Tetrahedron Letters No.7, pp. 625-628, 1971. Pergamon Press. Printed in Great Britain.

COORDINATION SITES AND THE USE OF CHEMICAL SHIFT REAGENTS IN POLYFUNCTIONAL MOLECULES

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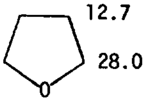
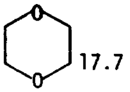
(Received in USA 23 December 1970; received in UK for publication 19 January 1971)

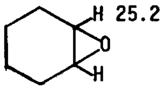
In order to use chemical shift reagents (1-8) such as $Eu(DPM)_3$ and $Pr(DPM)_3$ (9) most effectively with polyfunctional molecules, it will be important to accumulate information regarding preferred sites of complexation. This can be accomplished in either of two ways: (a) monofunctional molecules in the same solution can be allowed to compete for a limited quantity of the shift reagent (<u>inter</u>molecular competition), or (b) difunctional molecules with simple, easily interpretable nmr spectra can be treated with the shift reagent to determine whether the protons adjacent to one or the other of the functional groups are shifted to the greatest extent (<u>intra</u>molecular competition). We report here experiments which demonstrate the generality of both methods, and which establish that a preferred coordination order is ethers > thioethers > ketones $\cong$ esters, that unsaturation may alter these results and that esters coordinate at the carbonyl oxygen.

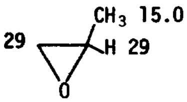
Numbers in the formulas which follow are ΔEu values, as defined by Demarco (4); they represent the downfield shift (in ppm, from the δ-value of the substrate protons in $CDCl_3$) which would be observed with a $Eu(DPM)_3$/substrate mol ratio of 1. In fact, the ΔEu values are the slopes of the straight lines obtained from plots of δ <u>vs</u> $Eu(DPM)_3$/substrate mol ratio, since it is inconvenient, unnecessary, and often impossible experimentally to go much above a mol ratio of 0.1-0.15 for weakly bonding substrates. Usually spectra were determined at 8-10 different mol ratios to obtain each slope. The larger the ΔEu value, the greater the particular proton is shifted downfield by the shift reagent (numbers in parentheses are for the corresponding upfield ΔPr values).

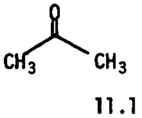
Observed ΔEu values for some monofunctional compounds are shown:

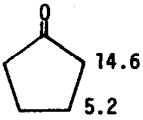


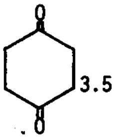


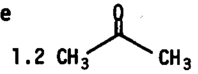
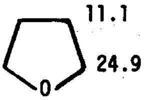






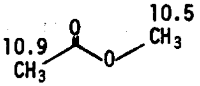




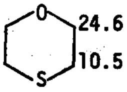
One ordinarily cannot compare ΔEu values directly from one compound to another, since they reflect not only the complexation constant between substrate and Eu(DPM)$_3$, but also depend on molecular geometry [*i.e.*, the Eu-proton distance and angle (4,7)]. But ΔEu values can be used to evaluate competition experiments in the following way. When equimolar amounts of acetone and THF, for example, were allowed to compete for Eu(DPM)$_3$, the observed slopes, plotted as if each substrate were present alone, were  and 

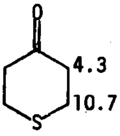
We conclude that THF is more effective than acetone at coordinating with Eu(DPM)$_3$ by a factor of about 8:1 (for acetone, 1.2/11.1 x 100 = 11%; for THF, 24.9/28.0 x 100 = 89% or 11.1/12.7 x 100 = 87%). In a similar manner, we found that dimethyl ether coordinates better than acetone (7:3) and dioxane wins over 1,4-cyclohexanedione (6:4).

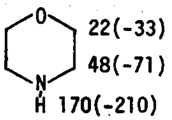
In contrast, esters appear to coordinate at the carbonyl rather than the ether oxygen. The ΔEu values for both methyl groups in methyl acetate are essentially identical. Although such comparisons can be dangerous, we note that the C-methyl has essentially the same slope as acetone, whereas the O-methyl has a smaller slope than the α-protons of most ethers. Consistent with these observations, intermolecular competition experiments showed that acetone and methyl acetate coordinate equally with Eu(DPM)$_3$, whereas dioxane is superior to methyl acetate (by 5:1).



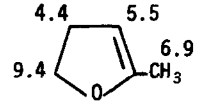
Thioethers were examined by the intramolecular competition method, and appear to be less effective than ethers, but more so than ketones. The comparison of sulfur (in thioxane) with nitrogen (in morpholine) is particularly striking (10).



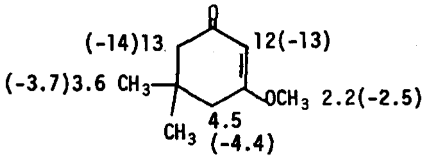




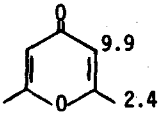
α,β-Unsaturated ethers coordinate with Eu(DPM)$_3$ less well than saturated ethers, as might have been expected. Compare, for example the α-methylene protons of THF and 4,5-dihydro-2-methylfuran:



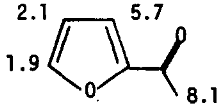
The geometries are sufficiently alike to make such a comparison valid. In dimedon methyl ether, coordination occurs at the carbonyl, rather than the ether oxygen:

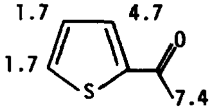


This result seems reasonable in comparison with ester results, since the compound is an ester vinylog (11). 2,6-Dimethyl-γ-pyrone coordinates at the carbonyl oxygen



and in an intermolecular competition experiment won out over dioxane (4:1). Finally, if the ether oxygen is part of an aromatic ring (as in furan), coordination with shift reagents is very weak. 2-Acetylfuran (and the corresponding thiophene) cordinate at the carbonyl oxygen:





Bidentate coordination appears to be unimportant (note that the 3-protons have a larger slope than the 5-protons).

We conclude that inter- and intramolecular competition experiments provide useful information about the coordinating effectiveness of various functional groups with chemical shift reagents. The collection of ΔEu data should enhance the utility of shift reagents with polyfunctional molecules.

Acknowledgment. We are indebted to the National Science Foundation for their generous support.

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9. DPM stands for dipivaloylmethane.
10. Since ΔEu values depend on the mol ratio of shift reagent to substrate, the shift reagent must be pure. We find that the measurement of ΔEu slopes is a better criterion of reagent purity than melting point, and have adopted morpholine as a standard compound because the slopes are large, and one obtains three slopes easily from one compound. Slopes are reproducible to 5%. We used commercially available, as well as synthetic shift reagent in the experiments reported here.
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