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A CONVENIENT METHOD FOR MIXING ^{1}H AND ^{13}C LANTHANIDE INDUCED SHIFT (LIS) CALCULATIONS. A TECHNIQUE FOR FACILITATING ^{13}C ASSIGNMENTS

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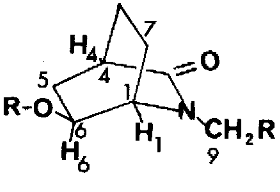
Although ^{1}H LIS data can generally be correlated by the McConnell-Robertson pseudo contact shift equation,[1] similar studies with ^{13}C data have met with mixed success presumably due to significant contact shift contributions,[2] and, in several cases, to an insufficient number of LIS data to define the lanthanide shift reagent (LSR)-substrate geometry.[3]

We wish to report a novel approach for the treatment of LSR data for ^{13}C assignments which builds upon our previously described method[4] for determining LSR-substrate geometries from ^{1}H shift data. The method depends on a computer program which uses LIS ratios to determine the best position of the lanthanide with respect to a substrate framework, by minimizing the shift ratio function $\sum_{i<j} (R_{obs,i,j}-R_{calc,i,j})^2$; nmr assignments, i.e. the association of LIS's with particular nuclear positions, are made as an integral part of the optimization process. Although the shift ratio $R_{i,j}$ is a function of the lanthanide position and the ith and jth nuclear positions, the scale constant K disappears from the ratio and the method provides a simple means for mixing ^{13}C

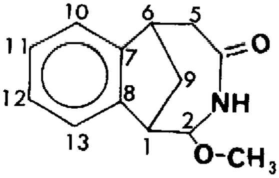
$$R_{calc,i,j} = \frac{LIS_{calc,i}}{LIS_{calc,j}} = \frac{K(3\cos^2\Theta_i - 1)/r_i^3}{K(3\cos^2\Theta_j - 1)/r_j^3} \; ; \quad R_{obs,i,j} = \frac{LIS_{obs,i}}{LIS_{obs,j}}$$

and ^{1}H data (as ^{13}C/^{13}C LIS and ^{1}H/^{1}H LIS ratios) in the same calculation.

The use of the method will be demonstrated for compounds 1 and 2.



1, R=C$_6$H$_5$



2

Compound 1. ^1H and ^{13}C shifted spectra were recorded with $Yb(FOD)_3$. Because of severe overlap in the ^1H-LSR spectra, accurate lanthanide induced shifts could be obtained for only three of the nine bicyclic proton resonances. Although these three data are insufficient to reliably determine the LSR-substrate geometry, our ratio method allows them to be combined with the seven ^{13}C-LIS data, and the Yb position determined from the mixed ^1H-^{13}C ratio calcations provides excellent agreement between the observed and calculated data (Table 1). The Yb...O distance is 2.99 Å, the Yb...O=C angle is 137°, and the ratio $(\sum_{i<j} |R_{obs,i,j} - R_{calc,i,j}| / \sum_{i<j} R_{obs,i,j})$ and shift $\sum_i |LIS_{obs,i} - LIS_{calc,i}| / \sum LIS_{obs,i})$ residuals are, respectively, 0.019 and 0.010. The program automatically makes ^{13}C assignments (Table 1) in the process of optimizing the lanthanide position, and the assignments were entirely consistent with those made on the basis of chemical shift and model compound studies on compound 1.[5] It should be noted that C_5 and C_8 could not be uniquely assigned with this method because the carbons are symmetrically disposed with respect to the Yb...O=C plane.

TABLE 1. $Yb(FOD)_3$ ^1H and ^{13}C LIS DATA FOR COMPOUND 1

	δ(ppm)	LIS(Hz) Obsd.	LIS(Hz) Calcd.	Assignments Possible	Assignments Correct
^1H	2.72	2063	2071	H_1, H_4, H_6	H_4
	3.75	891	882	H_1, H_4, H_6	H_1
	4.35	860	862	H_1, H_4, H_6	H_6
^{13}C	174.3	---[a]		C_3	C_3
	72.1	479	492	C_6, C_1	C_6
	53.5	644	627	C_1, C_6	C_1
	47.4	892	906	C_9	C_9
	38.4	1237	1234	C_4	C_4
	31.8	560	554	C_5, C_8, C_7	C_5
	23.9	560	553	C_8, C_5, C_7	C_8
	19.8	456	463	C_7, C_8, C_5	C_7

[a] The carbonyl carbon resonance could not be detected following addition of LSR.

Compound **2**: Obvious assignments were made from the ^{1}H, ^{13}C and ^{13}C off-resonance decoupled spectra on the basis of chemical shifts and couplings. In the ^{13}C spectrum, for example, the assignments for C_2 and C_{14} are clear, and the decoupled spectrum differentiates C_6 and C_1 from C_5 and C_9 as it does C_{10}, C_{13} and C_{11}, C_{12} from C_7, C_8 (Table 2). The ^{13}C and ^{1}H LSR-shifted spectra were recorded with Eu(DPM)$_3$ and Yb(DPM)$_3$ and the Yb/Eu LIS ratios used to identify contact shifted carbons: e.g. C_5 in the case of Eu(DPM)$_3$.[6,7]

An LSR-substrate geometry fit and ^{13}C assignment calculation were performed with the twelve ^{1}H and ten ^{13}C data giving ratio and shift residuals of 0.080 and 0.078 respectively, and a Eu...O distance of 2.46 Å and Eu...O=C angle of 147°. The number of possible ^{13}C assignments was limited to those possibilities consistent with the off-resonance and chemical shift data[8] (16 total combinations). The method uniquely assigns resonances

TABLE II. Eu(DPM)$_3$ ^{13}C LIS DATA FOR COMPOUND **2**[a,b]

δ(ppm)	LIS(Hz)	Decoupling Multiplicity	Yb LIS / Eu LIS	Assignments Possible	Assignments Correct
175.62	---[c]			C_4	C_4
145.45	162.75	s		C_7, C_8	C_7
142.55	111.77	s		C_7, C_8	C_8
127.59	84.14	d	3.20	C_{10}, C_{11}, C_{12}, C_{13}	C_{11}
127.12	60.66	d	3.53	C_{10}, C_{11}, C_{12}, C_{13}	C_{12}
124.07	129.62	d	3.46	C_{10}, C_{11}, C_{12}, C_{13}	C_{10}
123.47	71.53	d	3.88	C_{10}, C_{11}, C_{12}, C_{13}	C_{13}
85.76	183.84	d	3.33	C_2	C_2
55.30	- 17.31	q	1.59	C_{14}	C_{14}
47.02	123.69	d	3.72	C_1, C_6	C_1
44.88	110.49	t	14.50	C_5, C_9	C_5
38.26	193.80	d	3.68	C_1, C_6	C_6
36.05	111.83	t	4.06	C_5, C_9	C_9

(a) The twelve proton data were taken from ref. 4 and are not included in the table. (b) The Eu...O distance was 2.46 Å. Proton only calculations gave an O...Eu distance of 2.44 Å with ratio and shift residuals of 0.060 and 0.048. (c) The carbonyl carbon resonance could not be detected following addition of the LSR.

to C_1, C_6, C_{10}, C_{11}, C_{12}, and C_{13}, and, more importantly, it also assigns the ipso-carbons, C_7 and C_8. LSR calculations with LIS ratios are equivalent to computations which compare observed and calculated shifts[1,2], with the added advantage that LIS data from different nuclei can be readily mixed in the same analysis.[9] Although n shifts for a given nucleus can afford n(n-1)/2 ratios, it is important to realize that the ratio method generates no additional data. Specification of the three lanthanide coordinates and two K values in a $^{13}C-^{1}H$ analysis requires a minimum of five LIS data which result in three, unique K-less ratios.

Acknowledgment

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5. E. Colicelli - unpublished results.

6. Eu(DPM)$_3$ data are used here for demonstration purposes. A number of groups[7] have noted that Eu causes the largest contact shift contribution of the available lanthanides. The corresponding calculations using Yb(DPM)$_3$ data gave a O...Yb distance of 2.92 Å, a C=O...Yb angle of 143° and residuals of 0.102 (ratio) and 0.077 (shift). These calculations included C_5 but we were unable to accurately determine shifts for C_7 and C_8 due to broadening and intensity problems. In this, and other cases, the use of Eu data has advantages if contact shifted nuclei can be identified.

7. (a) O. A. Gansow, P. A. Loeffler, R. E. Davis, M. R. Willcott and R. E. Lenkinski, J. Am. Chem. Soc., 95, 3389 (1973). (b) A. A. Chalmers, K. G. R. Pachler, J. Chem. Soc. PII, 748 (1974). (c) J. Reuben J. Mag. Res., 11 103 (1973).

8. Allowing indiscriminate assignments solely on the basis of agreement of observed and calculated values can lead to incorrect results. For example, the Yb observed/calculated shifts for C_{13} and C_{11}, respectively 277.4/269.4 and 269.0/278.7, suggest that the assignments be switched. Similarly, for C_1 and C_9 the Yb data are 460.2/478.2, 454.6/506.2, and the Eu data are 123.7/117.2 and 111.8/122.2. However, initial chemical shifts and off-resonance decoupling data show that the initial assignments are correct.

9. The mixed calculations have also been successfully used for ^{13}C assignments in camphor, norcamphor, phenaleneone, a series of methoxy naphthalenes and 6-exo-phenoxy-2-benzyl-3-oxo-2-azabicyclo[2.2.1] heptane.