A Method for Compensating for Experimental Errors in Shift Reagent Work

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Summary A method is described which compensates for the experimental errors in shift reagent work; it is found that the slope ratios, in plots of lanthanide induced shifts *vs.* amount of shift reagent, are unaffected by experimental errors in the concentrations of shift reagent and substrate.

FOLLOWING Hinckley's discovery[1] a large number of papers on the use of shift reagents has appeared in the literature.[2] Usually lanthanide induced shifts, LIS, are plotted against the molar ratios of lanthanide shift reagent, LSR, and substrate. Invoking pseudo-contact interactions, the signs and magnitudes of the slopes are then used to estimate the relative positions of the corresponding protons and hence to aid in structure elucidation. Since the concentrations cannot be determined as accurately as the chemical shifts it might seem impossible to achieve the same precision as in other areas of n.m.r. spectroscopy.

We show in this communication that a knowledge of the concentrations of LSR and substrate is unnecessary and that shift reagent parameters can therefore be determined as accurately as the chemical shifts. Since the concentrations have to be exactly the same for all protons in any given sample we know that, in plots of LIS *vs.* amount of LSR, 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.

Suppose we define an array of points by the intercepts of a series of lines with arbitrary slopes and a series of vertical lines at arbitrary horizontal positions. Suppose now 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 (see below) except for an unknown scale factor along the horizontal axis. This scale factor affects the slopes but not the slope ratios. Moreover, it is found that these slope ratios are the same, to a sufficient number of decimal places (*vide infra*), as the ratios obtained from the best lines through the displaced points. Thus, without a knowledge of the horizontal co-ordinates a perfect plot and the correct slope ratios are obtained.

The same has to be true for the plots of LIS *vs*. LSR if the "true" curves are straight lines in the range of the experimental points. Conversely, the correction of the horizontal co-ordinates 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.
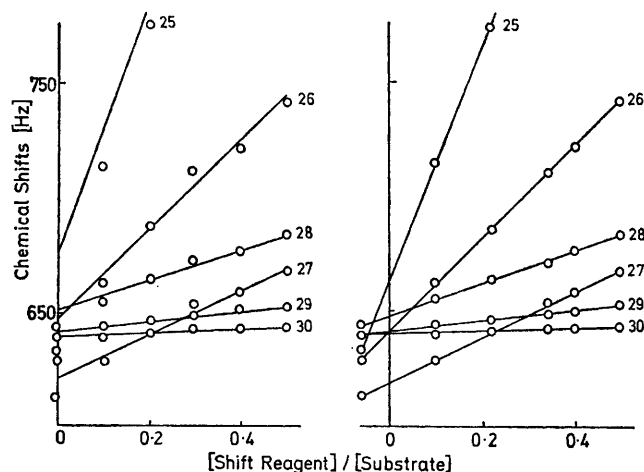

FIGURE. *Lanthanide induced shifts for some of the methyl groups of β-amyrin, plotted against the molar ratios of* Pr(fod)$_3$ *and β-amyrin. Left: before correction, right: after correction.*

The Figure shows plots of chemical shift† against ratio of LSR to substrate for the methyl groups of β-amyrin (**1**) omitting those at C-23 and C-24‡ (the figures on the various straight lines indicate the methyl signal being observed) before and after adjustment of the experimental data. In this and in all other cases where we have applied the adjusting procedure we invariably obtained greatly improved plots and the same slope ratios, to the decimal place beyond the last significant figure for the slopes. The maximum molar ratios of LSR and substrate were 0·5 and 1·0 for the fod and dpm complexes respectively.

Thus, the "corrected" molar ratios are obtained as described below. Then the experimental shifts are plotted,

to see whether there is signal crossover which now is much more readily detected and corrected, even in regions of extensive line crossings. The slopes are then determined numerically by the least-squares method.

Correction procedure for the molar ratios of LSR and substrate. Suppose there are *m* signals per spectrum and spectra for *n* different molar ratios of LSR and substrate. 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. For the chemical shift δ_{ij}, for the *i*'th proton in the *j*'th spectrum, to 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

$$(c_j - c_1)/(c_n - c_1) = (\delta_{ij} - \delta_{i1})/(\delta_{in} - \delta_{i1}) \qquad (1)$$

and therefore

$$c_j = (c_n - c_1)(\delta_{ij} - \delta_{i1})/(\delta_{in} - \delta_{i1}) + c_1 \qquad (2)$$

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 (1) is summed over all *i*, giving, after rearrangement

$$c_j = (c_n - c_1)(\Sigma\delta_{ij} - \Sigma\delta_{i1})/(\Sigma\delta_{in} - \Sigma\delta_{i1}) + c_1 \qquad (3)$$

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 (3) 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 is 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 LSR will in general be different from zero as a consequence of the arbitrary choice of the fixed points c_1 and c_n.
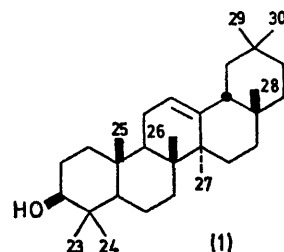
† Chemical shifts were determined on a Varian XL-100 spectrometer, in CCl_4 and are expressed in Hz upfield from benzene which was also used as the lock signal. The closeness of ligand peaks in the shift reagents to Me$_4$Si make it difficult to lock onto this signal.

‡ These signals were omitted simply for convenience in this illustration. The plots associated with these signals are of large slope and to include them here would have necessitated an expanded scale and consequently a less convincing demonstration of the power of the method.

[1] C. C. Hinckley, *J. Amer. Chem. Soc.*, 1969, **91**, 5160.

[2] See for instance W. De W. Horrocks, jun., J. P. Sipe tert., and J. R. Luber, *J. Amer. Chem. Soc.*, 1971, **93**, 5258 and references therein.