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CONFORMATIONAL ANALYSIS WITH LANTHANIDE SHIFT REAGENTS.
A NEW DETERMINATION OF THE CYCLOHEXANOL A-VALUE

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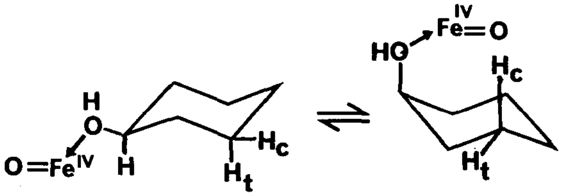
Recent studies in our laboratories have led to the conclusion that the selective 1,3-cis-hydrogen abstraction observed upon oxidation of cyclohexanol with ferrous ion-hydrogen peroxide proceeds through a bound iron-oxy species as in (1).[1] This proposal necessitates a reasonable abundance of the axial cyclohexanol-metal solvate complex since the rate of hydrogen abstraction by this reactive intermediate is likely to be rapid compared to chair-chair ring interconversion. This consideration has led us to examine possibly disadvantageous effects of metal complexation on the equilibrium (1) and to search for independent evidence that the cis proton on carbon-3 can be in close proximity to the metal oxidant.



(1)

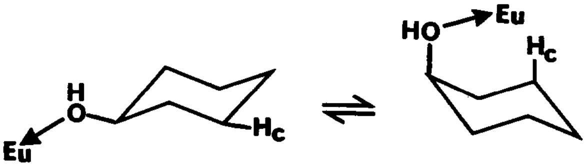
The use of lanthanide shift reagents in structural and stereochemical elucidations is now widespread[2] yet there have appeared relatively few tests of the effects of complex formation on potentially sensitive conformational equilibria.[3] We report here an analysis of the europium-shifted nmr spectrum of cyclohexanol and the determination that metal-alcohol complexation has a negligible effect upon the equatorial-axial ratio.

Unambiguous assignment of the resonances in the Eu(fod)$_3$-shifted nmr spectrum is complicated by overlap of two of the resonances and incomplete resolution of coupling. In contrast, the spectrum of trans-3-trans-5-cyclohexanol-d_2[4] is sufficiently well resolved to allow a definitive assignment (Figure 1).

The pseudocontact shift observed for each resonance in a conformationally mobile and time-averaged system can be expressed as a linear combination of shifts due to individual conformations.[5] For the case of cyclohexanol the observed shift (ΔEu^{obs}) can be related to the equatorial-axial equilibrium according to the expression

$$\Delta Eu^{obs} = Neq\ \Delta Eu^{eq} + Nax\ \Delta Eu^{ax}.$$

Comparison of ΔEu values for each position of cyclohexanol with those reported for cis- and trans-t-butylcyclohexanol[6] (Table I) led to a best fit of the data with Neq = 73 and Nax = 27. This result ($K_{27.4} = 2.70$) corresponds to an A-value of 0.59 kcal/mole for the equilibrium (2).



(2)

Examination of literature A-values for cyclohexanol reveals considerable variation with both solvent and measurement technique.[8] The value determined by slow exchange nmr techniques (0.9-1.0 kcal) is particularly large and apparently reflects the conformational effects of extensive hydrogen bonding at low temperature.[9] Interestingly, the determination reported here for the cyclohexanol-europium solvate complex gives a ΔF much more in accord with values determined for other non-hydrogen bonding oxygen substituents (0.52-0.59) and the expected radial size of the hydroxyl group.

We suggest, therefore, that conformational equilibria are not appreciably affected in Eu(DPM)$_3$ or Eu(fod)$_3$ complexes and that the A-value of 0.59 represents a good measure of the equilibrium constant for cyclohexanol in the absence of hydrogen bonding effects. Further, the observed equilibrium provides sufficient amounts of the axial conformer to explain the iron-hydrogen peroxide stereoselectivity.

Table I. ΔEu[a] Values of Cyclohexanols

Compound	H_1	H_2-*cis*	H_2-*trans*	H_3-*cis*	H_3-*trans*
trans-4-t-butyl cyclohexanol	-21.7	-14.7	-13.6	-4.4	-5.4
cis-4-t-butyl cyclohexanol	-24.7	-14.9	-8.2	-13.6	-6.7
cyclohexanol (observed)	-22.5[b]	-16.1	-13.1	-6.9	-5.8
cyclohexanol (calcd for 73:27)	-22.5	-14.8	-12.1	-6.9	-5.8

[a] For cyclohexanols in $CDCl_3$, *cf.* Ref. 6.

[b] Values for $Eu(DPM)_3$.

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Figure 1. Eu(fod)$_3$—Shifted nmr Spectrum of Cyclohexanol