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TOPOLOGICAL, STEREOCHEMICAL AND NMR LINE ASSIGNMENTS IN ALCOHOLS AND KETONES BY NORMALIZED NMR SHIFTS INDUCED BY YTTERBIUM

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Abstract—Yb(fod)$_3$-Induced ^{13}C- and ^{1}H-NMR shifts exhibit regular differences if normalized by setting the shift at the nucleus closest to the binding site to RS $\equiv$ 100%. ^{13}C-NMR data from 70 alcohols show RS = 47 ± 4% for Cβ (43 ± 3% for primary alcohols); the normalized RS at the other carbon atoms depend on the anti (a)/gauche (g) arrangements at the intervening bonds as follows: Cγ a 23%, g 33%; Cδ aa 11%, ag 16%, gg 25%; Cϵ aaa 5%, aga 9%, gga 14%, ggg 22%, etc. (± 2–4%). Similar observations are made with 20 ketones. The RS values agree with relative geometry factors RG predicted by calculations of the pseudo contact shifts for all significant conformations. Very flat minima are usually observed in these analyses; the impact of this and other ambiguities for accurate geometry investigations with the LIS method is discussed.

The use of lanthanide induced shifts (LIS) in NMR spectroscopy belongs to the most promising methods for structural analysis of molecules in solution, but also for signal assignments, particularly in ^{13}C-NMR spectra. Hundreds of applications have been described in the literature, and several recent reviews are available,$^{(1)}$ which allows us to restrict ourselves to the introduction of few elements and problems which are necessary for the understanding of the subsequent arguments. The LIS method is essentially based on the formation of complexes (LS or LS$_2$) between lanthanide shift reagents (L or LSR) and substrates which contain electron donating groups (Y). The anisotropic magnetic susceptibility tensor of the paramagnetic Ln^{3+} ion induces shifts at the different nuclei N, the relative magnitude of which, within a number of limitations, is determined by the geometry factor G in the pseudo contact equation $G = \text{const}(3\cos^2\theta - 1)r^{-3}$; θ is the angle between the Ln^{3+} shielding tensor (which usually is considered to coincide with the Ln^{3+}–Y axis) and the Ln^{3+}–N line, and r the distance between Ln^{3+} and N. For a given substrate geometry the relative LIS will then depend only on the localization of the Ln ion, which is described by the distance between Ln and the donor Y, the "bond" angle ρ (Ln ... Y–Cα), and a torsional angle φ (e.g. Ln ... Y–Cα–Cβ), as illustrated in Fig. 1. The usual procedure is to vary the Ln position, and possibly the substrate geometry also, until the best agreement, characterized, e.g. by a low agreement factor A,[2] is reached between all calculated geometry factors G and the LIS observed for the corresponding nuclei.[1]

The problem in quantitative LIS analysis in most cases is not to find good solutions, or agreement factors below an acceptability limit of, e.g. 4%,[1b] but frequently lies in the existence of too many solutions, or rather ill defined and flat minima in the agreement factor/geometry hypersurface.[1,3] It has been recognized that the rigorous LIS analysis is hampered by many complications.[1] (a) The induced shieldings can be contaminated by complex formation and contact shifts; their contributions must be evaluated, e.g. by measurement with different lanthanides, which is facilitated by the largely isomorphous structure of closely related Ln^{3+}-chelates.[4] (b) Under most experimental conditions the measured LIS result from the formation of both LS and LS$_2$ complexes with different intrinsic "bound" shifts Δ_1 and Δ_2;[5] these, and the quite variable equilibrium constants K$_1$ and K$_2$ are accessible only be laborious series of measurements,[1,5,6] which due to sensitivity problems are difficult to carry out with ^{13}C NMR. (c) Apart from the assumption of axial symmetry of the shift tensor along the Ln ... Y axis, which, even in view of time averaging, is less likely for the LS$_2$ complex,[5] the consideration of multiple complexation sites around, for example, an oxygen donor[8] leads to further ambiguity. (d) The finally obtained minima should be checked again by allowing for errors in the experimentally derived shifts and in the substrate model structures used, since both can lead to substantial changes of the calculated complex structure.[3b] As a consequence of the often heavily underdetermined analysis based on LIS measurements alone it is recommended for quantitative conformational studies always to include independent methods such as investigations of paramagnetic relaxations, NOE effects and coupling constants.[1,3b,d]

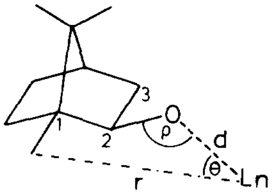


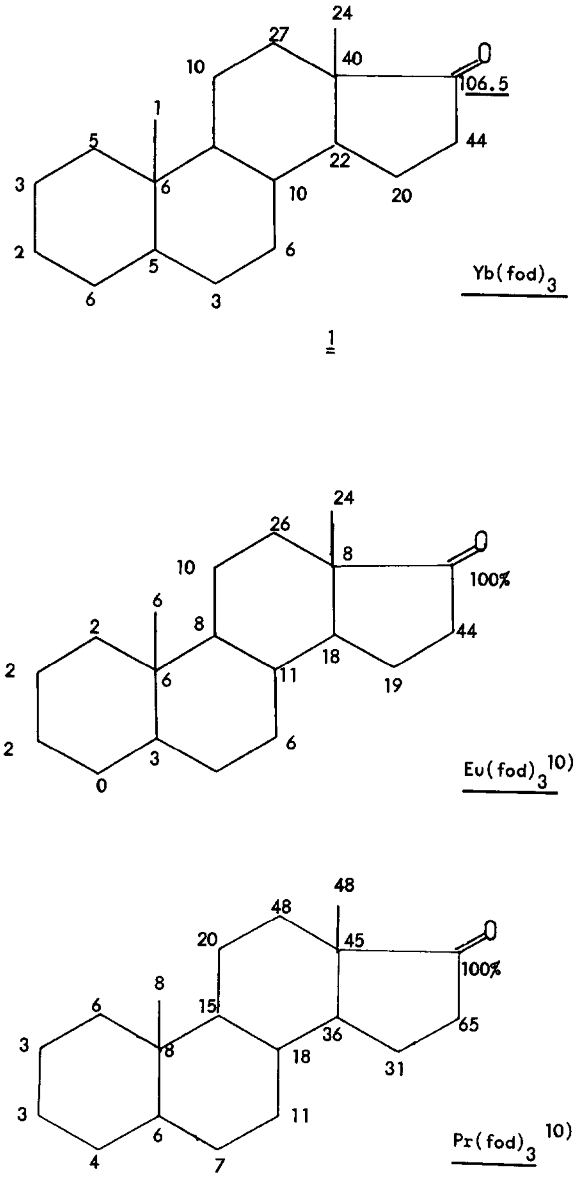
Fig. 1. Geometric parameters for lanthanide induced shifts, illustrated with the LIS on 1-*CH$_3$ of isoborneol. Torsional angle φ: Ln–O–C2–C1.

We wanted to see whether there is a way to explore the conformational space around different functionalities in organic structures without the need to undertake extensive quantitative studies with possibly ambigous results at the end. Such a method would operationally be reminiscent of the semiquantitative use of the octant rule in chiroptical studies, and should be helpful also for NMR signal assignments, as well as for a standardization in documenting and comparing LIS values.

Normalization of LIS

The examination of experimental LIS values in more than 90 alcohols and ketones combined with a numerical analysis of the relevant geometry factors shows, that a simple semiquantitative method for LIS analysis is available by referring the shifts induced by Yb(fod)$_3$ to the LIS observed on the functional carbon or hydrogen atom (RS ≡ 100%), and by a systematical comparison of the relative shifts (RS, in [%]) obtained for the other nuclei with other results, as well as with theoretical predictions. Although normalized LIS have been reported several times,[8,9] no use has been made to our knowledge of their close similarity in related structures and their topological and stereochemical significance as well as their theoretical basis has not been studied.

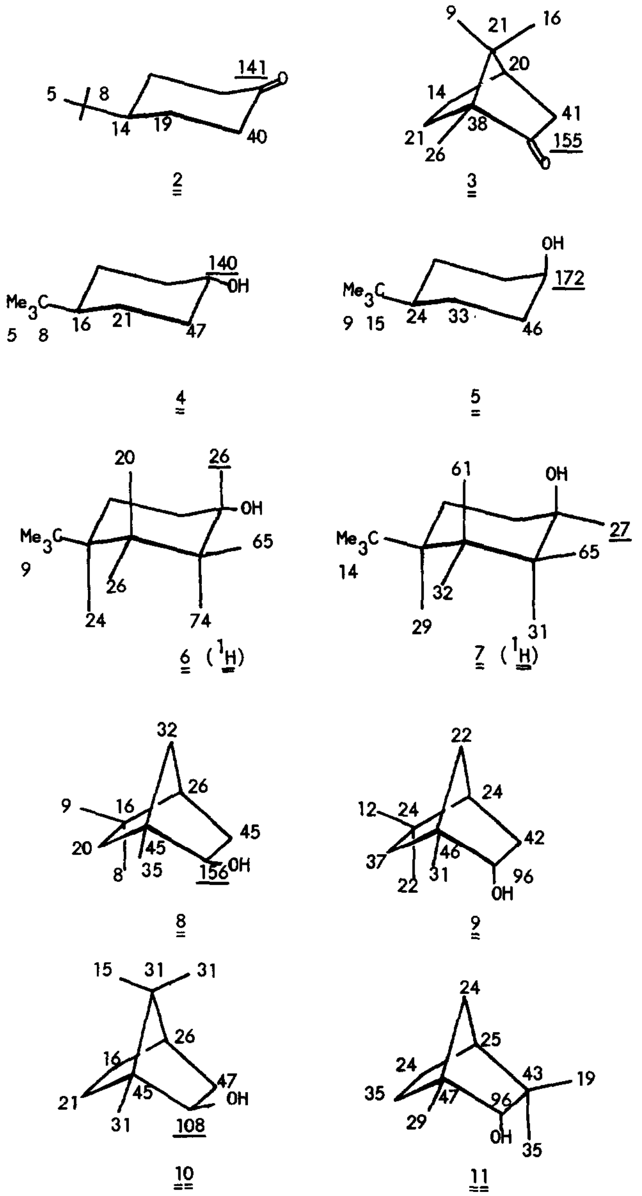
Due to its minimal contributions of complex formation and particularly contact shifts[1] ytterbium provides the most suitable shift reagent, at least for ^{13}C-NMR studies. This is illustrated by a comparison of relative shifts induced by different reagents, in which, opposite to Yb(fod)$_3$, Eu(fod)$_3$ and Pr(fod)$_3$ show strongly asymmetric effects, e.g. on the β-carbon atoms C13 and C16 in androstan-17-one (Scheme 1). Similar differences between Yb(fod)$_3$ and Eu or Pr(fod)$_3$ are observed in many other compounds; in particular, both Eu and Pr induce much



Scheme 1. Relative shifts induced by different LSR in androstane-17-one (1) (LIS is given in [ppm] for the 1:1 LSR:S-complex for C$_\alpha$, in [%] RS for the other signals).

less distinct and regular shielding differences between Cα, Cβ, Cγ etc., which becomes evident from a comparison of LIS data for several hydroxy compounds[11] (Table A of supplementary material,[12]), ketones[13] (Table B[12]) and amines.[14] Although the use of a single nucleus (as, e.g. Cα) for referencing the other shifts can be less appropriate for a quantitative conformational analysis,[1,8a] the disadvantages of this method are minimized with Yb reagents. For semiquantitative studies they are by far outweighted by the constancy of the relative shifts RS as compared to the absolute shifts, even in the presence of impurities or LSR scavengers (*cf* the values for the 1:1 LSR–S complex as given in the figures and tables, if available).

As in most studies, the LIS values were obtained from measurements using not more than 10 mole-% LSR. In view of the usually higher stability of the LS as compared to the LS_2 complex, however, this procedure is apt to yield ill defined shift data from both complexes.[5,6] As a consequence, the relative shifts could depend on both the LSR: substrate ratio and on the absolute concentrations. This, however, turns out to be the case only for a strongly hindered tertiary alcohol, such as trans-9-decalol (Tables H, I[12]). Even a severely hindered secondary hydroxy compound such as endo-fenchole (**11**) stands the test recommended by Raber *et al.*,[6b] showing RS variations of ΔRS < 4% at $Yb(fod)_3$ and substrate concentrations varying between 0.5 M and 4 M (table 1[12]). Such variations are almost prohibitive for an exact geometry analysis, but acceptable for our purpose, which relies on larger differences. The apparent insensitivity of RS against concentration changes is indicative of constant ratios of the intrinsic ("bound") ^{13}C shifts from the LS and the LS_2 complex, which



Scheme 2. Representative LIS values (explanations see Scheme 1).

Table 1. Relative shifts RS (^{13}C-NMR) induced by Yb(fod)$_3$ in oxygen compounds and theoretical geometry factors RG[a]

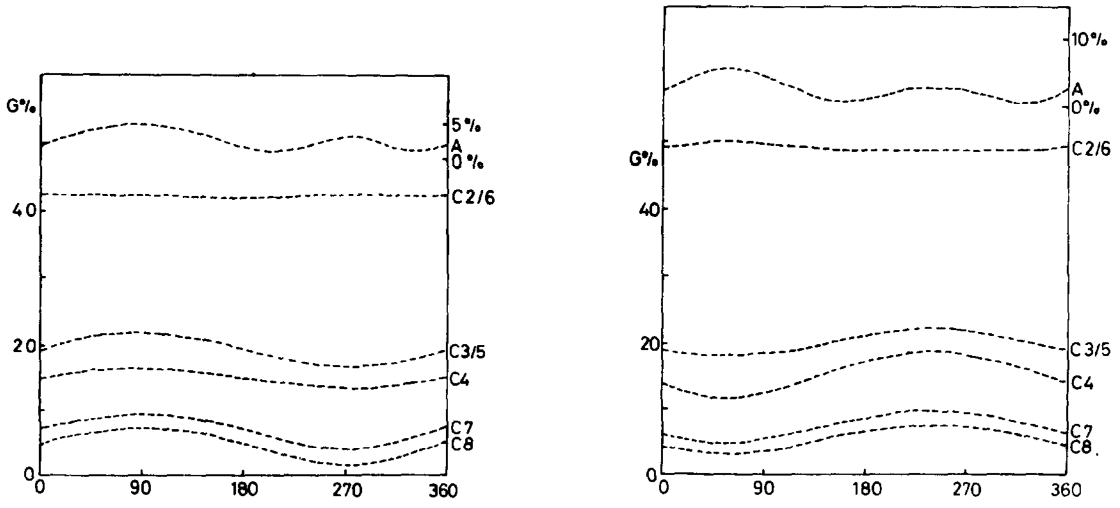
	X = OH	Exp. RS ± Δ	Theor. RG ± Δ	X = Oxo[b]	Exp. RS±Δ	Theor. RG ± Δ
Cβ	Prim.OH	43 ± 3			40±4	41 ± 1
	Sec,Tert.	47 4	47 ± 2			
Cγ	a	23 3	21 1	a(130-170°)	21 2	21 1
	g	33 4	32 1	g(20-95°)	27 2	27 2
Cδ	aa	11 3	11 0.5	aa	10	12 1
	ag	16 3	16 1	ag	13 2	14 1
	gg	25 4	24 1			
Cε	aaa	5	6 0.5	aaa	6	7 0.5
	aga*)	9 2	9 0.5	aga*		
	gga*)	14 2	13 0.5	gga*	8	10 1
	ggg	22	21 2			
Cζ	agag	5	6 0.5	agag	3	4 1

Relative to Cα (RS≡RG=100%). a and g denote anti (=130 to 180°) or gauche (40 to 80°) torsional angles along intervening bonds; experimental deviations from different observations, if available. *) or permuted combinations such as aag etc.. Theoretical RG factors and RG represent LS geometries with A $\leqq$ 4%, and allow for geometry variations characterized by Δφ = 40° with d = 2.8±0.2 Å and ρ = 45±10° (at least). Less experimental data available and therefore less deviations observed with ketones.

was demonstrated by Shapiro *et al.* already for ^{1}H-NMR shifts.[5] These workers also found a decreasing stability for the LS$_2$ as compared to the LS complex with increasing steric hindrance around the hydroxy donor group.

Comparison of experimental and theoretical results

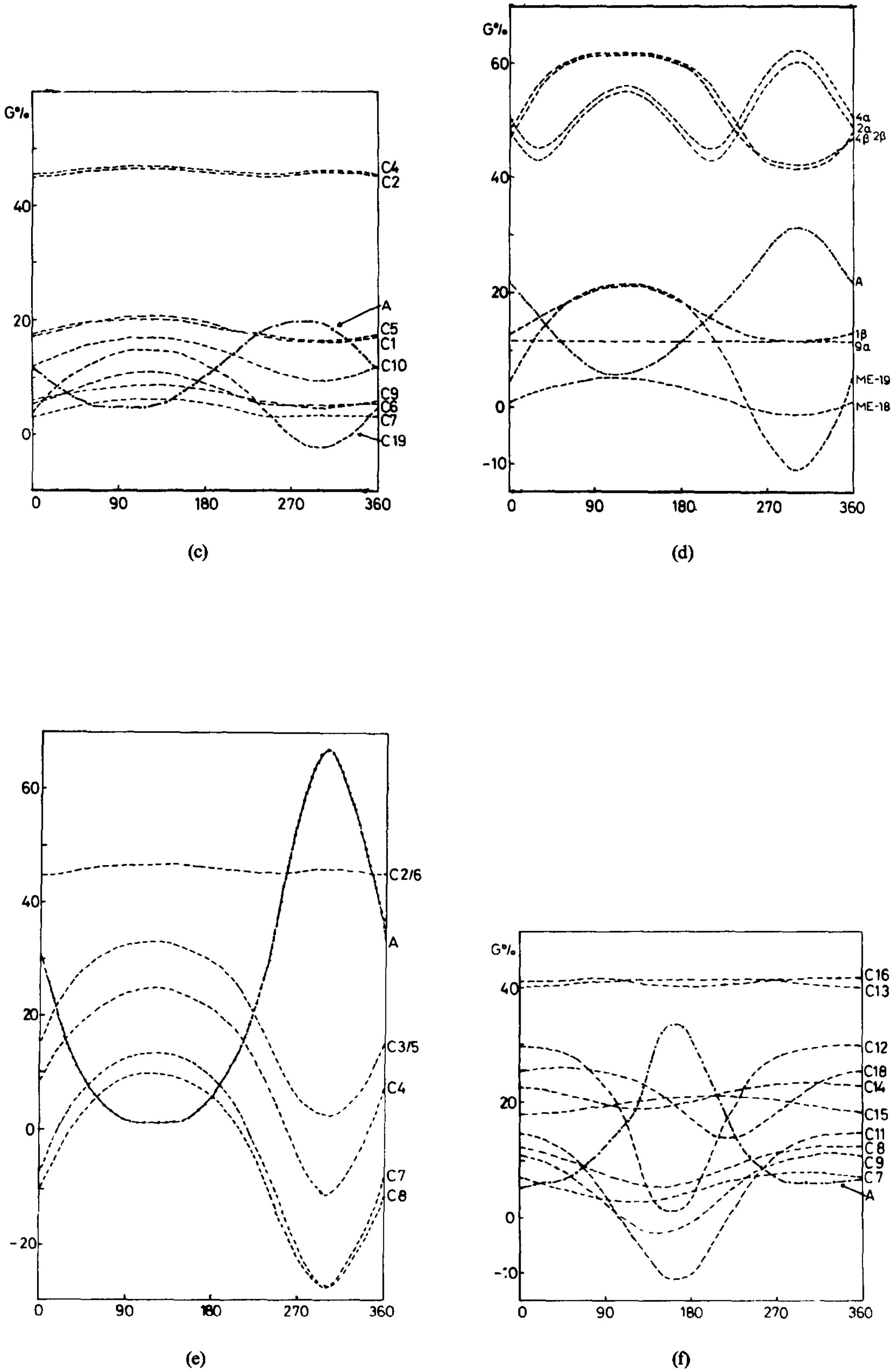
The examples represented in Scheme 2 together with many other tabulated[12] data show, that the normalized Yb(fod)$_3$ induced shifts exhibit a regular pattern (Table 1), which is most informative in particular with ^{13}C shifts. In order to understand the theoretical basis for the LIS behaviour, and to define the limitations of the method, we calculated relative geometry factors (RG), which should parallel the experimental RS values, as a function of *d*, ρ and φ (see Fig. 1), using the pseudo contact equation (see above). Conformationally rigid substrates were used in these calculations, the geometries of which were obtained from MM2 force field energy minimizations (table J[12]). Model calculations with cis-4-tert-butylcyclohexanol **5** (Table K[12]) show, that RS values change by < 3% if both bond length d and angle ρ vary considerably (d = 2.8 ± 0.2 Å, ρ = 45 ± 10°);



(a)

(b)

Fig. 2.



(c) (d)

(e) (f)

Fig. 2. (*Contd.*)

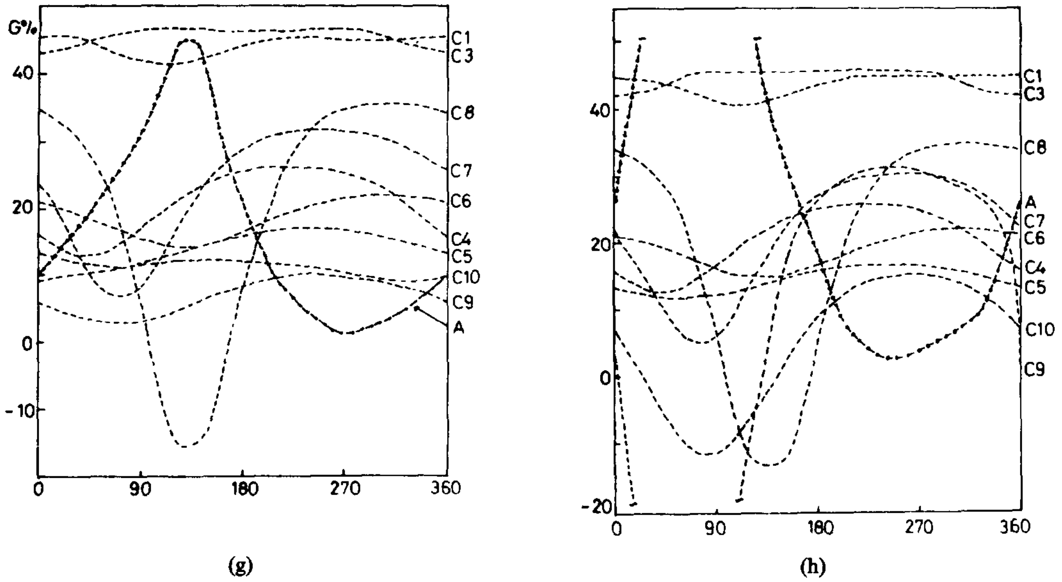


Fig. 2. Calculated geometry factors RG (in % relative to Hα or Cα = 100%) as a function of torsional angles (Ln–O–Cα–Cβ) in (a) 4-tert-butylcyclohexanone **2**(b) trans-4-tert-butyl-cyclohexanol **4**, (c) 5α-androstan-3-β-ol (C-atoms), (d) 5α-androstan-3β-ol (H-atoms), (e) cis-4-tert-butyl-cyclohexanol **5**, (f) 5α-androstan-17-one, (g) exo-isofenchol **8**, (h) isoborneol **10**, A: agreement factor.

these findings are in agreement with earlier results.[1,3a,b,8a,32] As a first consequence of this, Cβ RS/RG- values, which *only* depend on d and ρ, are constant throughout all alcohols and ketones (Table 1).

Larger RS variations could be expected for nuclei other than Cβ, as these depend necessarily on the torsional angles φ, which will change much more between the different structures than bond angles or lengths. Evaluation of the geometry factor RG as a function of φ, however, demonstrates, that "extended" conformations, such as in eq. substituted cyclohexanes, exhibit very flat profiles with rather constant RG values also for Cγ and Cδ (Figs. 2a–c). If the oxygen is axial, as in **5** (Fig. 2e), or if there is asymmetric substitution vicinal to the oxygen, as in **1** (Fig. 2f), the induced shifts obviously will be more sensitive to the lanthanide location. Still, the agreement factor A minimum is very broad; particularly systems such as **1** which contain many nuclei remote from the complexation site may yield almost meaningless low agreement factors. Even bicyclic compounds such as **8** or **10** which offer many geometrically different atoms around the binding site, show flat minima (Figs. 2g, h). This, together with the ambiguities described above, renders an exact geometry analysis extremely difficult even for conformationally fixed substrates, where the only degree of freedom is the localization of the lanthanide.[1a] Geometry calculations for Yb(fod)$_3$ complexes with **1**, **2**, **4**, **5**, **8**, **9**, **10** and 3β-hydroxyandrostane, based on ^{13}C and ^{1}H-LIS data without restriction on the Yb localization, also lead to widely variable geometries (Table L[12]). Thus, agreement factors $A < 3\%$ are obtained for **2** with $\Delta d = 1$ Å, $\Delta\rho = 55°$, $\Delta\varphi = 200°$, or even for **10** with $\Delta d = 0.4$ Å, $\Delta\rho = 11°$, $\Delta\varphi = 17°$. In addition, the use of different model geometries for the substrate again influences the apparent minimum[3b] (see also Table L[12]).

The *positive* consequence of the insensitivity of the combined geometry factors and the induced shifts against minor conformational changes is, that the normalized shifts RS are consistent within few per cent in very different compounds. It is gratifying, that the observed RS values not only show little overlap for topologically and stereochemically different nuclei, but also agree with the corresponding theoretical RG factors (Table 1). Inspection of the calculated profiles (e.g. Figs. 2a–h, and unpublished data[12] shows minima in which the lanthanide is invariably oriented away from vicinal Cα–Cβ bonds, but is allowed to change the torsional angle between $\Delta\varphi = 40°$ (Figs. 2f-h) and $\Delta\varphi = 360°$ (Figs. 2a, b) without changing the RG values by more than 2% (Table 1). Since this situation holds for all alcohols and ketones investigated in this study, normalized shifts are expected to follow the same pattern for other oxygen compounds as for those with other binding groups.[14]

EXPERIMENTAL AND COMPUTATIONAL DETAILS

Substrates were available commercially or from earlier studies.[3b,13f,g] LIS measurements were performed by adding up to 10 mole-% Yb(fod)$_3$ in 4–6 increments (by weight) to 1–2 mMol substrate in 1.3–1.5 ml CDCl$_3$.

^{13}C-NMR spectra were measured on Bruker HX 90 or WH 90 systems, at 22.63 MHz at 300 + 5 K. ^{1}H-NMR LIS studies on 3β-hydroxyandrostane were performed at 400 MHz (Bruker WH 400) with 0.04 M solutions and Eu(fod)$_3$. ^{1}H signal assignments were based on extended decoupling and 2D ^{13}C–^{1}H-shift correlated spectra.[33]

LIS for the different nuclei were usually obtained by least square analysis with 5–7 measurements, yielding at least correlation coefficients of $r > 0.99$ for RS > 30%, $r > 0.94$ for RS > 10%, and $r > 0.89$ for RS > 1%.

Regression analyses were performed on an Apple microcomputer, LIS-calculations with a modified LISB FORTRAN program[3b] on the Siemens 7761 of the Rechenzentrum der Universität des Saarlandes.

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