Tetrahedron Letters No. 13, pp 1189 - 1192, 1975. Pergamon Press. Printed in Great Britain.

NMR-LIS STUDIES BIFUNCTIONAL MOLECULES I ANHYDRIDES

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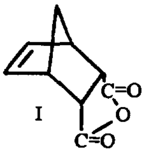
(Received in USA 29 October 1974; received in UK for publication 25 February 1975)

During the past five years, lanthanide shift reagents (LSR) of the paramagnetic metal complex type have received increasing attention because of their ability to simplify and resolve nmr spectra of organic substrate molecules containing various functional groups The magnitude of the lanthanide induced shift (LIS), $\Delta\delta$, depends on the distance and the angle of the magnetic axis between the lanthanide atom and the proton and may therefore provide information concerning the geometry and conformation of the organic substrate molecule in solution. Numerous reviews[1] demonstrate the extent to which systematic LSR investigations have been confined to monofunctional compounds Bifunctional and polyfunctional LSR studies have generally been limited to different functional groups relatively widely separated within the molecule [2] Therefore, it seemed of interest to undertake LSR studies of several series of bifunctional organic substrate molecules having the same functional groups on adjacent carbon atoms. An appropriate series, I-VI, [3aα, 4α, 7α, 7aα]-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione, (commonly known as 5-norbornene-2,3-endodicarboxylic anhydride) and its corresponding exo isomer with different spiro substituents in the 8 position provided both structural rigidity and bisected geometry.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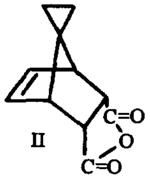
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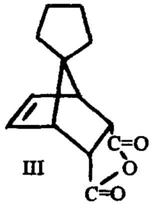
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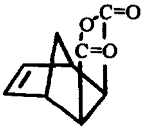
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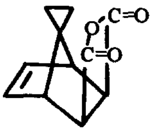
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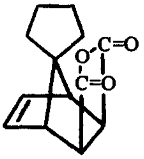
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For the initial study, choice of the anhydride, allowing two complex sites, ether and carbonyl, was made because of increased molecular rigidity over the other bifunctional groups currently under investigation in these laboratories Work on the corresponding diols, diesters, diacids and ethers of the same bicyclic parent compounds I - VI is in progress

The anhydrides, I - V, (VI has eluded preparation to date) are excellent choices for LSR work because of the distinct separation of the various proton resonances in the unshifted spectra Clarification of whether the coordination involved the ether oxygen or was a time averaging of shifts due to complexing at each of the carbonyl oxygens, provided further impetus to the problem Furthermore, X-ray crystallography data for compounds I[3] and IV[4] were available for use in the computational study X-ray crystallography studies of compounds II and V are currently being undertaken in our department and will augment the LSR studies.

LIS in bifunctional molecules are dependent on basicity and steric factors. If only basicity is considered, the magnitude of the induced shift is directly related to the basicity of the donor. If steric restrictions are present, complexing may revert to the weaker Lewis donor. In the case of the bicyclic anhydrides, I - V, if steric hindrance is absent, complexation should occur at the carbonyl site

Our results confirm this prediction. When the LIS for each of the five anhydrides are compared to shift factors calculated from the McConnell-Robertson pseudo-contact equation the evidence is clearcut in favor of averaged carbonyl oxygen over ether oxygen attachment

Our analysis proceeded as follows

Shifts were observed for the protons in each anhydride over a range of 0.1 to 1.0 europium FOD anhydride mole ratio. The experimental procedure for obtaining the shifts was nearly identical to that described by Ammon, et. al.[5] Plots of the chemical shift changes for each proton vs. europium FOD anhydride mole ratio showed excellent linearity in the 0.3 to 0 8 mole ratio region. The slope of the regression line was obtained in each case and taken as proportional to the bound chemical shift for that proton. Slopes, estimated standard deviations, and correlations for each of the protons in the five anhydrides are given in Table 1.

Table 1 OBSERVED SLOPES

Hydrogen Type	Slope (Sd)[a]	r[b]	Slope (Sd)	r	Slope (Sd)	r	Slope (Sd)	r	Slope (Sd)	r
Bridgehead (4,7)	68.3 (2.6)	992	68 3 (4 7)	.986	71.1 (3.7)	.990	63 4 (2.8)	992	77 4 (3 7)	.994
Endo or Exo (3a, 7a)	123.4 (6.8)	.992	120 9 (10.6)	.981	124.6 (6 4)	.992	90.0 (3.7)	.994	106 0 (4.3)	995
Vinyl (5, 6)	84.6 (3.7)	.992	78.6 (6.6)	.983	86.0 (4.3)	.993	14.6 (0 7)	.986	20.0 (1.4)	991
Bridge (8) or	43.1 (4.3)	977	18.3 (1.5)	.982	21.0 (1.9)[c]	.964	85.1 (4.6)	.992	86.0 (3.6)	.995
Ring	30.6 (1.7)	.993					38.6 (0.8)	993	30.0 (1 4)	988
Anhydride	I		II		III		IV		V	

[a] the slope is expressed in ΔH_z /unit change in europium FOD anhydride mole ratio, Sd is the estimated standard deviation of the slope [b] linear regression correlation coefficient.

[c] determined from shifts at 0.1 to 0 5 europium FOD anhydride mole ratio only.

It should be noted that protons in comparable positions in the three endo anhydrides have similar slopes (that is, similar LIS), as do comparable protons in the two exo anhydrides.

This observation argues for a single mode of complexation of the three endo anhydrides with the europium FOD reagent as well as a common mode for the two exo anhydrides and suggests that the bridge substituents do not strongly perturb the anhydride-europium FOD interaction.

Two methods were used to compare observed LIS with calculated shift factors. In the first calculated shift factors were generated for europium positions by placing the europium atom on a vector determined by two atoms of the anhydride, one of them always an oxygen and calculating factors every 0.2 Å from 2.4 Å to 3.5 Å from the oxygen atom. The principal magnetic axis of the europium FOD was considered co-linear with the Eu-O vector in each case. For each position the linear regression of the observed LIS on the calculated factors was done and the correlation coefficients obtained. If there was a maximum in the correlation coefficient along a particular vector within the limits 2.4 Å to 3.5 Å that position was deemed reasonable. For compounds I - IV, correlation coefficient maxima were found along vectors through the carbonyl oxygen but no maxima were noted along ether oxygen vectors. No maxima were found along any vectors chosen for compound V. The maximization of the correlation coefficient is the criterion used by Roberts[6] to evaluate lanthanide position in his more elaborate and sophisticated CHMSHIFT program We agree with Roberts that the softness of these fits preclude exact position determination of the europium but it is evident that carbonyl oxygen complexation is preferred over ether oxygen complexation.

Support for this conclusion derives from the second method of comparison. Observed LIS were fitted by calculated factors with the program PDIGM [7,8] All five anhydrides show excellent fits at physically reasonable positions for the europium atom when it is assumed attached at the carbonyl oxygen In contrast all five show poor fits for ether oxygen attachment and the best of those fits are at physically unreasonable positions. A summary of these results are given in Table 2

Table 2 BEST FIT POSITIONS FOR EUROPIUM ATOM FROM PDIGM

Moment Direction^a	r_o^b	r_c^c	α^d	R^e	r_o	r_c	α	R	r_o	r_c	α	R	r_o	r_c	α	R	r_o	r_c	α	R
Carbonyl O	3 1	4.2	151	1.8	2.8	3.9	150	1.9	2.8	3.9	155	0.7	3.2	4.3	154	2 5	3.4	4.5	153	2.1
Ether O	.58	1.1	64	4.8	58	1.1	64	9.2	.59	1.1	71	10	.63	99	57	15	.61	1.0	57	9 0
Anhydride	I				II				III				IV				V			

a in all cases the europium position was found out of the bisecting plane, therefore for each 'best fit' position there is an equivalent mirror position. b the distance in Å from the europium atom to the nearest oxygen atom, this is always a carbonyl oxygen. c the distance in Å from the europium atom to the nearest carbon atom, this is always the carbon bonded to the carbonyl oxygen. d the C-O-Eu angle for the nearest carbon and oxygen atoms. e the PDIGM agreement factor in percent, the lower the percent the better the fit.

It is obvious that minima in the ether oxygen calculations are artifacts, the europium position is far too close to many atoms and in fact lies over the more closed face of the anhydride ring in all five compounds. In contrast the carbonyl oxygen calculations give wholly reasonable europium positions The europium atom lies away from the molecule and is slightly elevated over the more open face of the anhydride ring in all five compounds.

The synthesis and characterization of compounds I, II, III and IV are adequately covered elsewhere,[9,10] with the exception of the nmr data which has been published for compounds I and IV only.[11]

Compound V, [3'a α, 4'β, 7'β, 7'aα]-3'a, 4', 7', 7'a -tetrahydrospiro [cyclopropane-1, 8'- [4, 7] - methanoisobenzofuran] 1', 3'-dione, which has not previously been reported, was prepared by heating compound II at an internal temperature of 123 ± 3°C for 21 hours. The resulting solid, after three recrystallizations from benzene formed clusters of opaque needles, m.p. (sealed cap.) 147 - 148°C. ^1H-nmr ($CDCl_3$). δ 0.633 (m, 4H, cyclopropyl), 2.900 (t, 2H, 4' and 7'H), 3.167 (s, 2H, 3'a and 7'aH), 6.433 (t, 2H, vinyl 5', 6'H). Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.47, H, 5.26 Found C, 69.58, H, 5.45.

Although attempts have failed to thermally rearrange compound III to compound VI, by varying both the temperature (120°, 140°, 160°, and 180°C) conditions and the length of the heating period (10-20 hours), further studies of this rearrangement are currently being investigated by our group. The results of previous work[12] are inconclusive.

More complete nmr data and experimental conditions will be provided in later publications.

Acknowledgments RERC wishes to acknowledge financial support for chemicals associated with this project from a grant-in-aid awarded by the Society of Sigma Xi and for financial assistance from the Endowment and Research Foundation of Montana State University. We are grateful to Mr. Gary Dirks of Montana State University for obtaining the PDIGM program from the authors in reference 7 and for making the alterations necessary for compatibility with our XDS SIGMA 7 computer system.

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8. The PDIGM program, using lanthanide positions selected by the user, calculates shift factors for all protons and assesses their agreement with experimental shifts. The ease of selection of lanthanide coordinates and the rapidity with which one can obtain the position of best fit makes the program useful.

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