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LANTHANIDE SHIFT REAGENT EFFECTS ON NMR SPECTRA OF ORGANOSULFUR COMPOUNDS-HSAB THEORY

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Because of the tremendous value of lanthanide shift reagents for simplification of NMR spectra of organic compounds, it is especially important to know the precise structural features that mark an organic substrate as amenable to shift reagent analysis. Despite the large amount of published work on shift reagents[1], surprisingly little work has been done to identify the microscopic details and theoretical basis for identification of substrates that will interact with shift reagents to a degree sufficient for analysis. The results of the work in our laboratories not only describe results on organosulfur compounds but implicate hard-soft acid-base (HSAB) theory[2] as a very important basis for anticipation of the degree of significant interaction of substrates with shift reagents.

During the course of our studies on polyfunctional substrates containing bivalent sulfur, we became aware of the need to rank such sulfur functional groups (relative to other functional groups) as to their ability to strongly "interact"[3] with shift reagents. It had been reported by one group of workers that thioether sulfur "interacts"[3] more strongly than ketocarbonyl oxygen[4]; another group reported exactly the reverse interaction order using a different, but structurally very similar, substrate[5] (both groups studied intramolecular competition). Our results (Tables I and II) seem to be more consistent with the stronger interaction of carbonyl oxygen[5].

Table I clearly shows that simple aliphatic thioethers interact much less strongly than do the corresponding classes of oxygen ethers.[1a,4,5] The results listed in Experiments 1-5 (Table I, also see footnote iv of this Table) indicate that the response of thioethers, relative to oxygen ethers,[1a,4] to shift reagents is an order of magnitude less. Experiment 4 implies the sensitivity of this approach to modest steric changes in the substrate. Experiments 5-7 clearly demonstrate the large decrease in ability of sulfur to interact when in conjugation with a π-system. It is interesting to note that the conjugation of a nonbonded electron pair (from the second sulfur of a disulfide) is sufficient to cause a dissipation of interaction[3] ability (Experiment 8). The results for the simple thioethers are in accord with those reported for dimethyl sulfide[6]. All of these results fit nicely with HSAB theory[2]; the shift reagents are hard acids and the thioethers are softer bases than the corresponding oxygen

Table I

$\Delta\delta^{i}$ values for a Variety of Organic Substrates [CCl_4 Solvent, $Eu(fod)_3$^{ii} Shift Reagent]

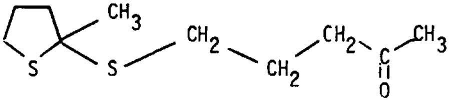
Experiment	Substrate**	$(L)/(S)^{iii}$	$\Delta\delta^{i}$
1	n-butyl sulfide	0.24	0.36
2	n-butyl sulfide	0.54	0.94
3	n-butyl sulfide	0.72	1.04^{iv}
4	iso-butyl sulfide	0.73	0.76
5	methyl phenyl sulfide	0.10	0.04
6	methyl phenyl sulfide	0.46	0.05
7	phenyl sulfide	0.93	0.07
8	n-butyl disulfide	0.27	0.07
9	2-thioadamantanone	0.36	0.25
9a.	2-adamantanone	0.13	2.57
10		0.57 0.57 0.57 0.57	9.20* 4.39* 9.48* 0.93*
11	t-butyl sulfide	0.38	0.11
12	benzyl sulfide	0.48	0.14

Table II

NMR Shift Reagent Intermolecular Competition Studies of
Thioether vs. Carbonyl Compounds (in CCl_4, with $Eu(fod)_3$^{ii})

Methyl Laurate (ML) vs. n-Butyl Sulfide (BS)

Substrate**	$(L)/(S)^{iii}$	(ML)/(BS)	$\Delta\delta^{i}$
ML	0.18	∞	2.80
BS	0.24	0	0.36
ML + BS	0.27	1/1	5.01 (α to CO of ML)
ML + BS	0.27	1/1	0.09 (α to S)

p-Bromoacetophenone (BA) vs. n-Butyl Sulfide (BS)

Substrate**	(L)/(S)	(BA)/(BS)	$\Delta\delta^{i}$
BA	0.10	∞	3.74
BS	0.10	0	0.18
BA + BS	0.10	1/1	3.72

*9.20 (for protons on CH_2 α to CO)
*4.39 (for CH_2 group α to exocyclic S sulfur)
*9.48 (for CH_3 α to CO)
*0.93 (for CH_2 α to ring)

i. $\Delta\delta = \delta - \delta o$, where δo = proton chemical shift in absence of shift reagent and δ = chemical shift induced by given (L)/(S) ratio. All $\Delta\delta$ values are for protons α to sulfur unless stated otherwise. Error in measuring $\delta = \pm 0.01$, Reproducibility= ±0.03

ii. $Eu(fod)_3$ = the fluorinated reagent: R.E. Sievers, et.al., Inorg.Chem.,6,1105 (1967).

iii. $(L)/(S)^3$= mole ratio of shift reagent (L)/to substrate (S). All experiments were carried out a sufficiently low [L],[S] and [L]/[S] values to preclude the necessity of graphical data manipulations (see Reference 1c).

iv. Extrapolation yields a value of ca.1.1 ppm/mole shift reagent/mole substrate. Oxygen ethers show values of 10-30 (references 1a,4) ppm/mole/mole.

Good results were obtained using yellow (nonhydrated) shift reagent from Aldrich.

**For all compounds, except for those with α CH_2 $\Delta\delta < 0.20$, data for the rest of the protons in the system will be furnished by the authors upon request; in all such cases the qualitative and/or quantitative data are in accord with the discussion in this paper.

ethers and thus coordinate less strongly to the shift reagents[7]. Delocalization of the nonbonded electrons on sulfur softens these bases. Substantiating these conclusions are the facts that 5-p-bromophenyl-2,3-dihydrothiophene, phenyl disulfide, and 2,4-dinitrophenyl benzyl thioether (all substrates with highly delocalized sulfur nonbonded electron pairs) showed no measurable effect of shift reagents to the point of saturated solution[8]. Steric effects also can inhibit shift reagent interactions (see Experiments 11 and 12). The intramolecular competition studies of sulfur vs. keto-carbonyl oxygen (Experiment 10) indicate weaker interaction[3] of sulfur. Although these intramolecular experimental results are hardly definitive, the veracity of the generalization just made will be clearly confirmed below. At least a portion of the reasons behind the result of Experiment 10 may be the reported[9] poor coordinating ability of the gem-dithio moiety of thio-ketals. Perhaps the (initially) most surprising result of Table I is that for thioadamantanone (Experiment 9). This compound was prepared and purified by the method of Greidanus[10] and was free (by NMR) of oxy-ketone. Despite the high polarizability of the C=S group[11] (and thus the high, partial negative charge on sulfur), the thioketone shows a much weaker interaction[3] than the oxyketone (Experiments 9 and 9a). This pair of results indicates HSAB theory[2] as the predominant criterion for recognizing the coordinating ability of organic functional groups.

The intermolecular competition studies described on Table II demonstrate clearly the inability of bivalent sulfur to significantly compete with keto and ester carbonyl oxygen. The carbonyl compound interacts with the shift reagent essentially the same in the presence or absence of an equivalent of thioether. The sensitivity of these studies to steric and/or electronic effects is shown by the substantial but diminished shifts with p-bromophenacyl bromide: $\Delta\delta$ of +1.53 at L/S = 0.15 (compare the p-bromoacetophenone results of Table II).

An interesting sidelight to this work is the position of the chemical shift of the fod ligand of $Eu(fod)_3$ (see footnote ii of Tables) in the presence of substrate. In the studies utilizing sulfides only the ligand appears in the δ1.5-1.8 region; this is typical as reported earlier.[1a] In the presence of carbonyl compounds only, the ligand resonance occurs in the δ0.35-0.70 region. This is useful for identifying interaction sites; in all of the competition studies, the ligand resonates in the higher field region, again consistent with the inferior interaction with thioether sulfur.

In summary, it seems clear that organic substrates' ability to coordinate[3] with lanthanide shift reagents is extremely sensitive to and proportional to the polarizability (HSAB character[2]) of the organic substrates' coordination sites. This sensitivity offers encouragement to measure the HSAB character quantitatively; previous HSAB measurements have been largely qualitative. Efforts along the quantitative lines will be carried out in our laboratory.

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References

1. A large number of lanthanide shift reagent studies are cited in a) J. R. Campbell, Aldrichimica Acta, 55 (1971), b) R. von Ammon and R. D. Fischer, Ang. Chem. Int. Ed. (Eng.), 11, 675 (1972), and c) C. B. C. Mayo, Chem. Soc. Rev., 49 (1973).

2. HSAB = hard-soft acid-base theory; see R. Pearson: J. Amer. Chem. Soc., 85, 3533 (1963), Chem. Eng. News, 90, May 31 (1965); Chem. Brit., 103, March (1967); J. Chem. Ed., 45, 581, 643 (1968).

3. "Stronger interaction" as used in this work means that a given substrate, likely due to a given structural Lewis basic coordination site, undergoes larger shifts due to a given increment of added shift reagent than does another substrate.

4. H. Hart and G. Love, Tetrahedron Letters, 625 (1971).

5. A. van Bruijnsvoort, et al., Tetrahedron Letters, 1737 (1972).

6. Dimethyl sulfide, using $Eu(fod)_3$, undergoes a shift of ca. 1.0 ppm/mole reagent/mole of substrate: I. Nielson and A. Kjaer, Acta. Chem. Scan., 26, 852 (1972).

7. Marks has pointed out the use of SHAB theory for shift reagent interpretations: J. Amer. Chem. Soc., 95, 3548 (1973), 165th ACS National Meeting, Dallas, Texas, April, 1973, Abstract No. 57.

8. Although solubilities of shift reagents in NMR solvents have been reported (ref. 1a.), the solubility is really a unique feature for each experiment as this property is dependent upon the coordinating ability (interaction) of the substrate and the shift reagent.

9. D. R. Crump, J. K. M. Saunders and D. H. Williams, Tetrahedron Letters, 4949 (1970).

10. J. W. Greidanus, Can. J. Chem., 48, 3530 (1970).

11. R. Mayer, et. al., Ang. Chem., 76, 157 (1964).

Footnotes

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