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Structure Elucidation with Lanthanide-Induced Shifts. 15. Blocking Groups for Polyfunctional Compounds[1]

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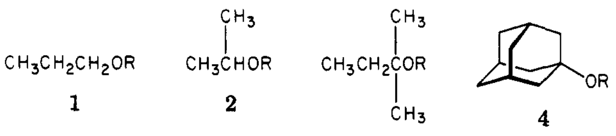
The analysis of molecular structure with lanthanide shift reagents (LSRs) is slowly becoming a routine procedure.[1-3] Most previous work has involved molecules containing a single functional group,[3] but a generally useful method for structure evaluation must also be applicable to polyfunctional molecules. With such molecules the observed lanthanide-induced shifts (LIS) result from the additive effects of complexation at the different binding sites,[3-9] but the relative contributions are unknown. This problem could be circumvented by converting one of the functional groups to a derivative which would not bind to the LSR, and we have investigated several potential blocking groups for hydroxyl groups. Conversion of an alcohol to the corresponding trifluoroacetate[7-10] or to the trimethylsilyl ether[7] has been suggested as a way to prevent complexation with LSRs. We now report results which demonstrate the successful use of silyl ethers as blocking groups and which also show the inadequacy of trifluoroacetate esters for this purpose.

In order to assess the effectiveness of these blocking groups in shift reagent work, we have prepared and studied derivatives of a series of monofunctional alcohols: 1-propanol (**1a**), 2-propanol (**2a**), 2-methyl-2-butanol (**3a**), and 1-adamantanol (**4a**) (Chart I). This provided the opportunity for evaluation of derivatives of primary, secondary, and tertiary alcohols. In addition to the trifluoroacetates and trimethylsilyl ethers we also investigated the corresponding *tert*-butyldimethylsilyl ethers.

The NMR spectra of these compounds were obtained in the presence of Eu(fod)$_3$ with CCl$_4$ or CDCl$_3$ as the solvent. The ratio of shift reagent to substrate was varied up to a maximum of 3 in order to simulate the conditions needed for accurate determination of the LIS.[2,11,12] The results are summarized in Table I which reports the maximum value of the LIS observed, the calculated value of the *bound shifts* (i.e., the LIS corresponding to the 1:1 complex), and the association constants. The bound shifts provide an upper limit to the possible magnitude of observed LIS and are approximately equal to the experimental LIS expected with a functional group that coordinates strongly to the shift reagent. When compared to the bound shifts in Table I, all of the observed LIS are substantially smaller. In other words, the trifluoroacetyl and both silyl groups do produce a decrease in binding ability. Nevertheless, some of the observed LIS are fairly large: 2.2 and 3.6 ppm for the α-hydrogens of the trifluoroacetates **1b** and **2b**, respectively, and 5.8 ppm for the α-hydrogens of trimethylsilyl ether **1c**. Shifts of this magnitude resulting from complexation at a "blocked" binding site would certainly interfere with structure evaluation of a difunctional compound.

Chart I[a]

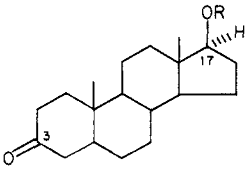


1 2 3 4

[a] a, R = H; b, R = COCF$_3$; c, R = Si(CH$_3$)$_3$; d, R = Si(CH$_3$)$_2$-*t*-C$_4$H$_9$.

The effectiveness of a blocking group can conveniently be assessed by the association constants in Table I. While accurate determination of bound shifts[11] is favored by equilibrium constants much larger than unity, an effective blocking group must result in an association constant of 0.1 or less. Only the *tert*-butyldimethylsilyl group meets this criterion for all compounds studied. The decreased binding ability of a trifluoroacetate presumably results from the strong electron-withdrawing effect of the CF$_3$ group, an expectation that is supported by the data in Table I. Complexation of these derivatives apparently occurs at carbonyl oxygen, and the comparable association constants for **1b**, **2b**, and **4b** are indicative of electronic rather than steric effects. Unfortunately, the magnitude of this electronic effect is not large enough to reduce the association constants to values of 0.1 or less. In contrast to the trifluoroacetates, the silyl derivatives show a consistent decrease in magnitude of the association constants along the series primary to secondary to tertiary, a result consistent with steric effects. However, only the bulkier *tert*-butyldimethylsilyl group meets the criterion of $K < 0.1$ for all three types of alcohols. The *tert*-butyldimethylsilyl group therefore appears to be the best of the three candidates. In contrast to previous suggestions[7-10] the trifluoroacetyl group does not effectively block complexation with shift reagents.

We have further evaluated these blocking groups by investigating several derivatives of the difunctional compounds, dihydrotestosterone (**5a**) and *trans*-androsterone (**6a**). The trifluoroacetates, **5b** and **6b**, the *tert*-butyldimethylsilyl ether, **5d**, and the trimethylsilyl ether, **6c**, were prepared, and their Eu(fod)$_3$-shifted spectra were analyzed. Bound shifts were determined by nonlinear regression analysis on the assumption that complexation occurs at only a single site in each of the substrate molecules. These observed shifts were then compared with values which were



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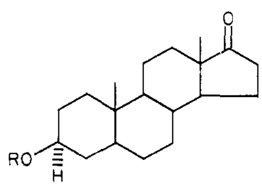

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Table I. Lanthanide-Induced Shifts and Association Constants for Derivatives of 1–4[a]

	b, R = COCF$_3$			c, R = Si(CH$_3$)$_3$			d, R = Si(CH$_3$)$_2$-t-C$_4$H$_9$		
compd	max[b,c] LIS	bound[c,d] shift	*K*	max[b] LIS	bound[c,e] shift	*K*	max[b] LIS	bound[c,e] shift	*K*
1	2.2	15.0	0.3	5.8	16.0[f]	1.1[f]	0.2	16.0	0.02
2	3.6	15.0	0.6	0.8	16.0	0.1	0.02	16.0	0.002
3				0.1	7.5	0.001	0.003	7.5	0.001
4	0.5	9.5	0.2[g]	0.11	13[d]	0.01			

[a] All shifts in parts per million relative to internal Me$_4$Si; equilibrium constants have units of M^{-1}. [b] At a LSR/substrate ratio of 3. [c] LIS of the hydrogens on the α-carbon for **1** and **2** and on the β-carbon for **3** and **4**. [d] Estimated from the bound shifts of analogous esters or ethers.[9] [e] Estimated from the LIS of **1c**. [f] Calculated[10] from the observed LIS. [g] Data from ref 9.

predicted[2] with the pseudocontact equation[13] in order to determine whether or not complexation with shift reagent occurs at more than one site. On the assumption that complexation of derivatives of **5** and **6** with Eu(fod)$_3$ occur exclusively at the 3-keto and 17-keto groups, respectively, the predicted[2,13] bound shifts of the respective hydrogens at C-17 of **5** and C-3 of **6** (i.e., α to the OR substituent) fall in the range of 0.5–0.7 ppm. Any complexation at the "blocked" position would result in a larger observed LIS for the corresponding proton. In the case of trifluoroacetates **5b** and **6b** the respective bound shifts of these hydrogens are 3.1 and approximately 1.0 ppm. Similarly, the experimental bound shift for the fluorines in **6b** is 0.8 ppm, but the value predicted for complexation at the 17 keto group is only 0.2 ppm. Clearly some complexation with Eu(fod)$_3$ occurs at the trifluoroacetoxy group as well as at the ketone oxygen, and this reaffirms our conclusion that a trifluoroacetate is not an adequate blocking group for LSR studies. On the other hand, the experimental bound shift of the 17α proton in the *tert*-butyldimethylsilyl ether **5d** is within 0.05 ppm of the predicted value of 0.7 ppm, and both the experimental and predicted LIS for the silyl methyl groups of the trimethylsilyl ether of **6c** are found to be 0.4 ppm. This demonstrates that silylation of the difunctional steroids **5a** and **6a** permits them to be accurately evaluated as monofunctional compounds. Recall, however, that the data in Table I indicate that a trimethylsilyl group does not always completely prevent complexation, particularly in the case of primary alcohols. The *tert*-butyldimethylsilyl group is therefore more reliable as a protective group for lanthanide-induced shift studies.

In summary, the effectiveness at preventing coordination with LSR and the remarkable ease with which this blocking group can be introduced and removed[14] combine to make *tert*-butyldimethylsilyl ethers the derivatives of choice for shift reagent studies. Since the site of complexation must be accurately known, previous attempts at rigorous evaluation of molecular structure with shift reagents have been resticted to monofunctional compounds. Our results demonstrate that *tert*-butyldimethylsilyl ethers allow, for the first time, the use of lanthanide shift reagents for reliable and accurate structure evaluation of polyfunctional organic compounds.

Experimental Section

Trifluoroacetates of 1-propanol and 2-propanol were prepared by H$_2$SO$_4$ catalyzed esterification of the alcohols with CF$_3$CO$_2$H in CHCl$_3$. Trifluoroacetates **4b**, **5b**, and **6b** were prepared by reaction of the alcohols with trifluoroacetic anhydride.

Trimethylsilyl ethers were prepared from the alcohols by using hexamethyldisilazane and chlorotrimethylsilane according to the procedure of Langer, Connell, and Wender.[15]

***tert*-Butyldimethylsilyl ethers** were prepared by reaction of the alcohols with *tert*-butylchlorodimethylsilane and imidazole in dimethylformamide using the procedure reported by Corey and Venkateswarlu.[14]

Nuclear magnetic resonance spectra were obtained by using Varian EM-360 (**1**-**4**, CCl$_4$) and JEOL FX90Q (**5** and **6**, CDCl$_3$) spectrometers at ambient temperature. Carbon and proton chemical shifts were measured relative to internal Me$_4$Si, and fluorine shifts were measured relative to the deuterium of the solvent. For shift reagent runs we employed the incremental dilution method[11] and utilized shift reagent (Aldrich, EuFOD, No. 16093-8) which had been sublimed [ca. 160 °C (0.05 torr)] prior to use.

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Registry No. **1a**, 71-23-8; **1b**, 383-66-4; **1c**, 1825-63-4; **1d**, 17348-67-3; **2a**, 67-63-0; **2b**, 400-38-4; **2c**, 1825-64-5; **2d**, 17348-66-2; **3a**, 75-85-4; **3c**, 6689-16-3; **3d**, 81898-29-5; **4a**, 768-95-6; **4b**, 58652-54-3; **4c**, 36960-53-9; **5a**, 521-18-6; **5b**, 2022-58-4; **5d**, 58701-44-3; **6a**, 481-29-8; **6b**, 3959-78-2; **6c**, 10426-95-6.

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Improved Procedure for Synthesis of Chiral Sulfoxides[1]

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Chiral sulfoxides have attracted much attention in the past 2 decades as model compounds in studies of sulfur stereochemistry.[2] Recently, they became key intermediates for highly efficient asymmetric syntheses.[3] For this reason, a variety of chemical methods have been developed for the synthesis of chiral sulfoxides in various states of opitcal purity.[4] Among these, the most important and

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