 CONTINUE
READ 101,N1,N2
IF(N1.EQ.0) PRINT 200; CALL EXIT
PRINT 200
DO 7 I=1,5
READ 201,(N11(J),J=1,20)
7 PRINT 201,(N11(J),J=1,20)
PRINT 203
DO 1 I=1,N1
1 READ 105,V(I),(Y(I,J),J=1,N2),TMS(I)
READ 103,CSO,CLO,VO
DO 2 I=1,N1
2 I=1,N1
CV(I)=VO+V(I); CS(I)=CSO+VO/CV(I); CL(I)=CLO+V(I)/CV(I)
R(I)=CL(I)/CS(I)
2 CONTINUE
DO 6 I=1,N1
6 I=1,N1

```

```

43.      DO 4 J=1,N2
44.        Y(I,J)=Y(I,J)-TMS(I)
45.      6 PRINT 108,I,V(I),CV(I),C9(I),CL(I),R(I),Y(I,J),J=1,N2)
46.      DO 8 J=1,N2
47.        REF=Y(I,J)
48.      DO 8 I=1,N1
49.        Y(I,J)=Y(I,J)-REF
50.      PRINT 200; PRINT 204
51.      DO 9 I=1,N1
52.      9 PRINT 108,I,V(I),CV(I),C9(I),CL(I),R(I),Y(I,J),J=1,N2)
53.      READ 103,CK
54.      DO 3 I=1,N1
55.        SY(I)=0.
56.      DO 3 J=1,N2
57.        CD(J)=Y(N1,J)
58.      3 SY(I)=SY(I)+Y(I,J)
59.        CDS=0.
60.      DO 14 J=1,N2
61.      14 CDS=CDS+Y(N1,J)
62.      DO 13 I=1,N1
63.      13 X(I)=(SY(I)-SY(I))/(SY(N1)-SY(I))
64.        SO=N1-I; SA=0.
65.      DO 11 J=1,N2
66.        S1=0.; S2=0.; T0=0.; T1=0.
67.      DO 12 I=2,N1
68.        S1=S1+X(I); S2=S2+X(I)**2; T0=T0+Y(I,J); T1=T1+X(I)*Y(I,J)
69.      12 CONTINUE
70.      SL(J)=(S0*T1-S1*T0)/(S0*S2-S1**2)
71.      11 SA=SA+SL(J)
72.      PRINT 200; PRINT 202
73.      L=0
74.      10 L=L+1
75.      C11=0.; C12=0.; C13=0.; C21=0.; C22=0.; C23=0.; SR(L)=0.
76.      DO 5 I=2,N1
77.        AS=CK*(CS(I)+CL(I))+1.; AP=4.*(CK**2)*CS(I)*CL(I)
78.        ARG=AS**2-AP; AR=DSORT(ARG); AF=CDS/(2.*CS(I)+CK)
79.        A(I)=AF*(AS-AR); AC=A(I)*CS(I)/CDS
80.        B(1)=AF*(CS(I)+CL(I)-2.*AC)*AR+AP/CK-AS*(CS(I)+CL(I))/AR
81.        B(2)=A(I)/CDS
82.        C11=C11+B(1)**2; C12=C12+B(1)*B(2); C13=C13+B(1)*(SY(I)-A(I))
83.        C21=C21+B(2)*B(1); C22=C22+B(2)**2; C23=C23+B(2)*(SY(I)-A(I))
84.      DO 15 J=1,N2

```

```

85. AE=CD(J)*(AS=AR)/(2.*CS(I)*CK)
86. SR(L)=SR(L)+(Y(I,J)=AE)*#2
87. 15 CONTINUE
88. 5 CONTINUE
89. RMS(L)=DSQRT(SR(L)/(N1*N2))
90. DO 16 J=1,N2
91. 16 CD(J)=SL(J)*CDS/SA
92. PRINT 102,L,RMS(L),CK,CDS,(CD(J),J=1,N2)
93. DCDS=(C11+C23-C13+C21)/(C11+C22-C12+C21), DCK=(C13-C12+DCDS)/C11
94. CDS=CDS+DCDS, CK=CK+DCK
95. IF(L.EQ.1) GO TO 10
96. ARG=RMS(L)-RMS(L-1)
97. IF(DABS(ARG).GT.0.02) GO TO 10
98. GO TO 30
99. 101 FORMAT(10I3)
100. 102 FORMAT(10,F10.2,2F10.1,2X,10F8.1)
101. 103 FORMAT(10F8.1)
102. 105 FORMAT(F8.3,9F8.1)
103. 108 FORMAT(10,F8.3,F8.2,8F8.1)
104. 200 FORMAT(1H1////)
105. 201 FORMAT(20A4)
106. 202 FORMAT(///9X,'L',4X,'RMS(L)',8X,'CK',7X,'CDS',5X,
107. 'C'BOUND SHIFTS'/)
108. 203 FORMAT(///9X,'I',4X,'V(I)',3X,'CV(I)',3X,'CS(I)',3X,'CL(I)',4X,
109. 'C'R(I)',3X,'SHIFTS FROM TMS'/)
110. 204 FORMAT(///9X,'I',4X,'V(I)',3X,'CV(I)',3X,'CS(I)',3X,'CL(I)',4X,
111. 'C'R(I)',3X,'INDUCED SHIFTS'/)
112. END

```


CALCULATION OF EQUILIBRIUM CONSTANTS FOR EQUILIBRIA $L + S = LS$
 AND SUMS OF BOUND SHIFTS
 TEST RUN FOR A HYPOTHETICAL CASE HAVING AN EXACT SOLUTION
 BOUND SHIFTS: 200 / 600 / 1000 / 127 EQUIL. CONSTANT: 500
 THE SHIFTS FROM TMS IN THE TABLE BELOW WERE CALC'D WITH THESE VALUES

I	V(I)	CV(I)	CS(I)	CL(I)	R(I)	SHIFTS FROM TMS
1	.000	.500	.100	.000	.00	.0
2	.020	.520	.096	.019	.20	39.0
3	.040	.540	.093	.037	.40	77.3
4	.060	.560	.089	.054	.60	114.1
5	.080	.580	.086	.069	.80	147.1
6	.100	.600	.083	.083	1.00	171.3
7	.150	.650	.077	.115	1.50	190.9
8	.200	.700	.071	.143	2.00	194.7
9	.300	.800	.062	.167	3.00	196.9
10	.400	.900	.056	.222	4.00	197.6
11	.500	1.000	.050	.250	5.00	198.0

I	V(I)	CV(I)	CS(I)	CL(I)	R(I)	INDUCED SHIFTS		
1	.000	.500	.100	.000	.00	.0	.0	.0
2	.020	.520	.096	.019	.20	39.0	117.0	195.0
3	.040	.540	.093	.037	.40	77.3	231.8	386.4
4	.060	.560	.089	.054	.60	114.1	342.2	570.3
5	.080	.580	.086	.069	.80	147.1	441.3	735.9
6	.100	.600	.083	.083	1.00	171.3	514.0	856.6
7	.150	.650	.077	.115	1.50	190.9	572.7	954.5
8	.200	.700	.071	.143	2.00	194.7	584.1	973.4
9	.300	.800	.062	.187	3.00	196.9	590.6	984.4
10	.400	.900	.056	.222	4.00	197.6	592.9	988.2
11	.500	1.000	.050	.250	5.00	198.0	594.1	990.1

L	RMS(L)	CK	CDS	BOUND	SHIFTS
1	4.51	750.0	1782.2	198.0	594.1 990.1
2	8.83	416.7	1798.7	199.8	599.6 999.3
3	.75	490.7	1799.6	199.9	599.9 999.8
4	.12	500.8	1799.9	200.0	600.0 1000.0
5	.07	500.9	1799.9	200.0	600.0 1000.0
6	.07	500.9	1799.9	200.0	600.0 1000.0

REFERENCES

1. C.C.Hinckley, J.Amer.Chem.Soc. 91, 5160 (1969).
2. P.V.Demarco, T.K.Elzey, R.S.Lewis, and E.Wenkert, J.Amer.Chem.Soc. 92, 5734 (1970).
3. E.de Boer and H.van Willigen, Progress in nmr Spectroscopy Vol. II. Edited by J.W.Emsley, J.Feeney, and L.H.Sutcliffe, Pergamon Press Oxford, 1967, p. 111.
4. H.J.Keller and K.E.Schwarzshans, Angew.Chem., Intern.Ed. Eng. 9, 196 (1970).
5. T.Moeller, Werner Centennial. Advances in Chemistry Series 62, 305. American Chemical Society Publications 1967.
6. B.N.Figgis, Introduction to Ligand Fields, p. 248. Interscience Publishers 1966.
7. H.M.McConnell and R.E.Robertson, J.Chem.Phys. 29, 1351 (1958).
8. D.F.Evans and M.Wyatt, Chem.Comm. 1972, 312.
9. G.H.Wahl and M.R.Peterson, Chem.Comm. 1970, 1167.
10. M.R.Willcott III, R.E.Lensinski, and R.E.Davis, J.Amer.Chem.Soc. 94, 1742 (1972); R.E.Davis and M.R.Willcott III, *ibid* 94, 1744 (1972).
11. J.Briggs, F.A.Hart, G.P.Moss, and E.W.Randall, Chem.Comm. 1971, 354.
12. O.A.Gansow, M.R.Willcott III, and R.E.Lensinski, J.Amer.Chem.Soc. 93, 4295 (1971).
13. J.K.M.Sanders and D.H.Williams, J.Amer.Chem.Soc. 93, 641 (1971).
14. A.van Bruijnsvoort, C.Kruk, E.R.de Waard, and H.O.Huisman, Tetrahedron Lett. 1972, 1737.
15. A.Ius, G.Vecchio, and G.Carrea, Tetrahedron Lett. 1972, 1543.
16. S.B.Tjan and F.R.Visser, Tetrahedron Lett. 1972, 2833.
17. P.H.Mazzechi, H.J.Tamburin, and G.R.Miller, Tetrahedron Lett. 1971, 1819.
18. M.R.Willcott III and J.F.M.Gth, Tetrahedron Lett. 1971, 1579.
19. H.Hart and G.M.Iove, Tetrahedron Lett. 1971, 625.
20. K.K.Anderson and J.J.Habel, Tetrahedron Lett. 1970, 5253.

21. A.F.Cockerill and D.M.Rackham, Tetrahedron Lett. 1970, 5149.
22. D.R.Crump, J.K.M.Sanders, and D.H.Williams, Tetrahedron Lett. 1970, 4419.
23. S.Farid, A.Ateya, and M.Maggio, Chem.Comm. 1971, 1285.
24. P.Belanger, C.Freppel, D.Tizane, and J.C.Richer, Chem. Comm. 1971, 266.
25. J.Reuben and J.S.Leigh, J.Amer.Chem.Soc. 94, 2789 (1972).
26. J.Briggs, F.A.Hart, and G.P.Moss, Chem.Comm. 1970, 1506.
27. C.Beaute, Z.W.Wolkowski, and N.Thoai, Tetrahedron Lett. 1971, 817.
28. D.R.Kelsey, J.Amer.Chem.Soc. 94, 1764 (1972).
29. K.Roth, M.Grosse, and D.Rewicki, Tetrahedron Lett. 1972, 435.
30. J.K.M.Sanders, S.W.Hanson, and D.H.Williams, J.Amer.Chem. Soc. 94, 5325 (1972).
31. B.L.Shapiro and M.D.Johnston, J.Amer.Chem.Soc., in press.
32. I.Armitage, G.Dunsmore, L.D.Hall, and A.G.Marshall, Can. J.Chem. 50, 2119 (1972).
33. J.Grandjean, Ind.Chim.Belg. 37, 220 (1972).
34. J.Bouquant and J.Chuche, Tetrahedron Lett. 1972, 2237.
35. J.F.Chiang, C.F.Wilcox, and S.H.Bauer, J.Amer.Chem.Soc. 90, 3149 (1968).
36. J.W.ApSimon and H.Beierbeck, Chem.Comm. 1972, 172.
37. J.W.ApSimon, H.Beierbeck, and A.Fruchier, Can.J.Chem. 50, 2725 (1972).
38. J.W.ApSimon, H.Beierbeck, and A.Fruchier, Can.J.Chem. 50, 2905 (1972).
39. J.W.ApSimon, H.Beierbeck, and A.Fruchier, J.Amer.Chem.Soc. submitted for publication.
40. J.W.ApSimon, H.Beierbeck, and A.Fruchier, Can.J.Chem. submitted for publication.