Effects of Random Coordinate Error in Analyses of Lanthanide-Induced Pseudocontact Shifts. Axially Symmetric Case

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Abstract: The computer analysis of induced axial pseudocontact shifts involves assessing goodness of fit between calculated and observed shifts. Calculated shifts may be obtained from assumed substrate structures which contain small random coordinate errors. Proceeding from the assumption that the coordinate errors are normally distributed, equations are derived which give expectations, variances, and fractional errors of individual and relative shifts. Hypothetical structures are examined to determine the effects of coordinate error on shift calculations. Results allow limits to be placed on the accuracy of calculations and make possible the partition of systematic and random errors.

The study of molecular structure through the analysis of lanthanide-induced pseudocontact shifts in NMR spectra is now a well established technique which has been successfully applied to many systems.[2-4] The technique involves relatively straightforward experimental procedures and offers means to obtain structural insights which are difficult, if not impossible, to obtain in any other way. Comparisons between shift reagent studies and much more precise x-ray analyses of molecular structure are natural, for the two methods share goals and general concerns. The problem of resolution in x-ray analysis has a parallel in shift reagent studies. Inevitably, shift reagent methods will be directed toward increasingly more difficult questions. It will be of value to know just how far the technique may be pressed and to know when the limits have been reached. Analyses of lanthanide-induced pseudocontact shifts incorporate some unique features. Sources of error are varied, and it is not clear what their ultimate effects are. In order to quantify these effects, we have begun an examination of error propagation in pseudocontact shift analyses, and in this article treat the axially symmetric case.

In outline, pseudocontact shift analyses proceed in the following way.[5,6] A structure of the substrate is assumed (one of perhaps several alternatives), and a position for the lanthanide ion in the shift reagent-substrate complex is found for which the calculated relative shifts, ν_{ic}, best correspond to those observed, ν_{io}, in an NMR experiment. It is usually adequate to describe the lanthanide-induced shifts, $\Delta\nu_i$, in terms of an "axial" relationship,[7-12]

$$\Delta\nu_i = K\left(\frac{3\cos^2\theta_i - 1}{R_i^3}\right) \tag{1}$$

where $\Delta\nu_i$ is the shift calculated for the ith resonance, R_i is the distance from the lanthanide ion in the complex and the ith nucleus, θ_i is the angle between the effective magnetic axis (often along the lanthanide substrate bond) and the radius vector to the nucleus, and K is a constant. Relative shifts are the ratios of observed shifts with one chosen as a standard. The quality of the correspondence (fit) between calculated and observed relative shifts may be assessed with the aid of the R factor,[13]

$$R = \left[\frac{\Sigma w_i(\nu_{10} - \nu_{ic})^2}{\Sigma w_i \nu_{10}^2}\right]^{1/2} \tag{2}$$

where w_i is a weighting factor usually taken as unity, and the summation index, i, ranges from 1 to n which is the number of shifts included in the analysis. The R factor is a convenient summary statistic which approaches zero as the fit improves, and additionally has applications in comparing alternative calculations. Hamilton[13] developed a ratio test used to determine whether or not two R factors, derived from alternative parameterizations, are significantly different. In the test, if the ratio of the R factors exceeds a tabulated significance point, the R factors are different at a stated confidence level. Wilcott and Davis[5] have used this test to evaluate LSR calculations with excellent success. The overall goal of the calculations is to confirm the assumed substrate structure. The assumed structure which gives the best fit of calculated to relative shifts is the preferred structure.

The assumed substrate structure plays a central role in these calculations. Errors in the substrate coordinates used to calculate relative shifts will be reflected in errors in the shift values obtained. Some level of coordinate error is unavoidable. Among sources of molecular coordinates are x-ray structure analyses which may specify the position of a nucleous to within 0.01 Å. Hydrogen nuclei are not so accurately placed and errors may be 0.05 Å for these small atoms. When substrate atom coordinates are derived from molecular models, larger error levels must be expected. Though very accurate measurements of the models are possible, design limitations may result in errors as high as 0.1 Å, or higher, depending upon the modeling system used.

Effects of various errors on the overall calculation have been examined, and some very elaborate calculation techniques have been employed.[12,14] The effects of random coordinate error on the accuracy of individual shift calculations have not been reported, however, and no relationships yielding the variances of calculated shifts have appeared. Such relationships will allow more realistic assessments of fit, and provide the means to develop expressions for the weighting factors[13] to be used in the R factor (eq 2).

In order to determine the effects of coordinate error on pseudocontact shift calculations, we have devised computer experiments designed to examine them. Equations for expectations and variances of shifts were derived. We obtain through computer experiments average shifts, standard deviations, and distributions of shifts for three levels of coordinate error (0.01, 0.05, and 0.1 Å) to test and verify the derived relationships. We find that, though calculation errors are often small, they are not *always* small and may exceed errors of measurement. Expressions for the variances and fractional errors of relative shifts are presented with example calculations. The sensitivity of residuals, ($\nu_{io} - \nu_{ic}$), to parameters of structure (angle and distance) is discussed, taking into account the errors of shift calculation. Finally, it

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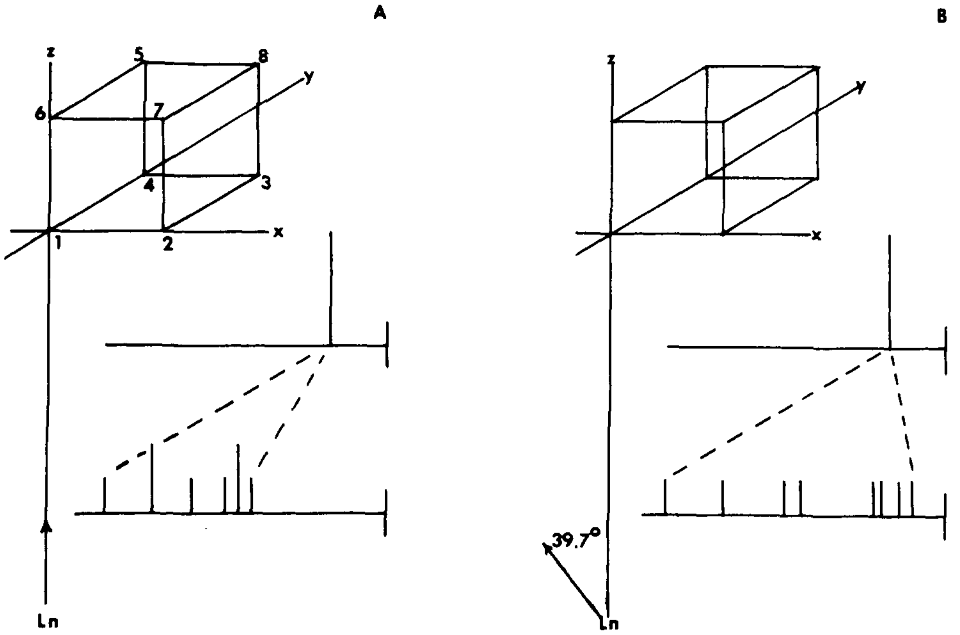

Figure 1. Cubical hypothetical molecules. Calculated relative shifts are schematically represented in line spectra.

is suggested that the sum of squares of residuals may be a useful fitting statistic. Making use of a result from statistics, the variances of shifts are shown to yield the expectation of that sum at best fit.

Classification of Error

Coordinate error in this paper is considered throughout to be normally distributed. That is, the distribution functions, g, for the atom coordinates are given by[15]

$$g_{xi} = N(\mu_{xi},\sigma_x) = \frac{1}{\sqrt{2\pi}\,\sigma_x}\exp\left[-\tfrac{1}{2}\left(\frac{x-\mu_{xi}}{\sigma_x}\right)^2\right] \qquad (3)$$

where μ_i is the expectation of the coordinate (x, y, z) of the ith atom, and σ_x is the standard deviation of the error. σ_x is taken to be the same for all coordinates.

Experimentally determined relative shifts are also considered normally distributed about an expectation μ_{io}, with standard deviation, σ_{io}, for the ith relative shift. The value of σ_{io} is not usually the experimental error associated with a single determination of a relative shift. Generally, averages of several observations are included in the determinations of μ_{io}.[16] If Δ_i is the error of measurement for each relative shift, and n measurements are included in the average, then $\sigma_{io} = \Delta_i/\sqrt{n}$.

It is convenient to classify error components. We will arbitrarily refer to sources of error which are reflected in changes in standard deviations as "random", and to errors which contribute to changes in expectation value as "systematic". Many systematic errors are, of course, of random origin, and in the event of a calculation, both systematic and random errors have similar effects. Systematic errors, however, may have nonrandom origin. A systematic error in coordinates would be the result of an erroneous placement of an atom (or groups of atoms) in a molecule which is altogether independent of the accuracy with which the supposed position may be determined. Misplacement of the lanthanide ion in the complex constitutes a systematic error. Contact shift contributions to the observed shifts will appear as systematic errors in a pseudocontact shift analysis. There are many possible sources of systematic error. In general, systematic errors cause the expectations of residuals, $(\mu_{io} - \mu_{ic})$, to be nonzero. We discuss some aspects of this component of error, but our primary effort. is directed toward defining the effects of random coordinate error.

Calculation Method

Two different arrangements of hypothetical atoms were used in the computer experiments. The first was a quarter circle of points in the zx plane equidistant from the origin, which was taken as the paramagnetic center. Several distances were chosen, all with the principal magnetic axis directed along the z axis ($\theta = 0°$). Shifts were calculated using eq 1 (with $K = 1$) for the points located at 5° intervals from 0 to 90°. The second arrangement was a unit (1.0 Å) cube placed at the origin with the paramagnetic center located 3.5 Å from the origin on the $-z$ axis. Two cubical cases were considered; case A having the principal magnetic axis directed along the z axis, and case B with the principal axis directed along a line 39.7° from the z axis in the $-zx$ plane. In Figure 1 the two cases are drawn along with schematic representation of the calculated shifts.

The initial coordinates of the (hypothetical) atoms were read directly from the figures, or calculated using a Cartesian coordinate program (CART). Quantities of interest were calculated and added to summation registers. Shifts were calculated by eq 1 with R and θ obtained from the coordinates of the figures.

Coordinate error was introduced by adding a computer-generated normal random deviate to the initial x, y, and z coordinate for each atom except the paramagnetic center.[17] The normal random deviates have a specified standard deviation, σ_x, and zero expectation. Quantities of interest were calculated using the new coordinate set and added to the appropriate summation register. The cycle is then repeated. Each new coordinate set is obtained by adding random error to the original coordinates in order to avoid random walk problems. One-thousand iterations have been found sufficient to obtain averaged quantities to three significant figures.

Average Shifts and Variances

If $H(x_1, x_2, \ldots)$ is a function of the set of random variables (x_i), an estimate of the expectation of H, $E(H)$, is[18,19]

$$E(H) = H(\mu_1, \mu_2, \ldots) + \tfrac{1}{2}\sum_i \left(\frac{\partial^2 H}{\partial x_i^2}\right)\sigma_i^2 \qquad (4)$$

where the equation is evaluated at the set of expectations, $\{\mu_i\}$, of the random variables, and the quantities σ_i^2 are

Table I. Average Calculated Shifts, $\Delta\nu$, Variances, σ^2, and Fractional Errors, f_i, for Three Levels of Coordinate Error as Functions of Angle[a,b]

	$\sigma_x = 0.01$ Å			$\sigma_x = 0.05$ Å			$\sigma_x = 0.1$ Å		
	$\Delta\nu \times 10^2$	$\sigma^2 \times 10^8$	$f_i \times 10^2$	$\Delta\nu \times 10^2$	$\sigma^2 \times 10^6$	$f_i \times 10^2$	$\Delta\nu \times 10^2$	$\sigma^2 \times 10^6$	$f_i \times 10^2$
0	3.12	4.9	0.708	3.12	1.2	3.54	3.11	4.8	7.08
10	2.98	4.5	0.714	2.98	1.1	3.58	2.97	4.5	7.19
20	2.58	4.0	0.776	2.58	1.0	3.89	2.57	4.1	7.84
30	1.95	3.1	0.899	1.96	0.78	4.52	1.96	3.2	9.09
40	1.19	2.2	1.23	1.19	0.54	6.16	1.20	2.2	12.3
50	0.375	1.4	3.18	0.380	0.36	15.7	0.885	1.4	31.0
55	−0.0195	1.2	55.8	−0.0157	0.30	346.6	−0.011	1.2	1020
60	−0.390	1.0	2.63	−0.386	0.26	13.3	−0.381	1.1	27.1
70	−1.01	1.0	0.996	−1.01	0.26	5.03	−1.01	1.1	10.2
80	−1.41	1.2	0.786	−1.42	0.32	3.95	−1.42	1.3	7.96
90	−1.56	1.4	0.758	−1.57	0.35	3.79	−1.57	1.4	7.64

[a] For these calculations, K in eq 1 is set equal to unity. [b] $R = 4.0$ Å for all shifts.

their variances. An estimate of the variance of H, $V(H)$, is given by,

$$V(H) = \sum_i \left(\frac{\partial H}{\partial x_i}\right)^2 \sigma_i^2 \tag{5}$$

and this equation is also evaluated at the set of expectations, $\{\mu_i\}$.

Equations 4 and 5 may be used to derive estimates for the expectations of pseudocontact shifts and their variances. Random variables, $R(x)$ and $\theta(y)$, are defined as

$$R(x)_i = R_i + x$$

$$\theta(y)_i = \theta_i + y \tag{6}$$

where R_i and θ_i are the expectations of distance and angle used in eq 1. x and y are normally distributed random increments with zero expectation and standard deviation σ_x and σ_y, respectively.

Assuming that

$$\sigma_y = \sin^{-1}(\sigma_x/R) \simeq \sigma_x/R \tag{7}$$

and making the appropriate substitutions in eq 4 and 5, we obtain

$$\overline{\Delta\nu_i} \simeq \frac{K(3\cos^2\theta_i - 1)}{R_i^3} + 3\left[\frac{-K\cos 2\theta_i}{R_i^3} + \frac{2K(3\cos^2\theta_i - 1)}{R_i^3}\right]\left(\frac{\sigma_x}{R_i}\right)^2 \tag{8}$$

and

$$\sigma_i^2 \simeq 9\left(\frac{K}{R_i^3}\right)^2 [4\cos^2\theta_i \sin^2\theta_i + (3\cos^2\theta_i - 1)^2]\left(\frac{\sigma_x}{R_i}\right)^2 \tag{9}$$

These equations indicate functional relationships which are observed in the calculated averages and variances and provide good estimates of these quantities.

Table I lists average shifts and variances as functions of angle, obtained by averaging 1000 calculations. Average shifts are essentially the same as those given by eq 1 for static atoms with distance and angle given by R_i and θ_i. Coordinate error levels were relatively small for all the calculations (σ_x = 0.01, 0.05, and 0.1 Å). If error levels were larger than those used, or if the coordinate error were not symmetrically distributed, differences between static atom and averaged shift calculations would be more noticeable. Variances listed in Table I are in overall agreement with the estimates provided by eq 9. The variances exhibit the expected dependence upon angle (Figure 2). Fractional errors, f_i, are given by the relation $f_i = \sigma_i/\Delta\nu_i$, and observed values

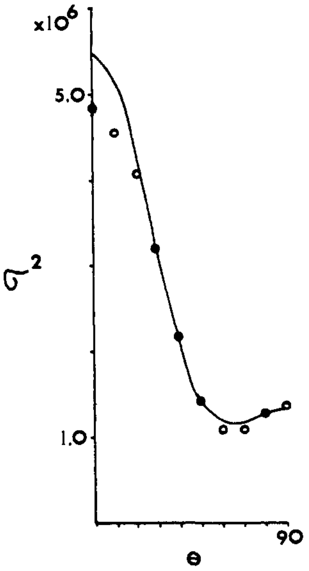

Figure 2. Angle dependence of shift variances, σ^2. The solid curve is a plot of eq 9, and the open circles are variances obtained from averages of 1000 calculations (R = 4.0 Å, σ_x = 0.1 Å).

are listed in Table I. These quantities are functions of angle and a relationship may be obtained by dividing the square root of eq 9 by eq 1, as,

$$f_i = \left[\frac{36\cos^2\theta_i \sin^2\theta_i}{(3\cos^2\theta_i - 1)^2} + 9\right]^{1/2}\left(\frac{\sigma_x}{R_i}\right) = G(\theta_i)\left(\frac{\sigma_x}{R_i}\right) \tag{10}$$

This relation increases without bound near 54.7° (the "magic angle") where the shift value given by eq 1 is zero. The behavior of eq 10 near the magic angle is due in part to the approximations of eq 5. Fractional errors of small shifts probably have an effective upper bound. Computer-generated values, however, closely follow eq 10. In Figure 3, f_i values taken from Table I are plotted as functions of angle.

The fractional error represents that level of error which will exceed 70% of errors calculated, if the errors are normally distributed. Equation 10 predicts, and calculations confirm, that errors of shift calculation increase dramatically as the magic angle is approached. This is a consequence of the fact that while the shifts given by eq 1 approach zero, the standard deviations do not. Variances for shifts of resonances of atoms near 54.7°, and larger angles, are less than those calculated for small angle shifts (Figure 2), and therefore, *absolute* errors of calculation for large angle shifts are somewhat smaller than those for shifts of resonance of atoms near 0°. The largest and smallest vari-

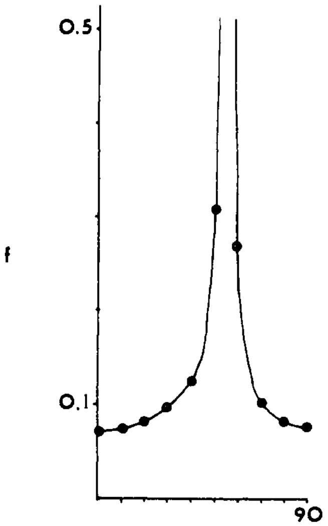

Figure 3. Fractional error, f_i, plotted as a function of angle. The solid line is a plot of eq 10, and the open circles are fractional error values taken from Table I (R = 4.0 Å, σ_x = 0.1 Å).

ances calculated at a particular distance differ by about a factor of 5.

The pseudocontact shift equation tends to magnify coordinate error. At 4.0 Å (Table I), an 0.1 Å coordinate error may amount to 2.5% error in the distance parameter R. This produces a fractional error at 0° of 7.1% in calculated shifts and larger percentages at higher angles. At greater distances calculation errors are less, following eq 10. At 8.0 Å the same coordinate error yields 3.5% error in calculated shift, while at 16.0 Å the error is 1.7% when the angle is 0°.

Relative Shifts

Average relative shifts, ν_{ic}, and fractional errors for the shifts, f_i, and relative shifts, F_i, were calculated for the cubical molecules pictured in Figure 1. The results paralleled the findings for individual shifts. Examples are given in Table II for coordinate error at σ_x = 0.1 Å. Average relative shifts are essentially those obtained from static atom calculations. In Figure 4, distributions of relative shifts obtained when σ_x = 0.05 Å are presented. To a good approximation, normally distributed coordinate error yields normally distributed relative shifts.

Variances of relative shifts, σ_{ic}^2, are dependent upon shift variances given by eq 9. An equation relating them, developed from eq 5, is[20]

$$\sigma_{ic}^2 = \left(\frac{\Delta\nu_i}{\Delta\nu_s}\right)^2\left[\left(\frac{\sigma_i}{\Delta\nu_i}\right)^2 + \left(\frac{\sigma_s}{\Delta\nu_s}\right)^2\right] = (\nu_{ic})^2(f_i^2 + f_s^2) \tag{11}$$

where i and s refer to the ith and standard shift, respectively. Equation 11 may be used, with appropriate substitutions, to calculate the variances of experimentally determined relative shifts. Values of fractional errors, f_i, of induced shifts calculated from eq 10 are given in Table II. Fractional errors of relative shifts, F_i, may be defined as,

$$F_i = \frac{\sigma_{ic}}{\nu_{ic}} = [f_i^2 + f_s^2]^{1/2} \tag{12}$$

F_i values also reflect the magnification of coordinate error noted previously (Table II).

Residuals

Coordinate error has the effect of softening the analysis of structure using pseudocontact shift data by increasing the errors involved in comparison of observed and calculated shifts. In such comparisons, if the residuals, $(\nu_{io} - \nu_{ic})$, are within limits defined by the standard deviations of the quantities, then the calculation is deemed successful. For normally distributed observations and calculations, the residuals are also normally distributed, $N[(\mu_{io} - \mu_{ic}), (\sigma_{io}^2 +$

Table II. Average Relative Shifts, ν_{ic}, Calculated for the Cubical Hypothetical Molecules (Figure 1) with Coordinate Error Level σ_x = 0.1 Å, and Fractional Errors

	Case A			Case B		
Atom	ν_{ic}	f_i[a]	F_i[b]	ν_{ic}	f_i[a]	F_i[b]
1	1.0	0.0857		1.0	0.138	
2	0.786	0.0860	0.1214	−0.0471	1.722	1.728
3	0.630	0.0868	0.1220	−0.107	0.655	0.669
4	0.784	0.0860	0.1214	0.736	0.152	0.205
5	0.407	0.0667	0.1086	0.393	0.114	0.179
6	0.470	0.0667	0.1086	0.474	0.108	0.175
7	0.406	0.0667	0.1086	0.0749	0.506	0.524
8	0.353	0.0670	0.1088	0.0433	0.816	0.828

[a] Calculated using eq 10. [b] Calculated from eq 12.

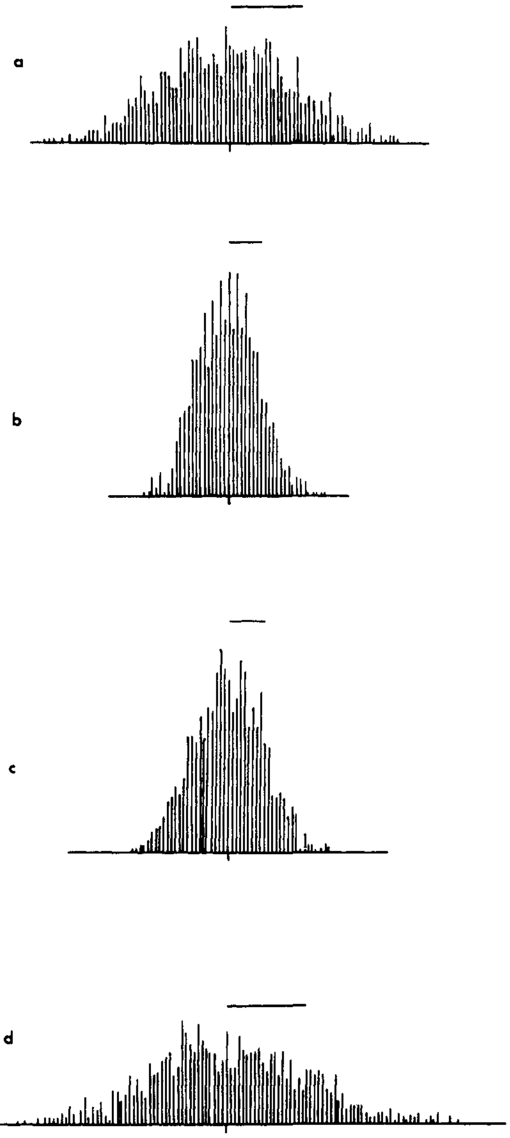

Figure 4. Distributions of relative shifts for the cubical molecule when σ_x = 0.05 Å: (a) case B, atom 2; (b) case B, atom 7; (c) case A, atom 5; (d) case A, atom 2. Horizontal lines indicate standard deviations.

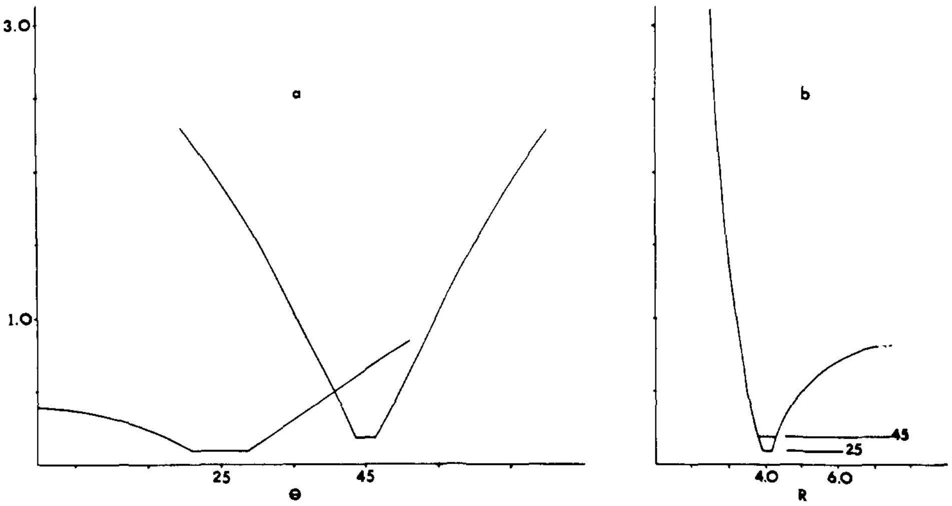

Figure 5. Plot of D (see text, eq 13) as a function of (a) angle and (b) distance for two shifts (σ_x = 0.1 Å).

Table III. Systematic Error Contributions to the Sum of Squares

	σ_x = 0.01 Å		σ_x = 0.05 Å		σ_x = 0.1 Å	
	IB	IIB	IB	IIB	IB	IIB
$E(d^2)$	3.81×10^{-4}	3.57×10^{-2}	9.40×10^{-3}	4.25×10^{-2}	3.73×10^{-2}	6.37×10^{-2}
$\Sigma\sigma^2$	3.79×10^{-4}	0.0293×10^{-2}	9.40×10^{-3}	0.73×10^{-2}	3.65×10^{-2}	2.84×10^{-2}
Diff		3.54×10^{-2}		3.52×10^{-2}		3.53×10^{-2}

$\sigma_{ic}{}^2)^{1/2}]$. The limits of acceptability are $\pm(\sigma_{io}{}^2 + \sigma_{ic}{}^2)^{1/2}$, a quantity that includes both errors of measurement and calculation. The contribution due to errors in coordinates is often small, but need not be. Indeed, errors in calculated relative shifts may be larger than errors of measurement.

It is possible to assess the significance of individual residuals by considering the ratio, D, as

$$D = \left|\frac{\nu_{io} - \nu_{ic}}{\nu_{io}}\right| \tag{13}$$

This ratio will approach zero as the calculated relative shift nears the observed. In a successful calculation, the value of D will be given by,

$$D \le D_m = \left|\frac{\sqrt{\sigma_{io}{}^2 + \sigma_{ic}{}^2}}{\sigma_{io}}\right| \tag{14}$$

The sensitivity of a particular residual to substrate structure (and to metal ion position) is a function of *both* the structure dependence of the calculated shift, ν_{ic}, and D_m. In Figure 5a, D is plotted as a function of angle for two cases. Two hypothetical shifts are considered, one having an angle parameter of 25° and the other 45° (both are for distances of 4.0 Å). Only errors of calculation are included, and the minima of the curves are determined by D_m. In a successful calculation, the value of D will be below D_m. The range of angles for which this condition applies is a measure of sensitivity, the wide range being the less sensitive. In the case of the 25° shift, errors limit the definition of the angle to 25.0 ± 4.0°, while for the 45° shift, the angle parameter is defined as 45.0 ± 1.5°. Shifts for which the angle parameter is near the "magic angle" are more sensitive to angular positions in spite of larger fractional errors of calculation.

In Figure 5b, D is plotted as a function of distance for the same two shifts. Since both these shifts are for distances of 4.0 Å, the R dependence of D is the same for both, and the 25.0° shift is the most sensitive.

Systematic Errors

If the residuals, $(\nu_{io} - \nu_{ic})$, are normally distributed $N[(\mu_{io} - \mu_{ic}), (\sigma_{io}{}^2 + \sigma_{ic}{}^2)^{1/2}]$, then the expectations of their squares are given by

$$E(\nu_{io} - \nu_{ic})^2 = (\mu_{io} - \mu_{ic})^2 + \sigma_{io}{}^2 + \sigma_{ic}{}^2 \tag{15}$$

The expectation for the sum of squares, $\Sigma_i(\nu_{io} - \nu_{ic})^2$, is[21]

$$E\left[\sum_i (\nu_{io} - \nu_{ic})^2\right] = \sum_i (\mu_{io} - \mu_{ic})^2 + \sum_i (\sigma_{io}{}^2 + \sigma_{ic}{}^2) \tag{16}$$

This relationship represents a factoring of systematic and random error as defined in this paper. At best fit, when $(\mu_{io} - \mu_{ic}) = 0$ for all i, the expectation will be equal to the second term only. Not best fit sums, when $(\mu_{io} - \mu_{ic}) \neq 0$, will include contributions from both terms. Since the quantity $\Sigma_i(\sigma_{io}{}^2 + \sigma_{ic}{}^2)$ may be calculated for best fit and not best fit cases, contributions to the overall sum of squares due to systematic errors may be estimated.

Table III lists the ults of calculations illustrating eq 15. In the table, $E(d^2)$ are average values of the sum of residuals obtained for the cubical structures designated IB and IIB at three levels of coordinate error. Structure IB is pictured in Figure 1b, and is a best fit case. Structure IIB is the same except that the magnetic center is 3.7 Å from the origin rather than 3.5 Å. Sums of variances, $\Sigma\sigma^2$, were also calculated. Within the accuracy of the calculation, the differences between these numbers are constant. These differences are measures of systematic error. For the IB structure (a best fit case) the differences are zero. In the case of the IIB structure, the differences are the same for each level of coordinate error. At the error levels used in these calculations, systematic error is essentially independent of σ_x.

Systematic error presents unique problems in pseudocontact shift analyses. If it originates from contact shift contributions, say, then it may be recognized through the difficulty in fitting calculated with observed shifts for some but not all resonances. Other sources of systematic error, however, may not be so obvious. Ammon and coworkers[14] reported an interesting calculation in which they lengthened the carbon-hydrogen bonds of the assumed substrate structure. They found that fits were obtained, albeit at higher R-factor values, at slightly increased lanthanide-substrate bond distances. The effect, they reported, is much like an expansion of scale of the molecule. Equation 16 provides a means to examine the effects of systematic error from these and other sources.[22]

Conclusions

There are errors of calculation in the analysis of pseudocontact shift data which arise out of unavoidable uncertainties in molecular coordinates. Random coordinate error is magnified in calculation of relative shifts, and errors of shift calculation may be larger than errors of measurement. The practical consequence of this, however, varies with the situation. When an accurate x-ray analysis is the source of molecular coordinates used in pseudocontact shift calculations, errors of calculation are likely to be small. If the choices to be made with the help of the shift calculation involve structures that are substantially different, then shifts for the various choices will be widely separated so that small adjustments will have no effect.

Errors of calculation will be important in pseudocontact shift analyses when the distinctions to be made involve closely related structures, or yield R factors whose ratio is only just significant. Such situations may arise in studies of molecular conformation or conformational mixing. Careful consideration of the effects of coordinate error on the accuracy of the calculations should accompany such studies, particularly when the source of substrate coordinates are molecular models. Though random errors in atomic coordinates cannot be entirely eliminated, effects of the errors on shift calculations can be recognized.

Variances and fractional errors of calculation for lanthanide-induced pseudocontact shifts and relative shifts may be estimated using equations developed in this paper. These quantities will allow the assessment of the effects on shift calculations of random coordinate error in the assumed substrate structure. More realistic limits of accuracy may be placed on the residuals. The sensitivity of a particular residual to parameters of structure is a function of the standard deviation of the residual *and* its angle and distance dependence. The overall effect of random coordinate error on a calculation, will, therefore, be dependent on the context. Error magnitudes suggested by calculations in this article, however, indicate that it is unwise to routinely discount coordinate uncertainties.

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(16) There are several methods for determining lanthanide-induced shifts.[2-4] A recent article, which also includes considerations of standard deviations, is M. D. Johnston, Jr., B. L. Shapiro, M. J. Shapiro, T. W. Proulx, A. D. Godwin, and H. L. Pearce, *J. Am. Chem. Soc.*, **97**, 542 (1975).
(17) The random number subroutine used is part of the IBM Scientific Substrative Package (SSP) based on an algorithm discussed in R. W. Haming, "Numerical Methods for Scientists and Engineers", 2nd ed, McGraw-Hill, New York, N.Y., 1973, pp 137–138, 143.
(18) W. C. Hamilton, "Statistics in Physical Science", Ronald Press, New York, N.Y., 1964, Chapter 1.
(19) P. L. Meyer, "Introductory Probability and Statistical Applications", Addison-Wesley, Reading, Mass., 1970, pp 139–141.
(20) For calculated shifts near the magic angle, eq 11 and 12 should be applied with caution. When f_i values are large, the approximations of eq 11 do not apply. Large F_i values ($F_i > 0.5$) indicate large variances of relative shifts but are not precise. See ref 18, p 33.
(21) Reference 15, p 222.
(22) A referee commented, "This error analysis is based on knowing a correct (i.e., accurate) set of lanthanide-substrate coordinates; then holding the lanthanide position fixed while varying some nuclear coordinates and evaluating R factors. The errors in the R factors so introduced are artificially large when compared to the R factors which are obtained after relocating the lanthanide relative to the new set of nuclear coordinates. This situation in practice leads to agreement between observed and calculated values of known precision, but produce a lanthanide-substrate array of unknown accuracy". Though the sum in eq 16 is not an R factor per se, they are closely related and the quoted observation is relevant. For the hypothetical systems examined in this paper, the lanthanide-substrate array was of known accuracy. Differences in Table III reflect changes in the precision-of-fit. In a study of systematic error, precision-of-fit is an issue. Equation 16 may be helpful in that regard.