examine the relative contact and pseudocontact shifts induced by the different lanthanides.

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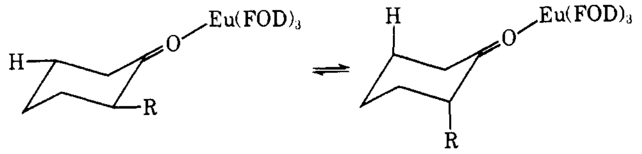
Conformational Analysis of 2-Alkylcyclohexanone–Lanthanide Chelate Complexes

Sir:

Induced shifts in nmr spectra which result from complexation of a substrate with lanthanide chelates[1] have found widespread use in structural[2] and stereochemical[3] analyses. In many cases, large differential shifts permit analysis of the nmr spectrum from which a structural assignment can be deduced.[4] For conformational analysis, quantitative values for the induced shifts are usually sought.[3a,3b] Several methods have been presented for obtaining intrinsic induced shifts but all seem to have limitations.[5] We now report on the conformational equilibria of alkylcyclohexanone–lanthanide chelate complexes obtained from induced shift ratios.

The complexity of the nmr spectra of 2-alkylcyclohexanones prevents a direct analysis of the spectra to obtain chemical shifts for use in conformational analysis.[6] Addition of Eu(FOD)$_3$ produces large differential downfield shifts which greatly simplify the spectra and allow assignments to be made.[7] In the limit of complete complexation, the induced shift, $\Delta_B{}^{av}$, for a ring proton should be the conformational average of the induced shifts for the proton in the two conformations of the complex



$$\Delta_B{}^{av} = n_{eq}\Delta_B{}^{eq} + n_{ax}\Delta_B{}^{ax}$$

where n_{eq} and n_{ax} are the mole fractions of equatorial and axial conformers and $\Delta_B{}^{eq}$ and $\Delta_B{}^{ax}$ are the characteristic induced shifts for protons in the equatorial and axial positions.

In order to obtain characteristic induced shifts for the protons in the equatorial and axial positions of complexed cyclohexanones, 4-*tert*-butylcyclohexanone was chosen as a model compound and the effect of varying Eu(FOD)$_3$ concentration on its nmr spectrum determined. Rather than attempting to use graphical or numerical methods to determine absolute values for the induced shifts of each of the ring protons in the complex, the ratio of induced shift of a ring proton relative to the sum of the induced shifts for the two protons at that ring position was obtained as outlined below.

When exchange of substrate between the complexed and uncomplexed state is rapid, the observed chemical shift in the presence of chelating agent, δ_{obsd}, for any proton of the substrate will be an average value of its chemical shift in the uncomplexed ketone, δ_0, and its chemical shift in the substrate–lanthanide chelate complex, $\Delta_B + \delta_0$. Thus

$$\delta_{obsd} = \delta_0 + F\Delta_B$$

where F is the fraction of substrate present as complex. For any two protons, H$_a$ and H$_b$, of the same substrate in one solution of any particular concentration of substrate and chelate the following relationship[8] can be derived

$$\delta_{obsd}{}^{H_a} = \delta_0{}^{H_a} + \left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b}}\right)(\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}) - \left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b}}\right)(\delta_0{}^{H_a} + \delta_0{}^{H_b})$$

For a different concentration of substrate or chelate, different chemical shifts, $\delta_{obsd}{}^{H_a}$ and $\delta_{obsd}{}^{H_b}$, will be observed. However, a plot of $\delta_{obsd}{}^{H_a}$ *vs.* $(\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b})$ for each of the different solutions should be linear with a slope equal to the relative induced chemical shifts, $\Delta_B{}^{H_a}/(\Delta_B{}^{H_a} + \Delta_B{}^{H_b})$.

The principal advantage of this procedure is that substrate and reagent concentrations need not be known and that no special precautions to exclude competitive scavengers need be taken. In addition, the often difficult task of determining chemical shifts of the uncomplexed substrate, δ_0, is avoided.[9,10] Such a plot

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(7) See Figure 4 of ref 4b.

(8) To derive this relationship, the separate equations for $\delta_{obsd}{}^{H_a}$ and $\delta_{obsd}{}^{H_b}$ are written and then summed. By substituting the solution for F from the $\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}$ equation into the $\delta_{obsd}{}^{H_a}$ equation, the relationship is obtained directly.

(9) The previous procedure employing internal protons as standards[5h] required chemical shift assignments for the uncomplexed substrate.

(10) The condition that the substrate concentration be much larger than the lanthanide chelate concentration must be maintained. Shapiro and Johnston have shown that under these conditions the major complex is the LS$_2$ species.[11] Our relative shifts then would apply to this species.

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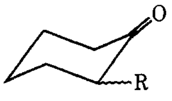
Table I. Conformational Equilibria for 2-Alkylcyclohexanones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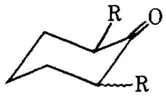
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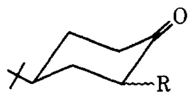
III

	Relative induced shifts			Base interconversion			
	I			II		III	
R	$\left[\frac{\Delta_B^{5eq}}{(\Delta_B^{5eq} + \Delta_B^{5ax})}\right]_{av}$	% eq	ΔG^a	% eq	ΔG^b	% eq	ΔG^c
Me	0.415 ± 0.003^d	89.7^e	−1.33	91.6	−1.82	93.1	−1.51
Et	0.424 ± 0.005	85.5	−1.05	79.4	−1.21	86.4	−1.06
i-Pr	0.443 ± 0.001	76.6	−0.71	56.7	−0.56	73.0	−0.57
t-Bu	0.408 ± 0.002	93.0	−1.57	86.6	−1.52	94.1	−1.61

[a] From relative shifts of H_{5a} and H_{5e} induced by $Eu(FOD)_3$ in $CDCl_3$ at 31.9°. [b] B. Rickborn, *J. Amer. Chem. Soc.*, **84**, 2414 (1962). Base was NaOMe in MeOH, at 25.0°. [c] N. Allinger and H. Blatter, *J. Amer. Chem. Soc.*, **83**, 994 (1961); at 25.0°. [d] Errors are standard deviations from least-squares analysis. [e] Estimated errors are ±0.3%.

for the equivalent 3- and 5-position protons of 4-*tert*-butylcyclohexanone is presented in Figure 1. As expected, δ_{obsd}^{5eq} is a linear function of $(\delta_{obsd}^{5eq} + \delta_{obsd}^{5ax})$ over a wide range of ketone and $Eu(FOD)_3$ concentrations. The slope of this line, 0.393, is therefore assumed to be the characteristic relative shift, $\Delta_B^{5eq}/(\Delta_B^{5eq} + \Delta_B^{5ax})$, for a 5-equatorial proton in a cyclohexanone–$Eu(FOD)_3$ complex in the absence of conformational averaging.

For a conformationally mobile cyclohexanone, the relative induced shifts of the two 5-position protons will be a conformationally weighted average of the relative induced shifts characteristic of 5-equatorial and 5-axial protons as determined from the 4-*tert*-butylcyclohexanone model.[12,13]

$$\left(\frac{\Delta_B^{5eq}}{\Delta_B^{5eq} + \Delta_B^{5ax}}\right)_{av} = n_{eq}\left(\frac{\Delta_B^{5eq}}{\Delta_B^{5eq} + \Delta_B^{5ax}}\right)_{4\text{-}t\text{-Bu}} + n_{ax}\left(\frac{\Delta_B^{5ax}}{\Delta_B^{5eq} + \Delta_B^{5ax}}\right)_{4\text{-}t\text{-Bu}}$$

From plots of δ_{obsd}^{5eq} *vs.* $(\delta_{obsd}^{5eq} + \delta_{obsd}^{5ax})$ for 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-*tert*-butylcyclohexanone in the presence of $Eu(FOD)_3$, the average relative induced chemical shifts, $(\Delta_B^{5eq}/(\Delta_B^{5eq} + \Delta_B^{5ax}))_{av}$, were determined and are listed in Table I. From the values of the slopes and the characteristic relative induced shifts for 4-*tert*-butylcyclohexanone, *the mole fractions of equatorial and axial conformers of the complexed ketone are obtained.*[15] The per cent 2-alkyl equatorial isomer and the conformational free-energy difference between the 2-alkyl equatorial and 2-alkyl axial isomers are included in Table I. The equilibrium data for cis–trans interconversions of 2-alkyl-4-*tert*-butylcyclohexanones[16] and for 2,6-dialkylcyclohexanones[17] are included for comparison.

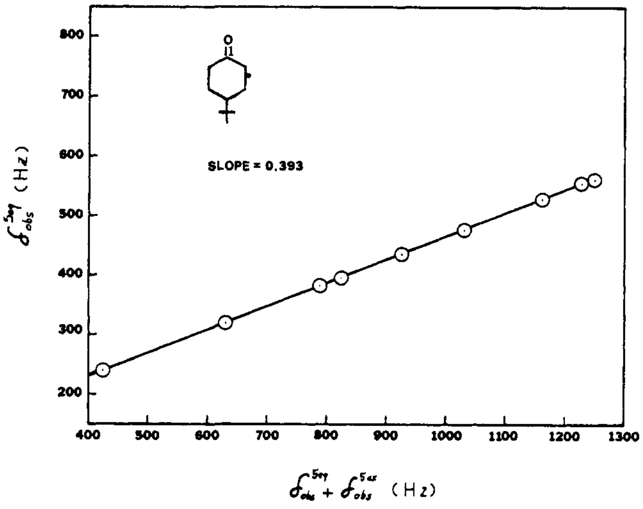

Figure 1. Observed chemical shift of the 5-equatorial proton of 4-*tert*-butylcyclohexanone (δ_{obsd}^{5eq}) *vs.* the sum of the observed chemical shifts of the 5-equatorial and 5-axial protons ($\delta_{obsd}^{5eq} + \delta_{obsd}^{5ax}$).

The conformational free-energy differences for the 2-alkylcyclohexanone–$Eu(FOD_3)$ complexes are nearly identical with those reported for 2-alkyl-4-*tert*-butylcyclohexanones and 2,6-dialkylcyclohexanones. As has been previously noted,[16,17] the fraction of equatorial isomer decreases in the order 2-methyl > 2-ethyl > 2-isopropyl. Further work is now in progress to elucidate the factors responsible for the observed trend.

Acknowledgments. The nmr spectrometers used in this research were purchased through National Science Foundation Departmental instrumentation grants.

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(12) This is in contrast to assuming that the average induced shifts can be used to calculate an average distance of the protons from the carbonyl oxygen. See ref 3b.

(13) This is a solution of the more general equation for the slope of δ_{obsd}^{5eq} *vs.* $(\delta_{obsd}^{5eq} + \delta_{obsd}^{5ax})$

$$\text{slope} = \frac{n_{eq}\Delta_B^{5eq} + n_{ax}\Delta_B^{5ax\prime}}{n_{eq}\Delta_B^{5eq} + n_{ax}\Delta_B^{5ax\prime} + n_{eq}\Delta_B^{5ax} + n_{ax}\Delta_B^{5eq\prime}}$$

where Δ_B^{5eq} and Δ_B^{5ax} are the induced shifts for the R-equatorial conformer of the complex, and $\Delta_B^{5eq\prime}$ and $\Delta_B^{5ax\prime}$ are the induced shifts for the R-axial conformer of the complex. If the assumption[14] that $\Delta_B^{5ax} = \Delta_B^{5ax\prime} = (\Delta_B^{5ax})_{4\text{-}t\text{-Bu}}$ and $\Delta_B^{5eq} = \Delta_B^{5eq\prime} = (\Delta_B^{5eq})_{4\text{-}t\text{-Bu}}$ is made, the simplified equation given in the text is obtained.

(14) This is equivalent to assuming that the location of Eu in the 2- and 4-alkylcyclohexanone complexes is the same. The best fit locations of the Eu from analysis[2d] of the complete LIS spectra of 4-*tert*-butylcyclohexanone and 2-methylcyclohexanone are indistinguishable.

(15) These values are independent of the binding constants of the axial and equatorial conformers of the free ketone. Equal binding constants are not assumed. To obtain the conformational equilibrium constant for the free ketone, the values for the two binding constants would be required. The similarity in the conformational equilibria for the free ketone models (Table I) and the complexed ketones suggests that the binding constants must be quite similar.

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(18) Alfred P. Sloan Research Fellow, 1969–1971.

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Transition States in Chromium(VI) Oxidation of Alcohols

Sir:

The structure of the transition state of chromic acid oxidation of alcohols to ketones has long been the subject of controversy.[1] The rapid formation of a chromate ester equilibrium in a two-step reaction mechanism was indicated both by direct[2] and indirect rate evidence.[3] This conclusion was strongly supported by subsequent work by Roček, *et al.*,[4] suggesting that with a highly hindered alcohol the rate-determining event can be diverted to the ester formation step. These and other authors[5,6] favored an acyclic mechanism in which the carbonyl product formation is largely complete (perhaps two-thirds to three-fourths of a carbonyl bond formed)[7a,8c] in the transition state, based on the normally large magnitude of the kinetic deuterium isotope effect and kinetic acceleration reflecting steric hindrance in the alcohol.[7–9] This mechanism has taken root in the literature and has been applied[8,9] as the basis for structural distinctions in alicyclic and bicyclic alcohols correlating with Cr(VI) oxidation rates. However, a mechanism involving a cyclic, concerted transition state for decomposition of the ester intermediate, in which the carbonyl product is just half-developed, has been advocated by Kwart and Francis[10,11] to account for the same type of rate data.

The kinetic deuterium isotope effect has often been applied[1,4] as a valid criterion for mechanistic identification in Cr(VI) oxidations. The recent demonstrations[12–14] that the symmetrical transition state in a variety of cyclic, concerted H-transfer processes could be verified through measurement of k_H/k_D as a function of temperature prompted us to apply this expanded criterion in evaluation of the mechanism of Cr(VI) oxidation of alcohols. Such measurements have now been carried out over a 45–60° range of temperatures using two different substrates, respectively, a typical alcohol (cyclohexanol) and a highly hindered alcohol (di-*tert*-butylcarbinol) exhibiting an essentially zero rate of bimolecular, carboxylic acid esterification.

The data for the unhindered alcohol listed in Table I, part A, and plotted in Figure 1a can be readily fitted to the familiar expression, $k_H/k_D = A_H/A_D \exp(-\Delta E_a/RT)$. They show direct correspondence with the properties of a symmetrical transition state in which the activation energy difference (ΔE_a) for k_H/k_D is equal to the zero-point energy difference for the respective C–H and C–D bonds (*ca.* 1 kcal/mol), and the frequency factors of the respective reactions are nearly identical (*i.e.*, $A_H/A_D \cong 1.0$ and $\Delta(\Delta S^{\ddagger}) \cong 0$). The graphs in Figure 1 also illustrate the coincidence of the so-called maximum isotope effect line with the experimental rate points for cyclohexanol-d_1 oxidation.[12–15] This theoretical line is calculated on the assumption that the k_H/k_D ratio stems only from the zero-point energy factor, $(\Delta E_0)_D{}^H$.

Rate data of entirely different character were ob-

Table I. Pseudo-First-Order Oxidation of ROH in 50% Aqueous Acetic Acid Solution[a]

(A) Cyclohexanol				(B) Di-*tert*-butylcarbinol			
Proteo		Deuterio		Proteo		Deuterio	
T, °K	10^2k, min^{-1}	T, °K	10^2k, min^{-1}	T, °K	10^2k, min^{-1}	T, °K	10^2k, min^{-1}
294.6	1.39	303.2	0.42	289.4	2.86	298.7	0.56
298.7	1.97	307.4	0.52	293.9	4.75	302.7	0.75
302.2	2.58	312.6	0.89	307.4	13.5	307.4	1.24
306.8	3.64	316.6	1.04	316.2	22.3	316.2	2.69
311.6	5.17	318.5	1.21	317.4	26.6	326.2	5.58
319.8	7.73	322.6	1.59	325.1	42.6	330.9	8.98
315.1	5.69	330.2	2.40	325.8	42.8	335.7	11.6
320.8	8.54	332.7	2.91	326.0	40.1	340.1	20.0
320.4	8.67	338.0	4.14	326.2	44.7	344.4	23.4
319.5	8.04	340.7	5.00	330.9	63.3	350.9	41.4
331.8	15.0	344.2	6.20	331.2	58.3		
340.2	25.2			334.8	76.8		
332.2	14.9			334.9	79.5		
348.7	44.0			339.4	110		
344.7	34.9			340.0	105		
345.7	35.3			344.9	165		
348.7	42.4			344.9	155		
				349.0	204		

	(A) Cyclohexanol		(B) Di-*tert*-butylcarbinol	
	Proteo	Deuterio	Proteo	Deuterio
E_a	12.6 ± 0.1	13.6 ± 0.1	14.1 ± 0.1	17.1 × 0.1
$-\Delta S^{\ddagger}$	27.5 ± 0.5	28.0 ± 0.7	20.3 ± 0.8	14.9 ± 0.9
A	3.27×10^7	2.44×10^7	1.22×10^9	18.4×10^9
R[b]	0.999	0.999	0.997	0.999

[a] At constant ionic strength ($NaClO_4$ = 0.20 M); acidity, H_0 = 0.658; h_0 = 0.220; $[Cr(VI)]_0 = 8.93 \times 10^{-4}$ M; rate = k[ROH]·[Cr(VI)]h_0. [b] The correlation coefficient.

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