3-(α-Naphthyl)-5,5-dimethylcyclohexanone and Derived Alcohols. Synthesis and Stereochemical Studies by Means of Lanthanide-Induced Proton Nuclear Magnetic Resonance Shifts[1a]

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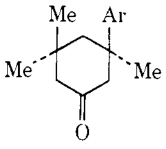
Abstract: The compound 3-(α-naphthyl)-5,5-dimethylcyclohexanone and its two tertiary alcohol analogs, *cis-* and *trans*-1,5,5-trimethyl-3-(α-naphthyl)cyclohexanol, were synthesized and characterized, and a detailed analysis of their conformations was carried out *via* the use of their Eu(fod)$_3$ lanthanide-induced shifts (LIS). Also, independent evidence, in the absence of a lanthanide shift reagent (LSR), is given to substantiate the reported conformations. In all three compounds, the structure is very strongly chair-like with the aromatic (α-naphthyl) substituent in an equatorial disposition. By employing the LSR in an "incremental dilution method," smooth plots were obtained for the concentration dependence of the LIS. The amount of curvature in the plots was sufficient for a qualitative comparison of the three substrates and it was found that the binding strength was cis (equatorial OH) alcohol > ketone > trans (axial OH) alcohol. Values for the incremental shift (Δ_2) of the pure LSR·(substrate)$_2$ complex were obtained from the initial slopes of the LIS curves. By use of these it is possible to affix in detail the general structural features of each molecule and, in the case of the trans alcoholic isomer, to determine an important orientation of the α-naphthyl substituent ($\chi = 300°$ where χ is the dihedral angle between the axial proton–carbon bond in the 3 position of the cyclohexane ring and the α-naphthyl ring, defined in a counterclockwise sense from the cyclohexane ring). Proton chemical shifts (including several otherwise observed) for the compounds in the absence of LSR were obtained by extrapolation of the linear (low LSR concentration) parts of the LIS curves and these agreed well with those chemical shifts which could be directly observed.

For some time work in this laboratory has been concerned with the synthesis, conformational analysis, and reactions of some 3,3,5,5-tetrasubstituted cyclohexanones (**1**) and their alcoholic derivatives (**2**).



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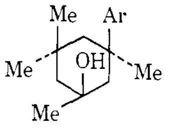
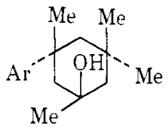


2a (cis)



2b (trans)

Ar = α-$C_{10}H_7$, C_6H_7, etc.

Compounds of type **1** have been shown to exist predominantly (if not solely) in a single-chair conformation with the aromatic substituent occupying an axial position.[2] The observation of an axial aromatic substituent in these types of compounds is in accord with subsequent computations[3] and has been confirmed by an X-ray crystallographic study for **1** where Ar = p-ClC_6H_4.[4]

Conformational analysis of such compounds is greatly facilitated by the use of lanthanide shift reagents (LSR).[5] The lanthanide-induced shifts (LIS) obtained have so far proven to be excellent *qualitative* measures of the time-averaged molecular conformation in a wide variety of compounds.[6] Quantitative applications[7–10] of LIS data have so far met with considerable success in the assessment of equilibrium constants, limiting chemical shifts, and molecular geometries.[11] The success of these methods points toward more promising uses of LIS data in the future.

In an extension of our studies of compound types **1** and **2** we now report the synthesis and conformational analysis of 3-(α-naphthyl)-5,5-dimethylcyclohexanone (**6**) and its epimeric alcoholic derivatives, *cis-* and *trans*-1,5,5-trimethyl-3-(α-naphthyl)cyclohexanols (**11** and **7**), our first examples of 3,5,5-trisubstituted cyclohexanoid compounds with one aromatic substituent. These studies were conducted primarily to determine the structural differences which would obtain between the tetra- and the trisubstituted ketone families (and in the corresponding penta- and tetrasubstituted cyclohexanols), in light of the possibilities for at least partial relief of the 1,3-diaxial interactions which form the basis of the unusual properties of compounds like **1** and **2**. Two types of structural features are of special interest: *viz.*, (i) the very strong axial preference of the aromatic substituent in ketones **1** and a variety of derivatives including alcohols **2a**, and (ii) the nature of the distortions in the cyclohexane ring away from a simple chair-like shape

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(1) (a) Lanthanide-Induced Shifts in Proton Nuclear Magnetic Resonance Spectra. VI. For part V see ref 5d. (b) Postdoctoral fellow of the Robert A. Welch Foundation. (c) Predoctoral fellow of the Robert A. Welch Foundation.

(2) B. L. Shapiro, M. J. Gattuso, N. F. Hepfinger, R. L. Shone and W. L. White, *Tetrahedron Lett.*, 219 (1971).

(3) N. L. Allinger and M. T. Tribble, *ibid.*, 3259 (1971).

(4) R. L. R. Towns and B. L. Shapiro, *Cryst. Struct. Commun.*, **1**, 151 (1972).

(5) (a) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971); (b) B. L. Shapiro, M. D. Johnston, Jr., and R. L. R. Towns, *ibid.*, **94**, 4381 (1972); (c) J. R. Hlubucek and B. L. Shapiro, *Org. Magn. Resonance*, in press; (d) B. L. Shapiro, M. D. Johnston, Jr., A. D. Godwin, T. W. Proulx, and M. J. Shapiro, *Tetrahedron Lett.*, 3233 (1972).

(6) See W. DeW. Horrocks, Jr., J. P. Sipe, III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258 (1971), and references therein.

(7) I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Commun.*, 1281 (1971); *Can. J. Chem.*, **50**, 2119 (1972).

(8) D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).

(9) K. Roth, M. Grosse, and D. Rweicki, *Tetrahedron Lett.*, 435 (1972).

(10) B. L. Shapiro and M. D. Johnston, Jr., *J. Amer. Chem. Soc.*, **94**, 8185 (1972).

(11) (a) M. R. Willcott, III, R. E. Lenkinski, and R. E. Davis, *ibid.*, **94**, 1742 (1972); (b) R. E. Davis and M. R. Willcott, III, *ibid.*, **94**, 1744 (1972).

forced upon these heavily substituted carbocycles.[2,4,5a] Evidence on these subjects is forthcoming from the present study, and additional matters of interest have been found. First, the results of some of the reactions in the synthetic scheme (see Figure 1) are unusual and have some interesting mechanistic as well as synthetic implications. Second, the LIS data of alcohol 7 indicate an *a priori* unanticipated rotational preference of the naphthyl substituent. LIS measurements have also been found useful in providing reasonably accurate estimates of proton chemical shifts which are wholly or partially obscured (either by spin system complexity and/or overlap causing signals to be unresolved). The shift *vs.* LSR concentration dependence curves also yield useful information about the relative binding strengths of different substrate types to the LSR. Finally, the initial slopes of these curves provide a basis for calculations of molecular geometry *via* the pseudocontact equation, and applications of this are discussed in relation to both the fixed and static parts of our molecular systems.

Synthesis

The synthetic route employed to obtain the compounds under discussion is outlined in Figure 1. Although the reactions employed are not unusual, the results obtained in two cases warrant discussion.

Ketone **6** was conveniently prepared from dimedone (**3**) by routine application of existing methods.[12] Its reaction with methylmagnesium bromide results in the formation of appreciable amounts of only *one* alcoholic isomer, mp 74–74.5° (identified below as the trans isomer **7**), as anticipated by the well-documented addition reactions of 3,5,5-trimethylcyclohexanone.[13] This result, although not unexpected, is of considerable interest in view of the production of *both* alcoholic isomers in comparable amounts in the case of **1** where Ar = α-$C_{10}H_7$.[5a] The mechanistic implications of these observations will form the subject of a separate report.

Since the Grignard reaction yields useful amounts of only one of the desired alcohols, it is necessary to obtain the cis isomer, **11**, in some other way. One useful method for obtaining alcohols epimeric with those obtainable from a Grignard reaction is to subject the corresponding *exo*-methylenecyclohexane to the oxymercuration–demercuration sequence developed by Brown.[14] After preparing the *exo*-methylene compound **8** by standard methods[15] an attempt was made to use the above method to prepare the cis alcohol **11**. However, the synthesis yielded the trans isomer, **7**, an unexpected result.[16] We are studying the implications of this finding further.

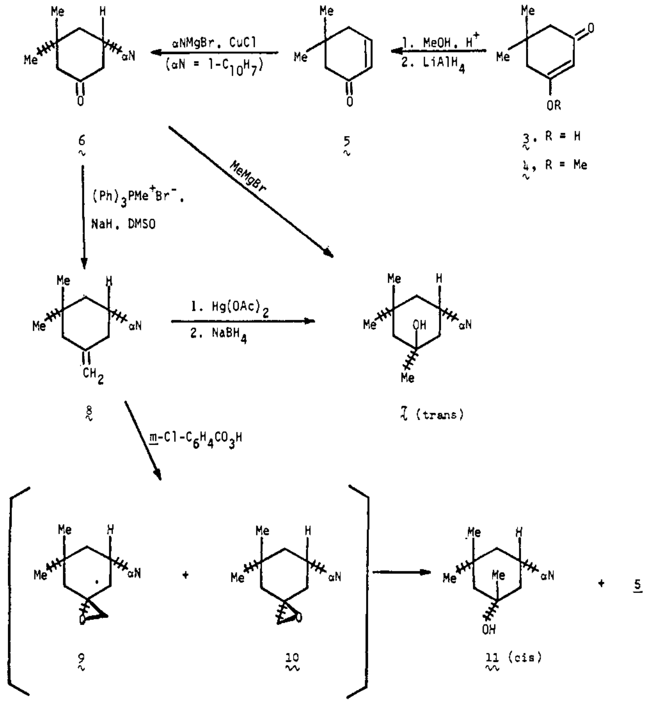
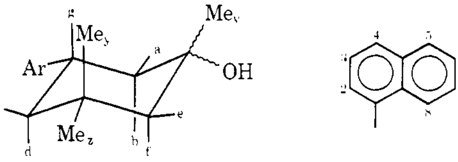


Figure 1. Synthetic scheme for the preparation of the compounds under discussion.

The desired cis isomer **11**, mp 58–59°, was obtained by epoxidation of the *exo*-methylene (**8**) followed by lithium aluminum hydride reduction of the epoxide mixture so obtained and chromatographic separation of the isomeric alcohols produced, as outlined in Figure 1.

Results and Discussion

Characterization. To facilitate discussion, the proton designations used throughout will be as shown below.



The characterization of the compounds under study was accomplished using standard chemical and physical techniques (see Experimental Section). The determination and assignment of configuration at C-1 (hydroxyl axial or equatorial and cis or trans to the naphthyl ring) was made as described below.

First, from the mode of preparation and properties of these compounds, it can be safely assumed that the two alcohols are tertiary and epimeric (*i.e.*, cis and trans relative to the naphthyl ring) at C-1. The epimeric nature of the alcohols is confirmed experimentally by the acid-catalyzed dehydration of each alcohol to the same mixture of 1- and 6-cyclohexenes.

Second, the determination of the axial or equatorial nature of the hydroxyl function and the assignment of the correct configuration to each isomer can be deduced. Since the hydroxyls are cis and trans to the aromatic ring, a determination of the disposition of the ring will fix the relative stereochemistry at C-1. Of course, it is expected that the α-naphthyl substituents will occupy an equatorial (assuming a chair or chair-like cyclohexane ring conformation) position, as denoted in structures **7** and **11**, rather than be axial as in the corresponding alternative possibilities **12** and **13**. In the latter two structures (or in any nonchair structures similar to these

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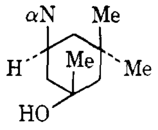
(12) M. J. Gattuso, Ph.D. Dissertation, Texas A&M University, 1970.

(13) (a) E. G. Peppiat and R. J. Wicker, *J. Chem. Soc.*, 3122 (1955); (b) R. J. Wicker, *ibid.*, 2156 (1956).

(14) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

(15) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 28, 1128 (1963).

(16) After several attempts it was possible to find conditions under which the desired cis isomer could be obtained. However, both isomers are obtained and the trans/cis ratio is 25/1.



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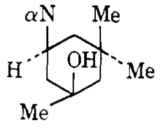

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in having an axial(-like) α-naphthyl group), much greater 1,3-syn-diaxial interactions would obtain. In any such unlikely event, however, the nmr spectra of the two alcohols would be characterized by the presence of a methyl resonance at unusually high fields (*i.e.*, $0 \lesssim \delta \lesssim 0.5$), by analogy with the shifts observed[5a] in the closely analogous axial α-naphthyl alcohol **2a** (methyl proton shifts found at $\delta = 0.47$, 0.89, 1.24, and 1.58). The methyl chemical shifts found (see Table III) in alcohols **7** and **11** are $\delta = 0.93$, 1.20, and 1.32 and $\delta = 1.00$, 1.22, and 1.49, respectively. Thus neither alcohol can have a methyl group exposed to the diamagnetic shielding effects of a 1,3-syn-axial-disposed α-naphthyl ring. This analysis, then, strongly suggests an epimeric disposition at C-1 between **7** and **11**; otherwise, the two isomers are conformationally identical, so far as the cyclohexane rings are concerned.

Third, additional convincing evidence arises from the appearance of the "benzylic" methine H_g resonance. In the ketone **6**, this resonance appears (in the first-order approximation) as a septet formed by the overlap of three triplets; in both of the derived alcohols, H_g gives rise to a completely resolved nine-line pattern easily recognizable as a first-order triplet-of-triplets. The coupling constants extracted from the spectra are listed in Table I. Since these values are inconsistent with an equatorial disposition of the *proton* (see Discussion below) the naphthyl ring must, of necessity, be equatorial in both compounds. Therefore the trans isomer has an axial hydroxyl and the cis isomer an equatorial hydroxyl, as depicted in **7** and **11**.

Table I. Vicinal Coupling Constants[a] for H_g to the Adjacent Methylene Protons

Compound	${}^3J_{\mathrm{ax,ax}}$, Hz	${}^3J_{\mathrm{eq,ax}}$, Hz
Ketone **6**	10.8 ± 0.3	5.5 ± 0.6
Trans alcohol **7**	12.1 ± 0.05	2.9 ± 0.05
Cis alcohol **11**	12.1 ± 0.1	2.8 ± 0.2

[a] These values were obtained using the first-order approximations: ${}^3J(H_g,H_c) \simeq {}^3J(H_g,H_a)$ (*i.e.*, ${}^3J_{\mathrm{ax,eq}}$) and ${}^3J(H_g,H_b) \simeq {}^3J(H_g,H_d)$ (*i.e.*, ${}^3J_{\mathrm{ax,ax}}$). The signs are assumed to be positive.

Finally, there remains only the matter of assigning the correct structure to a given isomer. These assignments are based on the following chemical shift observations: isomer I (say), mp 74–74.5°, $\delta(H_g) = 4.01$; isomer II, mp 58–59°, $\delta(H_g) = 3.57$. It is well documented[17] that the presence of a hydroxyl function close to a proton causes a downfield shift of the latter's resonance, due primarily to an electrostatic deshielding effect. Such a relationship obtains in the trans isomer **7**. The diaxial relationship between the hydroxyl and H_g places this proton well within the region affected by the hydroxyl. However, if the latter group be equatorial, H_g would be too far removed to experience significant deshielding. On this basis we assign to isomer I (mp 74–74.5°) the trans structure **7** and to isomer II (mp 58–59°) the cis structure **11**. These assignments are confirmed in detail by the LIS data discussed below.

Having deduced the relative hydroxyl–naphthyl dispositions in isomers **7** and **11** as well as the constant equatorial character of the naphthyl substituent, it is of interest to next consider the geometries of the cyclohexane rings. By analogy with previous results[2] one would expect these molecules to exist in conformations of a highly chair-like character. Inspection of the values of the coupling constants listed in Table I lends strong support to this view. Values one would expect for vicinal coupling constants in compounds deviating only minimally from a chair form are in the range, ${}^3J_{\mathrm{ax,ax}} = 8$ to 13 Hz and ${}^3J_{\mathrm{ax,eq}} = 2$ to 6 Hz.[18] As can be seen, the experimental values fall within the accepted range and thus strongly imply that the compounds in question are indeed in the chair form. Of equal importance, particularly when considering the present alcohol pair, is the magnitude of the (anti) diaxial vicinal coupling. These values are close to the maximum observed[19] for this type of coupling, thereby precluding any significant amount of rapid chair–chair interconversion. In addition, cyclohexanones which have a basic chair form are known to be slightly flattened,[4,20] owing to the introduction of a trigonal carbon atom. This ring flattening causes a change (decrease) in the dihedral angles from H_g to the adjacent methylene protons. A qualitative application of the Karplus rule[21] predicts that ${}^3J_{\mathrm{ax,eq}}$ should increase while ${}^3J_{\mathrm{ax,ax}}$ should decrease. This is indeed the observed effect in the systems described.

LIS Studies. The LIS data obtained for ketone **6** and the alcohol pair **7** and **11** are presented in Figures 2, 3, and 4.

The LSR employed was europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione ($\mathrm{Eu(fod)_3}$)[22] in carbon tetrachloride solution. In Figures 2, 3, and 4 the observed chemical shifts (usual δ scale) are plotted *vs.* ρ, defined as (total moles of LSR)/(total moles of substrate). Similar data are also obtained using europium(III) tris-2,2,6,6-tetramethyl-3,5-heptanedione ($\mathrm{Eu(dpm)_3}$) although the lower solubility of this reagent precludes the attainment of high ρ values; the latter are desirable since they yield data closer to the region of complete complexation.[10,23]

The first application of these LIS values is qualitative and diagnostic: the detailed confirmation of the structural and configurational assignments already presented for alcohols **7** and **11**. The arguments involved can be made either purely qualitatively, or using the "limiting shifts" (*vide infra*) in Table II in conjunction with the simplest possible form of the pseudocontact shift equation, conveniently expressed as

$$\Delta\delta_i = k(3\cos^2\theta_i - 1)(R_i^{-3}) \qquad (1)$$

where $\Delta\delta_i$ is the incremental LIS measured or deduced for a given proton, i, R_i is the internuclear distance be-

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(17) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, pp 80–81, and references therein.

(18) Reference 17, p 288.

(19) Reference 17, pp 289–294.

(20) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955).

(21) Reference 17, Chapters 2–4.

(22) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

(23) D. A. Deranleau, *ibid.*, **91**, 4044, 4050 (1969).

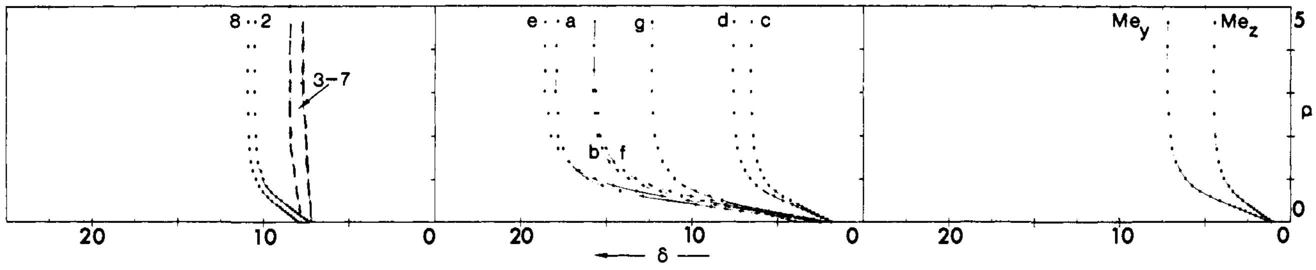

Figure 2. LIS data for ketone **6**.

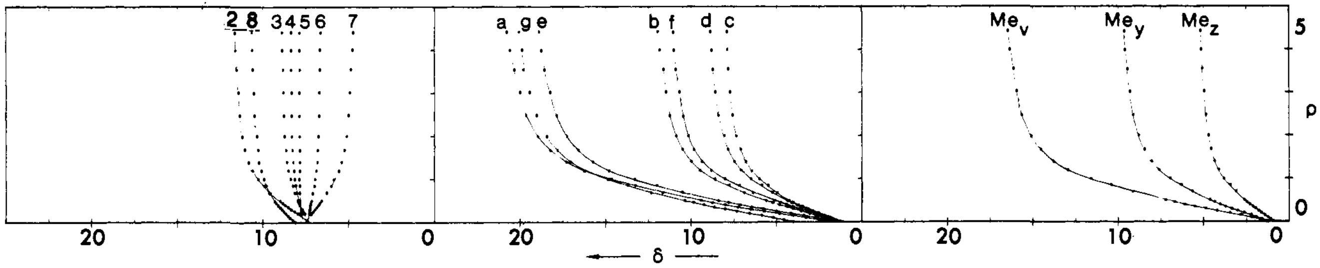

Figure 3. LIS data for trans alcohol **7**. The data for the hydroxyl proton are not shown since it moves rapidly off-scale (at $\rho < 0.1$) and undergoes considerable broadening.

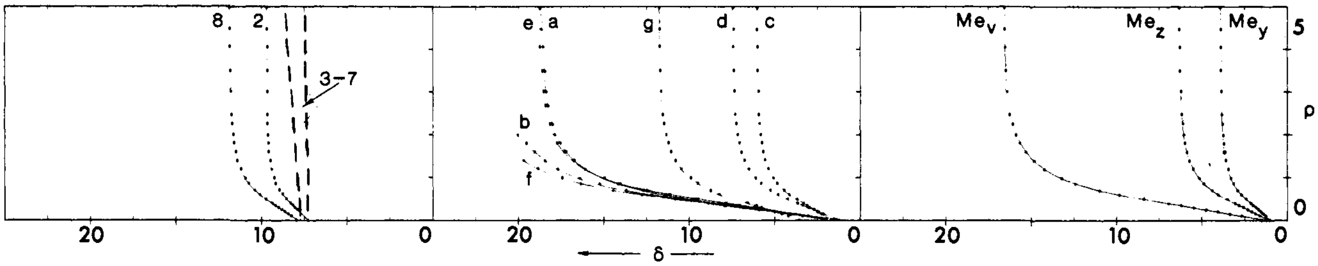

Figure 4. LIS data for cis alcohol **11**. The data for the hydroxyl proton are not shown since it moves rapidly off-scale (at $\rho < 0.1$) and undergoes considerable broadening.

Table II. Δ_2 Values (in ppm) for Nonaromatic Protons from the LIS Plots of **6**, **7**, and **11** with Eu(fod)$_3$[a]

Proton	Ketone **6**	Trans alcohol **7**	Cis alcohol **11**
Me$_v$		6.26	6.86
Me$_y$	3.01	3.41	1.46
Me$_z$	1.69	1.72	2.33
H$_a$	9.10	7.81	7.88
H$_b$	7.08	4.45	8.99
H$_c$	2.31	3.32	1.92
H$_d$	2.92	3.22	2.95
H$_e$	8.09	7.21	7.89
H$_f$	6.64	4.19	9.01
H$_g$	4.34	6.59	3.77

[a] Obtained from a linear regression analysis of LIS data for $\rho \leq 0.5$. All correlations were >99.9%. Δ_2 = slope × 0.5 (see ref 10). Standard deviations of the slopes were <1% in all cases.

tween the proton and the lanthanide atom, θ_i is the angle between the displacement vector of the proton and the lanthanide and the symmetry (magnetic) axis of the LSR, and k is a constant dependent on the LSR *and upon the experimental conditions.*[10] Although this equation is necessarily approximate, since it represents the magnetic tensor by a simple point dipole, it is still sufficiently accurate to adequately extract most conformational information of interest. Quantitative applications of this simple equation have been shown to be very successful.[11]

In this paper arguments used in deducing structures will be qualitative; no attempt will be made to do a detailed geometry fit, such considerations to form the subject of separate reports. The well-behaved character of the methylene resonances in **6**, **7**, and **11** allows one to obtain the relevant structural information from the qualitative behavior of the LIS only.[24] Protons H$_a$ and H$_e$, and H$_b$ and H$_f$, form complementary pairs in their LIS behavior. That is, these protons are symmetrically disposed toward the oxygen of either the ketone or the alcohols. Since the LIS curves of these complementary pairs are similar in shape and in initial slope,[10] it is quite reasonable to assume that the lanthanide atom is also symmetrically disposed to them.

First, considering the ketone, structure **6** is confirmed for this compound by the LIS data. The chair form is confirmed by the observation that H$_a$ and H$_e$ exhibit only slightly larger LIS than H$_b$ and H$_f$. The aromatic shifts are too small to be accounted for by other than an equatorial naphthyl disposition. Known axial aromatic substituents show far larger LIS.[5a,10] Further comparison of **6** to 3,5,5-trimethyl-substituted and other cyclohexanones, with axial aromatic substituents, is forthcoming.[25]

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(24) It has been previously shown that treatment of LIS data in a qualitative manner readily yields detailed information concerning molecular conformation (*cf.* ref 5 and 6).

(25) B. L. Shapiro, M. D. Johnston, Jr., and M. J. Shapiro, *Org. Magn. Resonance*, in press.

Turning to comparisons between alcohol isomers, the axial disposition of the hydroxyl group in alcohol **7** would place the bound europium substantially closer to H_a and H_e than to H_b and H_f. If the O–Eu–H *angles* are fairly similar, as is borne out by the inspection of models, the dominance of the distance term in the pseudocontact shift equation accounts well for the considerably larger LIS values observed for H_a and H_e relative to H_b and H_f. Conversely, in the equatorial alcohol **11**, there is much less difference in the relative dispositions of H_a and H_e and their geminal partners H_b and H_f with respect to sterically reasonable locations for the complexed europium. Consistent with this observation are the considerably lesser (relative) LIS *differences* observed (see Table II) in this cis isomer. Inspection of models indicates that in the equatorial alcohol **11**, the lanthanide might well prefer to bind more toward, or indeed slightly below, the cyclohexane ring plane. This hypothesis, which rationalizes the observation for H_a, H_b, H_e, and H_f, also is consistent with the observed relative shifts of *all* of the nonaromatic protons in the two isomers (with the exception of the C_1 methyl group, Me_v), and the individual arguments need not be made explicitly. The 10% larger shift observed for Me_v in the equatorial alcohol **11** can of course be readily accounted for both by the increased accessibility of the hydroxyl group in this isomer relative to that enjoyed by the axially disposed hydroxyl group in the trans isomer **7**, and by a possible further inhibition of binding in the latter due to the syn-axial methyl group (Me_y) at C-5 and by the particular rotational disposition preferred by the C-3 α-naphthyl group (*vide infra*).

On this basis, then, it is felt that a qualitative inspection of the relative LIS values confirms the stereochemistry of the cyclohexane ring substitution pattern in these alcohols in detail. It should be emphasized further that the specific assignments of the proton groups do not depend on the relative magnitudes of the LIS observed. Rather these assignments follow unambiguously from the multiplet nature of the resonances arising from each proton type, and are immediately deduced as soon as the LSR has provided sufficient spectral dispersion for even approximately first-order resonances to be observed. One specific example suffices; in both alcohol isomers, H_b appears as a triplet (with approximately equal coupling magnitudes to the geminal H_a and the vicinal H_g), whereas H_f has the first-order character of a doublet (only one large coupling, to H_e). The relative magnitudes of the LIS are, of course, involved in the initial assignments of H_c and H_d resonances to those methylene protons with the smallest observed LIS in a given isomer.

Limiting incremental shifts, Δ_2, for the methyl and methylene protons are given in Table II. These shifts are deduced from the initial slopes of the LIS curves (derived for $\rho \leq 0.5$). These are the limiting LIS for complexes containing *one* LSR molecule and *two* substrate molecules. These limiting shifts are equal to half the initial slope at low values of ρ, to at least a high approximation. Detailed discussion of these points is given elsewhere.[10]

Additional stereochemical information is obtained from considerations of the LIS experienced by the *aromatic* protons of these compounds (Δ_2 values for these are in Table III). First taking the cases of the ketone **6** and the cis alcohol **11**, attention is drawn to the following observation: (i) only downfield shifts, *i.e.*, positive Δ_2 values, are observed for all protons, in contrast to results obtained for the trans alcohol (axial OH) **7** (and for the axial alcohol (here, the cis isomer) **2a**[5a] in the series containing four methyl groups); and (ii) in the cases of **6**, **11**, and **2b**, H_8 and H_2 (again, identified independently of their LIS magnitudes) are shifted the same amount as each other, and much more than any of the other five aromatic resonances. In all three compounds, the five "slower moving" resonances arising from H_3 through H_7 inclusive are never well enough resolved to permit individual chemical shift determinations, and hence only the broad range of LIS indicated in Figures 2 and 4 and in Table III is possible.

Table III. Δ_2 Values (in ppm) for Aromatic Protons from the LIS Plots of **6**, **7**, and **11** with Eu(fod)$_3$[a]

Proton	Ketone **6**	Trans alcohol **7**	Cis alcohol **11**
H_2	1.64	+1.94	1.28
H_3	*b*	+0.80	*c*
H_4	*b*	+0.20	*c*
H_5	*b*	+0.21	*c*
H_6	*b*	−0.20	*c*
H_7	*b*	−0.94	*c*
H_8	1.58	+1.34	1.84

[a] See footnote *a*, Table II. [b] Insufficient dispersion to resolve these. The approximate range is $+0.26 \lesssim \Delta_2 \lesssim +0.35$ ppm. [c] Insufficient dispersion to resolve these. The approximate range is $+0.2 \lesssim \Delta_2 \lesssim +0.4$ ppm.

In contrast to these observations, the trans alcohol **7** gives rise to a highly dispersed spectrum on addition of Eu(fod)$_3$, and presents a virtually first-order pattern at quite modest doping levels (see Figure 3). Particular attention is drawn to the *negative*, *i.e.*, upfield, shifts experienced by the resonances of H_6 and H_7 (the identification of these resonances follows immediately from their gross triplet character with intensities skewed toward each other, whereas H_3, the only other proton giving rise to a first-order triplet, can be seen independently and its identity checked by intensity skewing and confirmed by appropriate double resonance experiments). Clearly the negative sign of these shifts is a consequence of the angle term in the pseudocontact shift equation, and implies some very definite and useful restrictions on the appropriate O–Eu–H angles involved (*cf.* ref 5a). The very substantial size of the upfield shifts seen for H_6 and H_7 permits useful semiquantitative geometry calculations to be performed. Using geometrical parameters derived from Dreiding models, one can readily make quantitative estimates of the relative shifts of any proton groups in the molecule, assuming a particular position of the europium atom. For any reasonable O–Eu distance and the Eu–O–C-1 angle, such calculations show clearly that negative shifts can be obtained only when the α-naphthyl substituent at C-3 is rotated "forward" into a position like that indicated in structure **14a** (as differentiated from **14b** and **14c**). A conformation such as that of structure **14a** must therefore be an important contributor to any time-averaged conformational position occupied by the naphthyl ring (Figure 5). It is tempting to speculate that one possible reason for the predominance of conformation **14a** may be the substantially smaller molec-

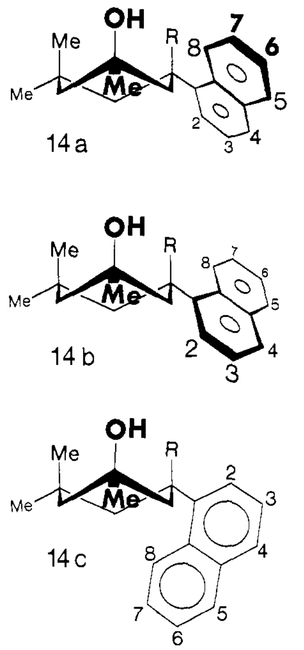

Figure 5.

ular volume which obtains for alcohol **7** in this conformation relative to conformations **14b** and **14c** as pictured in Figure 6. This possibility is being actively investigated.

When LIS experiments are performed by this "incremental dilution" method (ref 10), the plots of observed shifts are linear with increasing ρ as long as ρ is below approximately 0.6. This finding, for which abundant experimental verification is seen in Figures 2, 3, and 4, permits one to make good-to-excellent estimates of chemical shifts otherwise obscured by spin system complexity and/or by fortuitous overlaps and coincidences. These chemical shifts of the uncomplexed substrate (δ_0 values) are conveniently obtained by desk calculator linear extrapolations. It is also convenient and desirable to use the linear least-squares regression correlation coefficient to check both the quality of the shift data at low ρ values, and to ensure that the high ρ end of the extrapolation is truncated before the onset of curvature. Data so obtained on our compounds are given in Table IV, and compared with shift values obtained by direct observation in those cases where this was possible. We have applied this technique to the estimation of many chemical shifts, and believe them to be good in most cases (the exceptions occur for *some* of those protons having large incremental shifts) to better than 0.05 ppm, and often to within ±0.01 ppm of the best values observable for sharp, completely resolved resonances. Certainly, such extrapolation values provide excellent trial parameters for iterative computer-aided spin system simulations (*e.g.*, H_6 and H_7 of monosubstituted naphthalenes which generally have very similar chemical shifts).

Table IV. Chemical Shifts (in ppm) of **6**, **7**, and **11** (no LSR Present)[a]

Proton	Ketone **6**	Trans alcohol **7**	Cis alcohol **11**
Me_v		1.04 (1.20)	1.47 (1.49)
Me_y	1.17 (1.16)	1.28 (1.32)	1.00 (1.00)
Me_z	1.10 (1.11)	0.90 (0.93)	1.21 (1.22)
H_a	2.53 (2.56)	1.73	1.97
H_b	2.41 (2.46)	1.30	1.57
H_c	1.94 (1.93)	1.31	1.75
H_d	1.78 (1.81)	1.22	1.36
H_e	2.14 (2.18)	1.32	1.61
H_f	2.17 (2.22)	1.09	1.45
H_g	3.91 (3.95)	3.95 (4.01)	3.56 (3.57)
H_2	7.31 (7.32)	7.18	*b*
H_3–H_7	*b*	*b*	*b*
H_8	7.94 (7.94)	8.12 (8.11)	7.97 (7.98)

[a] Obtained from a linear regression analysis with $\rho \leq 0.5$. Values obtained directly are in parentheses, where available. [b] Insufficient dispersion for unambiguous resolution.

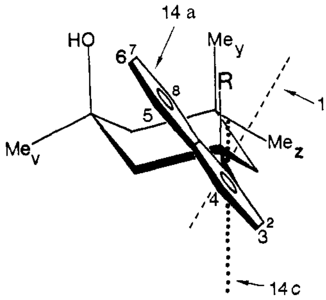

Figure 6. Side view of the conformations depicted in Figure 5. Conformations **14b** and **14c** are indicated by the dashed and dotted lines, respectively.

Finally, even in the absence of detailed equilibrium constant evaluations, it is possible to estimate the relative binding abilities of the substrates **6**, **7**, and **11** by looking at the shapes of the total LIS curves (in the range $0 \leq \rho \lesssim 5$). The initial slopes, at small ρ, cannot give information on the binding strength in themselves since these slopes are mainly dependent on Δ_2. Relative binding strengths of different substrates can, however, be assessed qualitatively by observing the amount of curvature in each plot. The stronger curvature observed in **11** indicates that the equatorial –OH function is more effective in binding than an axial –OH (**7**) or a carbonyl (**6**). Of the latter two, the ketone (**6**) exhibits greater curvature, perhaps owing to the steric hindrance encountered by the LSR in **7** being actually large enough to exhibit a case in which a ketone is a better binder than an alcohol.

Experimental Section

All boiling points and melting points reported are uncorrected. Capillary melting points were determined on a Mel-temp melting point apparatus. Infrared spectra were determined with a Beckman Model IR 8 infrared recording spectrophotometer, calibrated by means of the 1603 cm^{-1} absorption of a polystyrene film. Refractive indices were determined on a Bausch and Lomb Abbé 3L refractometer. Nmr spectra were obtained on a Varian HA-100 spectrometer (probe temperature 31 ± 1°), operating in the frequency sweep mode. Chemical shifts are reported on the δ scale [*i.e.*, in parts per million downfield from internal tetramethylsilane (TMS)]. Unless otherwise stated concentrations are 10% w/v, with CCl_4 as solvent. Coupling constants were determined from spectra with a 50-Hz sweep width and a sweep time of 0.1 Hz/sec.

LIS data were obtained by an incremental dilution method as described by Shapiro and Johnston,[10] using europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione, $Eu(fod)_3$, as the LSR. Substrate concentrations were held constant at 0.15 *M*.

5,5-Dimethyl-3-methoxy-2-cyclohexen-1-one. Standard esterification (*cf.* ref 12) of 5,5-dimethyl-1,3-cyclohexanedione (Aldrich Chemical Co.) using methanol and *p*-toluenesulfonic acid gave the product in 90% yield: bp 85–88° at 0.7–0.8 Torr (lit.[12] bp 90° at 1.0 Torr); $n^{27}D$ = 1.4913; nmr δ 1.04 [$C(CH_3)_2$], 3.68 (OCH_3), 5.24 (=CH), 2.08 (C_6, CH_2), 2.24 (C_4, CH_2).

5,5-Dimethyl-2-cyclohexen-1-one. Lithium aluminum hydride reduction of 5,5-dimethyl-3-methoxy-2-cyclohexen-1-one by the method of Blanchard and Goering[26] gave the product as a colorless liquid (bp 86–87° (34 Torr)) in 85% yield. (Blanchard and Goering report a 92% yield for 3-ethoxy-5-methyl-2-cyclohexen-1-one.) This compound had $n^{27}\text{D} = 1.4676$ (lit.[27] $n^{20}\text{D} = 1.4710$); nmr δ 1.04 [$C(CH_3)_2$], 5.88 (C_2, HC=), 6.81 (C_3, HC=), 2.26 (C_4, CH_2), 2.18 (C_6, $-CH_2$).

5,5-Dimethyl-3-(α-naphthyl)cyclohexanone (6). To a flamed-out, 100-ml round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and condenser and swept with a slow stream of nitrogen were added 12.2 g (0.5 g-atom) of magnesium shavings and 150 ml of absolute ether. A solution of 103.5 g (0.5 mol) of 1-bromonaphthalene in 200 ml of absolute ether was added dropwise with stirring. (If the reaction had not started after 15 min, as evidenced by a pronounced cloudiness of the solution, 0.5 ml of 1,2-dibromoethane was added to initiate it.) The solution was stirred until all the magnesium had dissolved. Anhydrous cuprous chloride, freshly prepared by the method of Jolly[28] [1.0 g (1 mol %)], was added and the mixture was stirred for 15 min, giving a black reaction mixture. (Lack of a black color at this point indicates that the cuprous chloride has not complexed with the Grignard. Such reactions generally give little or no yield of the desired conjugate addition product.) The flask was cooled in a Dry Ice–acetone bath (maintained at −80°) and a solution of 62.0 g (0.5 mol) of 5,5-dimethyl-2-cyclohexen-1-one in 150 ml of absolute ether was added dropwise and with stirring. Thirty minutes after completion of the addition, the cooling bath was removed and the flask was allowed to come to room temperature. The mixture was stirred for an additional 20 hr.

Hydrolysis was effected by the dropwise addition of 62 ml of a saturated ammonium chloride solution. The ether layer was decanted and the residue washed with three 50-ml portions of ether. The ether solutions were combined and dried over sodium sulfate, and the ether was removed. The mixture crystallized on standing, and recrystallization from ether yielded 40.0 g (31.7%) of **6**, mp 81–83°. Evaporation of the mother liquor yielded 30.9 g of an oil, from which chromatography on alumina using 50% hexane–benzene as the eluent yielded an additional 32.2 g (18.3%) of **6**. Recrystallization from ether yielded a total of 63.1 g (50%) of pure **6**: mp 82.5–83.5°; ir (10% w/v in CCl_4) 1713 cm^{-1} (C=O stretch); nmr δ 1.08, 1.14 [$C(Me_2)$], 3.92 (methine). *Anal.* Calcd for $C_{18}H_{20}O$: C, 85.66; H, 8.00. Found: C, 85.90, 85.89; H, 81.7, 8.05.

The 2,4-dinitrophenylhydrazone had mp 197–198°. *Anal.* Calcd for $C_{24}H_{23}N_4O_4$: C, 67.42; H, 5.43; N, 13.11. Found: C, 67.36, 67.09; H, 5.54, 5.70; N, 12.96, 13.11.

***trans*-1,5,5-Trimethyl-3-(α-naphthyl)cyclohexanol (7).** A solution of 40.0 g (0.16 mol) of **6** in 250 ml of absolute ether was added dropwise with stirring to 150 ml (0.45 mol) of 3 *M* methylmagnesium bromide in ether (Alfa Inorganics). The mixture was stirred for an additional 42 hr after completion of the addition. Hydrolysis and destruction of unreacted methylmagnesium bromide were effected by the dropwise addition of 45 ml of a saturated aqueous ammonium chloride solution. The ether layer was decanted and the precipitate washed with three 100-ml portions of ether. The ether washings were combined and dried over sodium sulfate, and the ether removed yielding 38.4 (93.8%) of a yellow oil which solidified on standing. Recrystallization from ether gave 36.7 g (89.9%) of pure **7**, as a white crystalline solid: mp 74–74.5°; ir (10% w/v in CCl_4) 3623 cm^{-1} (O–H stretch); nmr δ 1.33, 1.20, 0.94 (Me's), 4.00 (methine), 9.96 (OH). *Anal.* Calcd for $C_{19}H_{24}O$: C, 85.01; H, 9.03. Found: C, 85.01, 85.12; H, 8.83, 8.94. The alcohol was further characterized by acid-catalyzed dehydration to two isomeric olefins which were identified by nmr.

5,5-Dimethyl-3-(α-naphthyl)-1-methylenecyclohexane (8). Reaction of 10.0 g (0.04 mol) of **6**, 2.1 g (0.05 mol) of sodium hydride (57% oil dispersion), and 17.8 g (0.05 mol) of triphenylmethylphosphonium bromide by the modified Wittig procedure of Corey[15] gave 9.92 g (99%) of **8** as a colorless liquid: $n^{27}\text{D} = 1.5833$; ir (neat) 2940, 2910 cm^{-1} (=C—H stretch); nmr δ 1.01, 1.10 ($C—CH_3$), 3.60 (benzylic H), 4.68 and 4.77 (=C—H); for H_g ${}^3J_{ax,ax} = 12.0$ Hz and ${}^3J_{ax,eq} = 3.75$ Hz. *Anal.* Calcd for $C_{19}H_{22}$: C, 91.13; H, 8.87. Found: C, 91.10; H, 8.94.

***cis*- and *trans*-5,5-Dimethyl-3-(α-naphthyl)cyclohexanespiro-2′-oxiranes (9 and 10).** Standard epoxidation of 5.0 g (0.020 mol) of **8** employing *m*-chloroperbenzoic acid (*cf.* ref 29) gave 4.95 g (93.5%) of a mixture of **9** and **10** as a colorless liquid, bp 125° (0.1 Torr). Nmr (cis): δ 1.00, 1.21 (Me's), 3.75 (methine), 2.59 ($O–CH_2$) (center of an AB pair), ${}^2J_{AB} = \pm 5.0$ Hz. The AB pattern observed for the epoxymethylene protons is further complicated since each of the lines is split into a doublet due to long-range coupling to the adjacent ring protons. The observation of such long-range coupling is the basis for assigning the cis structure (**9**) to this isomer.[30] Nmr (trans): δ 1.00, 1.31 (Me's), 4.08 (methine), 2.41 ($O–CH_2$). *Anal.* Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.55, 85.46; H, 8.39, 8.38.

***cis*-1,5,5-Trimethyl-3-(α-naphthyl)cyclohexanol (11).** Standard lithium aluminum hydride reduction (*cf.* ref 31) of 14.0 g (0.053 mol) of the mixture of 9 and **10** as obtained above yielded 12.9 g of the crude alcoholic products as a yellow oil. Chromatography of this oil on 400 g of Woelm silica gel (activity I, neutral) using acetone–hexane mixtures (1% acetone–hexane through 20% acetone–hexane) as eluents yielded 4.28 g (30%) of **7** and 8.44 g (51.5%) of **11**. Crystallization from pentane afforded **11** as colorless needles; mp 58–59°; ir (10% w/v CCl_4) 3425 cm^{-1} (O–H stretch); nmr δ 0.98, 1.20, 1.47 (Me's), 3.53 (methine). *Anal.* Calcd for $C_{19}H_{24}O$: C, 85.01; H, 9.03. Found: C, 85.03, 85.05; H, 8.99, 8.98.

Synthesis of 7 and 8 using Mercuric Acetate–Sodium Borohydride. Reaction of 1.25 g (0.005 mol) of exo-methylene **8** by the oxymercuration–demercuration procedure of Brown[14] gave (after recrystallization from ether) 1.2 g (89.3%) of a white crystalline solid (mp 74–75°). The product was identified by melting point, mixture melting point, and nmr as **7**.

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