

ON THE LACK OF EVIDENCE FOR CONTACT CONTRIBUTIONS TO LANTHANIDE-INDUCED  
N.M.R. SHIFTS (L.I.S.'s) IN AROMATIC ALDEHYDES: A RIGOROUS ERROR ANALYSIS AND THE  
ISOLATION OF DIAMAGNETIC (COMPLEXATION) SHIFTS.

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**Summary.** The adoption of a rigorous error analysis of L.I.S.'s allows the non-pseudo-contact components of the Yb(fod)<sub>3</sub> induced shifts in benzaldehyde and thiophen-2-aldehyde to be isolated. They are largest at the carbonyl carbon and at the ortho and para carbons and appear to be entirely due to complexation (diamagnetic) shifts. Estimation of these with La (fod)<sub>3</sub> allows a precise analysis of the <sup>1</sup>H and <sup>13</sup>C L.I.S.'s of these aldehydes without the need to invoke any contact shifts.

The use of L.I.S.'s as probes of molecular structure and conformational energy differences depends crucially on both the correctness of the substrate-shift reagent binding model, as we have recently emphasised,<sup>1</sup> and on the accuracy of the procedure used in the computational search for the best agreement between the observed and calculated shifts. We note here that the procedure used in the majority of previous investigations is open to question and present a mathematically rigorous alternative. The use of this refined method allows the recognition of non-pseudo-contact contributions to the L.I.S.'s of benzaldehyde and thiophen-2-aldehyde and these are shown to be primarily due to diamagnetic complexation shifts, and not contact shifts as has been assumed previously.<sup>2</sup>

The usual procedure adopted in L.I.S. investigations is to obtain the slope, for each nucleus 'i', of the chemical shift versus ratio of added lanthanide plot, the  $\Delta M_{\text{obs}}^i$  value, and to compare this with the shift calculated from the McConnell-Robertson equation.<sup>3</sup> As the constant in this equation involves both the anisotropic magnetic susceptibility of the lanthanide and the formation constant of the lanthanide-substrate complex, both of which are unknown, it is necessary to compare ratios of observed and calculated  $\Delta M^i$  values, with a particular nucleus chosen as a normalising atom. This implicitly assumes that the normalising atom is 'reliable', i.e. error-free, without any non-pseudo contact contribution, of well defined geometry etc. Inevitably, the agreement between calculated and observed L.I.S.'s depends on the choice of the normalising atom and hence is to some extent an arbitrary quantity.<sup>4</sup>

In the extension of our L.I.S. studies<sup>1</sup> to aromatic aldehydes and ketones, it became clear that some, but not all, of the nuclei were affected by non-pseudo contact contributions: it was therefore necessary to develop an approach which did not involve the subjective choice of a

normalising atom. Our procedure is to judge the goodness of fit between calculated and observed L.I.S.'s by calculation of an agreement (R) factor defined in equation (1), with the normalising factor (f) which minimises R for any given solution defined as in equation (2). This procedure

$$R = \sqrt{\left\{ \sum_i (\Delta M_{\text{obs}}^i - f \Delta M_{\text{calc}}^i)^2 / \sum_i (\Delta M_{\text{obs}}^i)^2 \right\}} \quad (1)$$

$$f = \sum_i (\Delta M_{\text{obs}}^i \times \Delta M_{\text{calc}}^i) / \sum_i (\Delta M_{\text{calc}}^i)^2 \quad (2)$$

requires neither normalising atom nor any implicit assumptions and we strongly recommend its use for all future L.I.S. studies.<sup>5</sup> As examples of its use we include here analyses of benzaldehyde and thiophen-2-aldehyde L.I.S.'s.

Previous investigations<sup>4,6</sup> have shown that whereas the proton shifts can be safely assumed to have only pseudo-contact contributions, the carbon shifts have additional contributions. However, if only the protons are considered, the L.I.S. analysis is not mathematically over-determined since in both molecules there are only four different proton  $\Delta M$  values and all these are required merely to define the lanthanide position. (Although there is no normalising atom equations (1) and (2) still imply a normalising procedure involving the loss of one degree of freedom). Thus the carbon  $\Delta M$  values are necessary to obtain a well-determined set of equations but which ones, if any, can be used?

Table 1 Observed ( $\delta_o$ ), Bond ( $\Delta M$ ) and Diamagnetic ( $\Delta D$ ) Shifts (p.p.m.)  
for Benzaldehyde and Thiophen-2-Aldehyde.

a) Benzaldehyde.

|              | C=O    | C <sub>1</sub> | C <sub>2</sub> <sup>6</sup> | C <sub>3</sub> <sup>5</sup> | C <sub>4</sub> | H <sub>F</sub> | H <sub>2</sub> <sup>6</sup> | H <sub>3</sub> <sup>5</sup> | H <sub>4</sub> |
|--------------|--------|----------------|-----------------------------|-----------------------------|----------------|----------------|-----------------------------|-----------------------------|----------------|
| $\delta_o^a$ | 192.34 | 134.46         | 129.75                      | 129.03                      | 134.48         | 10.01          | 7.88                        | 7.52                        | 7.63           |
| $\Delta M^b$ | 131.92 | 46.55          | 31.50                       | 15.54                       | 14.54          | 69.75          | 29.98                       | 10.07                       | 7.96           |
| $\Delta D$   | 10.01  | -2.11          | 2.52                        | <0.5                        | 2.89           | -              | -                           | -                           | -              |

b) Thiophen-2-aldehyde

|              | C=O    | C <sub>2</sub> | C <sub>3</sub> | C <sub>4</sub> | C <sub>5</sub> | H <sub>F</sub> | H <sub>3</sub> | H <sub>4</sub> | H <sub>5</sub> |
|--------------|--------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| $\delta_o^a$ | 182.88 | 144.18         | 136.21         | 128.35         | 135.06         | 9.94           | 7.76           | 7.21           | 7.76           |
| $\Delta M$   | 151.2  | 52.8           | 32.9           | 18.5           | 23.1           | 81.52          | 22.57          | 11.52          | 12.63          |
| $\Delta D$   | 11.0   | -3.1           | 6.9            | 1.7            | 7.0            | -              | -              | -              | -              |

<sup>a</sup> ca. 0.9 m/l in CDCl<sub>3</sub>, <sup>b</sup> from at least 3 additions of Yb(fod)<sub>3</sub>, all corr. coeff.  $\geq 0.999$

Table 1 contains Yb(fod)<sub>3</sub> and La(fod)<sub>3</sub> (see later) L.I.S.'s for all the protons and carbons of benzaldehyde and thiophen-2-aldehyde, and table 2 summarises the results of the analyses from computer program LIRAS-3, using substrate geometries from combined microwave and ab-initio calculations.<sup>7,8</sup> For benzaldehyde, three different cases were considered. Initially all the

measured  $\Delta M$  values were input, except for the carbonyl carbon.<sup>1</sup> This analysis gives eight equations in five unknowns (one normalising factor, three lanthanide co-ordinates and exo/endo lanthanide populations on the two-site C=O lone-pair binding model), and produces (case A, table 2) an unacceptably large R value. However, the lanthanide position is as expected ( $\phi$  80-90°,  $\psi$  ca. 140°) and is essentially one-site (population 95%). This is to be expected as the approach of the lanthanide on the 'endo' side of the carbonyl will be severely restricted by the phenyl group.

Table 2. Results of Analysis of L.I.S. Shifts.

|   | <u>Benzaldehyde.</u> |                     | Lanthanide |          | Co-ordinates. |  | Pop. <sup>c</sup> |
|---|----------------------|---------------------|------------|----------|---------------|--|-------------------|
|   | R <sup>a</sup>       | R.M.S. <sup>b</sup> | r(A°)      | $\phi$ ° | $\psi$ °      |  |                   |
| A) All nuclei (-C=O)                        | .028                 | 1.0                 | 2.90       | 80-90    | 140-145       |  | 95%               |
| B) -CO, C <sub>2</sub> , & C <sub>3,5</sub> | .015                 | 0.6                 | 2.60       | 90       | 130           |  | 100%              |
| C) Corrected Shifts                         | .006                 | 0.3                 | 2.60       | 60       | 145           |  | 100%              |
| <u>Thiophen-2-aldehyde.</u>                 |                      |                     |            |          |               |  |                   |
| A) All nuclei (-CO)                         | .051                 | 2.0                 | 3.3        | 80-90    | 145           |  | 100%              |
| B) -CO, C <sub>3</sub> , C <sub>5</sub>     | .012                 | 0.5                 | 3.0        | 90       | 140           |  | 100%              |
| C) Corrected Shifts                         | .015                 | 0.9                 | 2.6        | 90       | 140           |  | 95%               |

<sup>a</sup> Agreement (R) factor, <sup>b</sup> r.m.s. error, <sup>c</sup> % Population of exo w.r.t. endo (see text)

Trial and error eventually identified the erroneous  $\Delta M$  values. Case B, table 2 shows the results of the analysis in which the carbon atoms C<sub>2,6</sub> and C<sub>4</sub> (as well as C=O) have been removed. This analysis gives an acceptable R value (0.015) and a reasonable solution but does not provide any indication as to the cause of this non pseudo contact contribution. This is immediately identified as a diamagnetic complexation shift by the results of an identical L.I.S. experiment in which the diamagnetic La(fod)<sub>3</sub> replaces Yb(fod)<sub>3</sub><sup>+</sup>. These complexation shifts ( $\Delta D^i$ ) values are given in table 1 and can be seen to make a significant contribution to the  $\Delta M^i$  values, particularly at the C=O, C<sub>2,6</sub> and C<sub>4</sub> carbons, precisely as indicated by the above analysis. Unequivocal proof of the correctness of this interpretation is provided by the results of the analysis of the residual ( $\Delta M^i - \Delta D^i$ ) shifts (Case C, table 2). The R-value (.006) is now well within the acceptable error limits and the analysis gives a chemically reasonable solution with again essentially a 100% population on the unhindered 'exo' side of the aldehyde. Most surprisingly, this solution has been obtained from an analysis, utilising all the  $\Delta M$  values (including even the carbonyl) and demonstrates unequivocally that a quantitative explanation of all the observed proton and carbon L.I.S.'s in benzaldehyde can be obtained by considering only the pseudo-contact and diamagnetic

<sup>+</sup> We assume, following previous workers,<sup>9</sup> that the diamagnetic contribution of the Yb(fod)<sub>3</sub> shifts may be obtained to a very good approximation, from the La(fod)<sub>3</sub> shifts.

contributions without the need to invoke contact shifts at all.

In order to demonstrate that this intriguing result is not an artefact of a particular molecule, an identical analysis of thiophen-2-aldehyde has been carried out. The results of the analysis follow precisely the pattern of the benzaldehyde example. In the initial (Case A) in which all the proton and carbon  $\Delta M$  values are used (except C=O) very large R-values are again obtained, well above any experimental error. Removal of the analogous carbons (C=O, C<sub>3</sub> and C<sub>5</sub>) gives acceptable R-values and a chemically reasonable solution (Case B); an equally good solution is obtained (Case C) by subtraction of the analogous  $\Delta D^i$  values. The diamagnetic shifts for thiophen-2-aldehyde are even larger than in benzaldehyde and illustrate very clearly the errors which could result from L.I.S. analyses of such molecules if these shifts are not removed.

The most exciting aspect of these results to us is the apparent lack of any contact shift contribution, as almost all previous investigations of aromatic compounds have found large contact contributions to the carbon L.I.S.'s.<sup>2</sup> We are currently investigating the generality of these results.

We acknowledge a British Council Substantive Award and thank Dr. R. Podesta for considerable computing assistance in writing LIRAS-3, and Miss C. Lasagna for technical assistance.

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(Received in UK 25 March 1981)