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Conformational Analysis of 2-Alkylcyclohexanone-Lanthanide Chelate Complexes

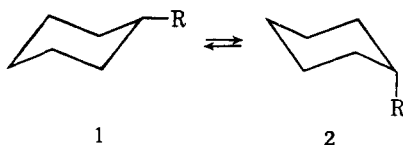
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Abstract: The effect of added $\text{Eu}(\text{fod})_3$ on the proton chemical shifts of 4-*tert*-butyl-, 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-*tert*-butylcyclohexanone has been analyzed to give the induced shift ratios for the two 5-position protons in the bound complex. Equations are derived for the use of induced shift ratios in conformational analysis and are used to obtain the conformational equilibrium constants for these substituted cyclohexanone-lanthanide chelate complexes. The factors responsible for the conformational preference of the 2-position alkyl groups are discussed.

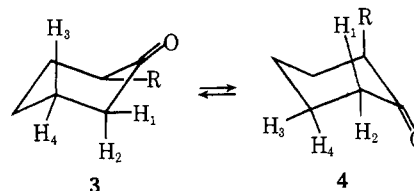
Proton nmr spectroscopy has been a widely used tool for structural,¹ stereochemical,¹ and conformational analysis.² One critical limitation in the application of this tool is often insufficient chemical shift difference between protons in stereochemically different environments.² Hinckley's³ observation that the dipyrindine adduct of tris(dipivaloyl-methanato)europium(III) caused large differential shifts in the proton nmr spectrum of molecules containing a Lewis base functionality held the promise of a way around this limitation. During the intervening years since Hinckley's observation, the efficiency,⁴ understanding,⁵ and application⁵ of shift reagents has been greatly advanced by the many reports of the use of these reagents for structural,⁶ stereochemical,⁷ and conformational analysis.⁸

Nmr spectroscopy is particularly useful for conformational analysis of molecules in dynamic equilibrium.² A classic example is the chair-chair equilibrium of a substituted cyclohexane:



Proton nmr spectroscopy provides several methods for determining the mole fractions of **1** and **2** at equilibrium. The observed vicinal coupling constants for the equilibrium mixture are the mole fraction weighted averages of the characteristic coupling constants for each of the conformers. Similarly, the observed proton chemical shifts for the equilibrium mixture are the mole fraction weighted averages of the characteristic chemical shifts for the protons in each of the conformers. The choice of a suitable model compound from which characteristic chemical shifts and coupling constants can be obtained is a critical step in the application of this method. Regardless of which approach is used, sufficient spectral clarity is required so that coupling constant or chemical shift data may be readily and accurately obtained. An example in which this is not the case is provided by the nmr spectra of 2-alkylcyclohexanones.⁹

Although 2-alkylcyclohexanones (alkyl = Me, Et, *i*-Pr, and *t*-Bu) are known to undergo rapid ring inversion² (**3** \rightleftharpoons **4**), the complexity of the nmr spectra of these ketones pre-



cludes determination of the equilibrium constant by nmr spectroscopy. The conformational preference of a 2-alkyl group has been studied by base epimerization of the *cis* or *trans* isomers of either 2-alkyl-4-*tert*-butylcyclohexanones¹⁰ or 2,6-dialkylcyclohexanones¹¹ (alkyl = Me, Et, *i*-Pr, and *t*-Bu). In each case, a blocking group was required to fix the stereochemistry of the cyclohexanone ring.

The successful application of lanthanide shift reagents to structural studies suggested that they might also be used to study problems involving dynamic equilibria. The ring inversion of 2-alkylcyclohexanones seemed to be a good problem on which to test this approach. The nmr spectra of the ketones are complex, the molecules contain the necessary basic functionality, there are only two isomers present at equilibrium, and the necessary model compound, 4-*tert*-butylcyclohexanone, is readily available.

Recently, we reported¹² preliminary results on the use of relative induced shifts to determine mole fractions of the axial and equatorial conformers of the 2-alkylcyclohexanones. We now report a more complete study of the 2-alkylcyclohexanone equilibria using lanthanide shift reagents. In the following paper, the application of lanthanide shift reagents to the determination of the rotational conformation of the 2-alkyl side chain of the *cis* and *trans* isomers of 2-ethyl- and 2-isopropyl-4-*tert*-butylcyclohexanone is reported.¹³

Results

The cyclohexanones used in this study were prepared by

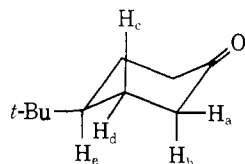
routes analogous to literature procedures. Structural assignments were confirmed using nmr spectroscopy on samples containing lanthanide shift reagents, either $\text{Eu}(\text{fod})_3\text{-}d_{27}$ or $\text{Pr}(\text{fod})_3$. Enough shift reagent was added to obtain a well-resolved spectrum. No effort was made to determine the amount of shift reagent added to obtain these spectra.

The multiplet assignments for 4-*tert*-butylcyclohexanone in the presence of $\text{Pr}(\text{fod})_3$ are as follows: δ -6.3 (d, $J = 14$ Hz, 2-equatorial); -4.5 (t, $J = 13$ Hz, of d, $J = 5.9$ Hz, 2-axial); -2.4 (q, $J = 13$ Hz of d, $J = 3.1$ Hz, 3-axial); -1.4 (t, $J = 13$ Hz, of t, $J = 2.9$ Hz, 4-axial); -0.3 (br m, 3-equatorial). These assignments are based on the fact that the protons closest to the carbonyl should shift furthest upon addition of shift reagent and upon the basis of the following decoupling experiments. Irradiation of the multiplet at δ -6.3 caused the multiplet at δ -4.1 to collapse to a doublet ($J = 13$ Hz) of doublets ($J = 5.9$ Hz) and the multiplet at δ -2.4 to collapse to a quartet ($J = 13$ Hz); irradiation of the multiplet at δ -4.1 resulted in the collapse of the multiplet at δ -6.3 to a broadened singlet and the multiplet at δ -2.4 to a triplet ($J = 13$ Hz) of doublets ($J = 3.1$ Hz); irradiation of the multiplet at δ -2.4 resulted in the collapse of the multiplet at δ -4.1 to a doublet ($J = 14$ Hz) of doublets ($J = 5.9$ Hz); irradiation of the multiplet at δ -0.3 caused the multiplet at δ -2.4 to collapse to a broadened triplet ($J = 13$ Hz) and the multiplet at δ -4.1 to collapse to a triplet ($J = 13$ Hz).

Multiplet assignments for 4-*tert*-butylcyclohexanone in the presence of $\text{Eu}(\text{fod})_3$ are as follows: δ 11.7 (2-equatorial), 10.5 (2-axial), 5.5 (3-axial); 4.8 (4-axial and 3-equatorial).

The coupling constants between the ring protons of 4-*tert*-butylcyclohexanone as determined from the nmr spectrum of the ketone in the presence of $\text{Pr}(\text{fod})_3$ are tabulated in Table I. The values of the coupling constants between the

Table I. Coupling Constants of 4-*tert*-Butylcyclohexanone^a



$J_{a,b} = 14.8$	$J_{c,d} = 13.5$
$J_{b,d} = 5.9$	$J_{e,e} = 11.9$
$J_{b,c} = 13.2$	$J_{d,e} = 2.9$
$J_{a,c} = 2.9$	$J_{a,d} = 1.2^b$

^a Obtained in the presence of $\text{Pr}(\text{fod})_3$ (0.1120 g), absolute values in hertz. ^b Obtained by computer analysis using LACON III program.

2-equatorial and the 3-equatorial protons and between the 3-axial and 3-equatorial protons could not be obtained directly from the nmr spectra; attempts to completely decouple the 3-axial and 3-equatorial protons from the other ring protons were not successful. Broadening by the lanthanide of the multiplet corresponding to the 2-equatorial proton prevented the determination of the value of the coupling constant between the 2-equatorial and the 3-equatorial protons from this multiplet.

Values for these coupling constants were obtained by determining those values which gave the best fit to the experimental spectra using the LACON III computer program. The best fit was obtained when the 2-equatorial to 3-equatorial coupling constant was set equal to 1.2 Hz, and the 3-axial to 3-equatorial coupling constant was set equal to 13.5 Hz.

The nmr spectra for 2-methyl- and 2-ethylcyclohexanone

in the presence of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ were assigned by analogy to the assignments of 4-*tert*-butylcyclohexanone. For 2-methylcyclohexanone assignments were as follows: (10% v/v TMS in CDCl_3) δ 11.6 (br d, $J = 14$ Hz, 6-equatorial); 10.0 (m, 2- and 6-axial); 7.0 (d, $J = 7$ Hz, methyl group); 5.9 (q, $J = 13$ Hz, of d, $J = 4$ Hz, 3-axial); 5.5 (q, $J = 13$ Hz, of t, $J = 4$ Hz, 5-axial); 5.2 (m, 3-equatorial); 4.7 (m, 4-axial and 5-equatorial); 4.2 (m, 4-equatorial). For 2-ethylcyclohexanone assignments were as follows: δ 13.9 (d, $J = 14$ Hz, of t, $J = 3.75$ Hz, 6-equatorial); 12.7 (m, 2- and 6-axial); 11.8 (sextet, $J = 7$ Hz, methylene proton on ethyl side chain); 8.7 (sextet, $J = 7$ Hz, methylene proton on ethyl side chain); 7.4 (q, $J = 13$ Hz, of d, $J = 4$ Hz, 3-axial); 6.5 (br q, $J = 13$ Hz, 5-axial); 6.2 (m, 3-equatorial); 5.3 (m, 5-equatorial and 4-axial); 4.9 (m, 4-equatorial); 4.8 (t, $J = 7$ Hz, methyl group of ethyl side chain).

For 2-methyl- and 2-ethylcyclohexanone, only a few of the coupling constants between the ring protons could be accurately determined. These are listed in Table II. The

Table II. Coupling Constants (Hz) of 2-Methyl- and 2-Ethylcyclohexanone

	2-Methyl	2-Ethyl
$(J_{1,3} + J_{1,4})/2$	3.45 ^a	3.75 ^a
$J_{2,3}$	12.7 ^{b,c}	
$J_{1,3}$	2.95 ^{c,d}	

^a Obtained in the presence of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ (0.1044 g). ^b Obtained from the multiplet corresponding to 3 H_{ax} . ^c Obtained in the presence of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ (0.1815 g). ^d Obtained from the multiplet corresponding to 3 H_{ax} . ^e Obtained in the presence of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ (0.1264 g).

rest of the coupling constants could not be determined from the spectra. Only the average of the couplings between the 6-equatorial and the 5-axial and 5-equatorial protons could be measured since the individual coupling constants could not be resolved in the multiplet corresponding to the 6-equatorial proton. These couplings could not be determined from the multiplets corresponding to the 5-equatorial and 5-axial protons because of the complex splitting patterns for these protons. No coupling constant information could be obtained from the 2-axial and 6-axial protons, because these two multiplets overlapped one another. Increasing the shift reagent concentration did not lead to a separation of these multiplets.

Multiplet assignments for 2-isopropylcyclohexanone in the presence of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ are as follows: (10% v/v TMS in CDCl_3) δ 12.7 (d, $J = 14$ Hz, of t, $J = 5$ Hz, 6-equatorial); 11.6 (m, 2- and 6-axial); 10.9 (m, $J = 7$ Hz, methine proton on isopropyl side chain); 6.8 (q, $J = 10$ Hz of t, $J = 4$ Hz, 3-axial); 6.0 (m, 3- and 5-axial); 5.4-4.8 (m, 5-axial, 5-equatorial, 4-axial, and 4-equatorial); 5.1 (d, $J = 7$ Hz, methyl group on isopropyl side chain); 4.9 (d, $J = 7$ Hz, methyl group on isopropyl side chain).

Multiplet assignments for 2-*tert*-butylcyclohexanone in the presence of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ are as follows: (10% v/v TMS in CDCl_3) δ 9.6 (br d, $J = 14$ Hz, 6-equatorial); 8.5 (t, $J = 12$ Hz, of d, $J = 6$ Hz, 6-axial); 8.2 (d, $J = 12$ Hz, of d, $J = 5$ Hz, 2-axial); 5.6 (q, $J = 12$ Hz, of d, $J = 4$ Hz, 3-axial); 5.0-4.2 (m, 5-axial, 3-equatorial, and 4-axial); 4.4-3.9 (m, 5-equatorial and 4-equatorial).

The effect of the addition of $\text{Eu}(\text{fod})_3\text{-}d_{27}$ on the chemical shifts of the 5-equatorial and 5-axial protons of 4-*tert*-butylcyclohexanone and the 2-alkylcyclohexanones was studied by diluting a weighed amount of shift reagent with aliquots of a deuteriochloroform solution of the ketone. Proton chemical shifts were determined from the spectrum for

Table III. Chemical Shift Data for 4-*tert*-Butyl- and 2-Alkylcyclohexanones in the Presence of Eu(fod)₃-d₂₇^a

Eu(fod) ₃ , mol/l.	[C=O], mol/l.	H ^{5ax}	H ^{5eq}	Σ
2-Ethylcyclohexanone				
0.240	0.498	4.44	4.02	8.46
0.390	0.498	5.74	4.97	10.71
0.575	0.498	6.63	5.55	12.18
0.747	0.498	6.90	5.80	12.70
0.975	0.498	7.22	6.04	13.26
0.238	0.441	4.71	4.23	8.94
2- <i>tert</i> -Butylcyclohexanone				
0.950	1.150	5.55	4.44	9.99
0.477	0.577	5.34	4.31	9.65
0.318	0.385	5.23	4.23	9.46
0.239	0.289	5.08	4.13	9.21
0.212	0.257	4.81	3.93	8.74
0.147	0.178	4.63	3.81	8.44
0.326	0.326	6.00	4.75	10.75
2-Methylcyclohexanone				
1.000	1.340	4.50	4.01	8.51
0.667	0.893	4.36	3.95	8.28
0.500	0.670	4.26	3.84	8.10
0.400	0.536	4.19	3.77	7.96
0.333	0.447	4.13	3.72	7.85
0.286	0.383	4.09	3.68	7.77
0.340	0.508	5.48	4.68	10.16
0.508	0.524	6.11	5.14	11.25
2-Isopropylcyclohexanone				
0.520	0.501	5.71	4.77	10.48
0.348	0.337	5.65	4.73	10.38
0.348	0.337	5.61	4.69	10.30
0.261	0.252	5.53	4.61	10.14
0.209	0.202	5.43	4.55	9.98
0.174	0.168	5.32	4.46	9.78
0.237	0.168	5.95	4.99	10.94
0.257	0.349	4.42	3.76	8.18
4- <i>tert</i> -Butylcyclohexanone				
		H ^{3ax}	H ^{3eq}	
0.208	0.460	4.04	3.84	7.88
0.355	0.460	5.55	4.75	10.30
0.572	0.460	6.37	5.25	11.62
0.740	0.460	6.72	5.55	12.27
0.975	0.460	6.90	5.60	12.50
0.042	0.423	1.88	2.37	4.25
0.103	0.423	3.15	3.15	6.30
0.169	0.423	4.33	3.93	8.26
0.221	0.423	4.97	4.30	9.27

^a In parts per million.

each of these solutions. These chemical shifts as a function of the concentrations of ketone and Eu(fod)₃-d₂₇ are recorded in Table III.

The effect of added Eu(fod)₃-d₂₇ on the proton chemical shifts of 2-butanone was also studied. A weighed amount of Eu(fod)₃-d₂₇ was successively diluted with a deuteriochloroform solution of the ketone containing various amounts of methanol. Proton chemical shifts (at 60 MHz) were determined from the spectrum of each of these solutions. These chemical shifts as a function of the concentrations of 2-butanone and Eu(fod)-d₂₇ are reported in Tables IV-VI.

Discussion

Although the proton nmr spectra of 2-alkylcyclohexanones cannot be directly analyzed, the addition of Pr(fod)₃ produces sufficient spectral simplification to allow most of the coupling constants between the ring protons to be obtained. For the equilibrium between the R-equatorial isomer, **3**, and the R-axial isomer, **4**, the observed vicinal coupling constants $J_{1,3}$, $J_{1,4}$, $J_{2,3}$, and $J_{2,4}$ should be the

Table IV. Proton Chemical Shifts for 2-Butanone in the Presence of Eu(fod)₃-d₂₇

2-Butanone, μmol	Eu(fod) ₃ , μmol	CH ₂ , ppm	CH ₃ , ppm	CH ₃ , ppm	Σ, ppm
22.32	8.70	9.33	9.00	5.72	24.05
27.90	8.70	9.21	8.90	5.67	23.78
41.86	8.70	8.82	8.50	5.37	22.68
69.76	8.70	7.80	7.80	4.90	20.50
97.66	8.70	6.33	6.07	3.72	16.12
15.91	53.05	14.82	14.40	9.38	38.60
21.49	53.05	14.83	14.47	9.42	38.72
26.51	53.05	14.80	14.43	9.38	38.62
36.55	53.05	14.77	14.38	9.37	38.52
46.04	53.05	14.57	14.23	9.25	38.05
66.12	53.05	14.23	13.90	9.01	37.14
86.21	53.05	14.20	13.83	9.00	37.03
96.25	53.05	13.72	13.37	8.67	35.75
107.4	53.05	12.82	12.53	8.08	33.43
118.6	53.05	11.92	11.65	7.48	31.05

Table V. Proton Chemical Shifts for 2-Butanone in the Presence of Eu(fod)₃-d₂₇, for a Methanol:2-Butanone Ratio of 1.26

2-Butanone, μmol	Eu(fod) ₃ , μmol	CH ₂ , ppm	CH ₃ , ppm	CH ₃ , ppm	Σ, ppm
8.639	0.9813	2.70	2.40	1.23	6.33
8.682	1.963	3.02	2.73	1.47	7.22
8.725	2.944	3.43	3.15	1.75	8.33
8.766	3.925	3.70	3.42	1.93	9.05
8.811	4.906	4.20	3.97	2.30	10.47
8.854	5.888	4.50	4.23	2.48	11.22
7.45	4.906	4.57	4.27	2.48	11.32
8.897	6.869	5.13	4.85	2.90	12.88
7.54	6.868	5.57	5.30	3.20	14.07
7.58	7.850	6.03	5.77	3.52	15.32
7.63	8.831	6.60	6.33	3.90	16.83
7.71	10.79	7.40	7.13	4.45	18.98
7.81	12.76	8.13	7.85	4.93	20.92
7.88	14.72	8.76	8.47	5.18	22.42
9.348	17.17	9.43	9.17	5.83	24.43
9.434	19.13	9.83	9.57	6.10	25.50
9.542	21.59	10.33	10.03	6.43	26.80
9.649	24.04	10.63	10.37	6.63	27.63
9.756	26.49	10.97	10.67	6.85	28.48
9.864	28.95	11.22	10.93	7.01	29.17
10.08	33.85	11.53	11.23	7.21	29.98

weighted averages of the coupling constants in the absence of inversion.²

$$J_{1,3}^{\text{obsd}} = n_3 J_{\text{H}_{6\text{eq}}, \text{H}_{5\text{ax}}} + n_4 J_{\text{H}_{6\text{ax}}, \text{H}_{5\text{eq}}}$$

$$J_{1,4}^{\text{obsd}} = n_3 J_{\text{H}_{6\text{eq}}, \text{H}_{5\text{eq}}} + n_4 J_{\text{H}_{6\text{ax}}, \text{H}_{5\text{ax}}}$$

$$J_{2,3}^{\text{obsd}} = n_3 J_{\text{H}_{6\text{ax}}, \text{H}_{5\text{ax}}} + n_4 J_{\text{H}_{6\text{eq}}, \text{H}_{5\text{eq}}}$$

$$J_{2,4}^{\text{obsd}} = n_3 J_{\text{H}_{6\text{ax}}, \text{H}_{5\text{eq}}} + n_4 J_{\text{H}_{6\text{eq}}, \text{H}_{5\text{ax}}}$$

n_3 and n_4 are the mole fractions of **3** and **4**. If the coupling constants in the absence of inversion are set equal to the observed coupling constants of 4-*tert*-butylcyclohexanone, the equilibrium concentrations of the R-axial and R-equatorial isomers can be determined. The calculated values of n_3 for 2-methyl- and 2-ethylcyclohexanone are given in Table VII together with values reported in the literature.¹⁰

The use of the different observed vicinal coupling constants for the analysis produces somewhat different values for the calculated equilibrium ratio. As already noted, individual values of $J_{1,3}$ and $J_{1,4}$ could not be obtained for 2-methyl- and 2-ethylcyclohexanone. The averaged value, $(J_{1,3} + J_{1,4})/2$, which was determined, was small for both 2-methylcyclohexanone (3.45 Hz) and for 2-ethylcyclohexanone (3.75 Hz). In the analysis, multiplication of the average value of the two coupling constants, $J_{\text{H}_{6\text{eq}}, \text{H}_{5\text{ax}}}$ and

Table VI. Proton Chemical Shifts for 2-Butanone in the Presence of Eu(fod)₃-d₂₇, for a Methanol: 2-Butanone Ratio of 2.72

2-Butanone, μmol	Eu(fod) ₃ , μmol	CH ₂ , ppm	CH ₃ , ppm	CH ₃ , ppm	Σ, ppm
8.565	5.192	4.45	4.18	2.43	11.07
8.676	7.269	5.53	5.27	3.18	13.98
8.759	8.826	6.20	5.92	3.62	15.73
8.842	10.38	6.28	6.02	3.70	16.00
8.703	7.788	6.33	6.07	3.73	16.13
8.786	9.346	7.03	6.72	4.17	17.91
8.952	12.46	7.67	7.40	4.67	19.73
9.035	14.02	8.00	7.73	4.85	20.58
9.118	15.58	8.87	8.60	5.45	22.92
9.201	17.13	8.93	8.67	5.50	23.10
9.284	18.69	9.00	8.73	5.57	23.30
9.422	21.29	9.10	8.83	5.63	23.57
38.68	56.51	9.83	9.67	6.15	25.65
33.16	56.51	10.60	10.42	6.65	27.67
22.10	56.51	11.47	11.23	7.22	29.92
16.58	56.51	13.42	13.08	8.50	35.00
11.05	56.51	14.15	13.80	8.97	36.92

Table VII. Conformational Analysis of 2-Methyl- and 2-Ethylcyclohexanone Using Vicinal Coupling Constants

	Coupling constant		100% R-ax		100% R-eq		n-eq	
	obsd				Calcd ^a	Lit. ^{b,c}		
2-Methylcyclohexanone								
(J _{1,3} + J _{1,4})/2	3.45	9.55	2.05		0.81	0.93		
J _{2,3}	12.7	1.2	13.2		0.96	0.93		
J _{1,3}	2.95	5.9	2.9		0.98	0.93		
2-Ethylcyclohexanone								
(J _{1,3} + J _{1,4})/2	3.75	9.55	2.05		0.79	0.86		

^a At 31.9°. ^b At 25.0°. ^c N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.*, **83**, 994 (1961).

$J_{H_{6eq},H_{5eq}}$ for 4-*tert*-butylcyclohexanone (2.05 Hz) which has a large relative uncertainty (about 10%) by n_3 which is presumably large¹⁰ leads to a large relative error in n_3 . Since the multiplets corresponding to the 2-axial and 6-axial protons in both 2-methyl- and 2-ethylcyclohexanone overlapped, the presumably large couplings, $J_{2,3}$ and $J_{2,4}$, could not be determined directly.

A commonly encountered difficulty in attempts to use coupling constant data for conformational analysis occurs when the fraction of one of the isomers becomes large. In these circumstances, the choice of model compound becomes particularly critical. If, for example, the value of $J_{H_{6eq},H_{5ax}}$ were 2.8 Hz rather than 2.9 Hz as determined for 4-*tert*-butylcyclohexanone, then the mole fraction of the R-axial isomer would be 0.09 rather than the 0.02 calculated. Uncertainties of this magnitude in the coupling constants would not be unexpected. The coupling constants for the protons adjacent to the carbonyl group in camphor and in 3,3,5-trimethyl-3-(*p*-chlorophenyl)cyclohexanone have been shown to vary upon addition of Eu(dpm)₃ and Eu(fod)₃.¹⁴

As a result of the rapid association-dissociation rate of the substrate-lanthanide chelate complex, the observed chemical shift for any proton of the substrate in the presence of the lanthanide chelate, δ_{obsd} , will be an average value of its chemical shift in the uncomplexed ketone, δ_O , and its chemical shift in the substrate-lanthanide chelate complex, $\Delta_B + \delta_O$.¹⁵ Thus

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

where F is the fraction of substrate present as complex. Several methods have been reported for obtaining intrinsic

induced shifts, Δ_B , from the dependence of the observed shift on the concentrations of the substrate and the lanthanide chelate.¹⁶ These procedures require that the substrate and reagent concentrations be accurately known and that competitive scavengers be scrupulously excluded.

For many applications, only the intrinsic induced shifts and not the substrate-lanthanide chelate complexation constant is of primary interest. We have shown that for any two (or more) protons, H_a and H_b, of the same substrate the ratio of induced shifts, $\Delta_B^{H_a}/(\Delta_B^{H_a} + \Delta_B^{H_b})$ can be directly and simply determined from a plot of $\delta_{obsd}^{H_a}$ vs. ($\delta_{obsd}^{H_a} + \delta_{obsd}^{H_b}$) for each of the different solutions with different substrate or reagent concentrations.¹²

In order to evaluate the usefulness of this procedure, we have determined the lanthanide induced shift ratios for 2-butanone in the presence of varying amounts of methanol as a scavenger. For solutions with molar ratios of methanol to 2-butanone of 0.0, 1.26, and 2.72, the plots of $\delta_{obsd}^{H_i}$ vs. $\sum_{i=1}^n \delta_{obsd}^{H_i}$ were linear over the entire lanthanide chelate concentration range studied with slopes which were independent of the methanol concentration. The induced shift ratios determined from these plots are given in Table VIII.

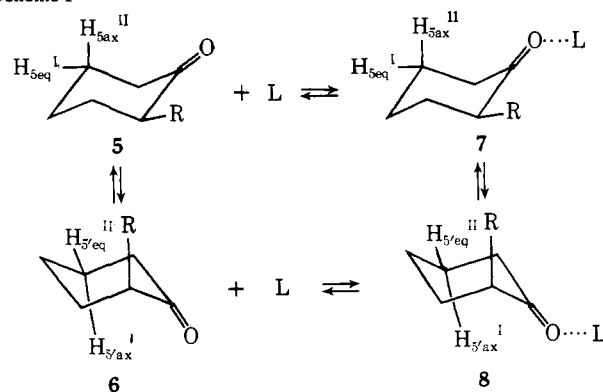
Table VIII. Lanthanide Induced Shift Ratios for 2-Butanone with and without Added Methanol^{b,c}

[MeOH]/[C=O]	$\Delta_B^{1-H}/\Sigma\Delta_B^a$	$\Delta_B^{3-H}/\Sigma\Delta_B$	$\Delta_B^{4-H}/\Sigma\Delta_B$
0.00	0.3721 ±0.0008	0.3757 ±0.0008	0.2522 ±0.0005
1.26	0.3730 ±0.0005	0.3734 ±0.0005	0.2525 ±0.0003
2.72	0.3733 ±0.0007	0.3734 ±0.0007	0.2528 ±0.0005

^a 1-H, 3-H, and 4-H represent the hydrogens on C₁, C₃, and C₄ of 2-butanone. $\Sigma\Delta_B$ represents the sum of the induced shifts of 1-H, 3-H, and 4-H. ^b Eu(fod)₃-d₂₇ was the shift reagent used. Solvent was deuteriochloroform. ^c The slopes were determined by the method of least-squares. The errors are standard deviations.

It appears from these results that the induced shift ratios can be determined with a high degree of precision and that no special precautions to exclude scavengers need be taken.^{17,18}

For a conformationally mobile 2-alkylcyclohexanone, the R-axial and R-equatorial isomers of both the free ketone and the ketone-lanthanide chelate complex will be present simultaneously in solution (Scheme I).

Scheme I

$$n_{eq} = [5]/([5] + [6]) \quad n'_{eq} = [7]/([7] + [8])$$

$$F = ([7] + [8])/([5] + [6] + [7] + [8])$$

The observed chemical shifts of H^I and H^{II} in the presence of a particular concentration of lanthanide shift re-

Table IX. Conformational Equilibria for 2-Alkylcyclohexanones and Alkylcyclohexanes

R	Relative induced shifts		ΔG^a	Base interconversion		
	$\left[\frac{\Delta_B^{5eq}}{\Delta_B^{5eq} + \Delta_B^{5ax}} \right]_{av}$	% eq		II ΔG^b	III ΔG^c	IV ΔG^f
Me	0.415 ± 0.003^d	89.7 ^e	-1.33	-1.82	-1.51	-1.60
Et	0.424 ± 0.005	85.5	-1.05	-1.21	-1.06	-1.77
<i>i</i> -Pr	0.443 ± 0.001	76.6	-0.71	-0.56	-0.57	-2.25
<i>t</i> -Bu	0.408 ± 0.002	93.0	-1.57	-1.52	-1.61	> -4.2 ^g

^a From relative shifts of H_{3a} and H_{3e} induced by Eu(fod)₃ in CDCl₃ at 31.9°. ^b B. Rickborn, *J. Amer. Chem. Soc.*, **84**, 2414 (1962). Base was NaOMe in MeOH, at 25.0°. ^c N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.*, **83**, 994 (1961); at 25.0°. ^d Errors are standard deviations from least-squares analysis. ^e Estimated errors are $\pm 0.3\%$. ^f A. H. Lewis and S. Winstein, *J. Amer. Chem. Soc.*, **84**, 2464 (1962). ^g N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960).

agent will be the weighted averages of their chemical shifts in each of the four species in equilibrium:

$$\delta_{\text{obsd}}^{\text{H}^{\text{I}}} = n_{\text{eq}}\delta_{\text{O}}^{5\text{eq}} + n_{\text{ax}}\delta_{\text{O}}^{5'\text{ax}} + F(n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}) \quad (1a)$$

$$\delta_{\text{obsd}}^{\text{H}^{\text{II}}} = n_{\text{eq}}\delta_{\text{O}}^{5\text{ax}} + n_{\text{ax}}\delta_{\text{O}}^{5'\text{eq}} + F(n'_{\text{eq}}\Delta_{\text{B}}^{5\text{ax}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{eq}}) \quad (1b)$$

Simultaneous solution of these two equations by eliminating F gives, after rearrangement, eq 2. The averaged induced

$$\delta_{\text{obsd}}^{\text{H}^{\text{I}}} = n_{\text{eq}}\delta_{\text{O}}^{5\text{eq}} + n_{\text{ax}}\delta_{\text{O}}^{5'\text{ax}} + (\delta_{\text{obsd}}^{\text{H}^{\text{I}}} + \delta_{\text{obsd}}^{\text{H}^{\text{II}}}) \times \left[\frac{n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}}{n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{eq}} + n'_{\text{eq}}\Delta_{\text{B}}^{5\text{ax}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}} \right] - (n_{\text{eq}}\delta_{\text{O}}^{5\text{eq}} + n_{\text{eq}}\delta_{\text{O}}^{5\text{ax}} + n_{\text{ax}}\delta_{\text{O}}^{5'\text{ax}} + n_{\text{ax}}\delta_{\text{O}}^{5'\text{eq}}) \times \left[\frac{n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}}{n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{eq}} + n'_{\text{eq}}\Delta_{\text{B}}^{5\text{ax}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}} \right] \quad (2)$$

shift ratio, $(\Delta_{\text{B}}^{\text{H}^{\text{I}}}/\Delta_{\text{B}}^{\text{H}^{\text{I}}} + \Delta_{\text{B}}^{\text{H}^{\text{II}}})_{av}$, then is the slope of the plot of $\delta_{\text{obsd}}^{\text{H}^{\text{I}}}$ vs. $(\delta_{\text{obsd}}^{\text{H}^{\text{I}}} + \delta_{\text{obsd}}^{\text{H}^{\text{II}}})$ for the various solutions (eq 3). If it is assumed that the induced shifts for the

$$\left(\frac{\Delta_{\text{B}}^{\text{H}^{\text{I}}}}{\Delta_{\text{B}}^{\text{H}^{\text{I}}} + \Delta_{\text{B}}^{\text{H}^{\text{II}}}} \right)_{av} = \frac{n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}}{n'_{\text{eq}}\Delta_{\text{B}}^{5\text{eq}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{eq}} + n'_{\text{eq}}\Delta_{\text{B}}^{5\text{ax}} + n'_{\text{ax}}\Delta_{\text{B}}^{5'\text{ax}}} \quad (3)$$

5-position protons are not dependent on the location of the alkyl substituent group, *i.e.*, $\Delta_{\text{B}}^{5\text{eq}} = \Delta_{\text{B}}^{5'\text{eq}}$ and $\Delta_{\text{B}}^{5\text{ax}} = \Delta_{\text{B}}^{5'\text{ax}}$, then the following simplified relationship is obtained (eq 4).

$$\left(\frac{\Delta_{\text{B}}^{\text{H}^{\text{I}}}}{\Delta_{\text{B}}^{\text{H}^{\text{I}}} + \Delta_{\text{B}}^{\text{H}^{\text{II}}}} \right)_{av} = n'_{\text{eq}} \left(\frac{\Delta_{\text{B}}^{5\text{eq}}}{\Delta_{\text{B}}^{5\text{eq}} + \Delta_{\text{B}}^{5\text{ax}}} \right) + n'_{\text{ax}} \left(\frac{\Delta_{\text{B}}^{5\text{ax}}}{\Delta_{\text{B}}^{5\text{eq}} + \Delta_{\text{B}}^{5\text{ax}}} \right) \quad (4)$$

For a conformationally mobile cyclohexanone, the concentration ratio of the two isomers in equilibrium can then be determined from the averaged induced shift ratio and characteristic values of the induced shift ratio for each of the isomers.

The ratio of the induced shifts for the 5-equatorial and 5-axial protons were chosen for use in this conformational analysis. These protons are not adjacent to the carbonyl

moiety, and consequently any contact contribution to the induced shift should be minimal.¹⁹ In addition, these two protons are located in sites which are stereochemically very different with respect to the carbonyl complexation site. For each of the 2-alkylcyclohexanones, $\delta_{\text{obsd}}^{5\text{eq}}$ was found to be a linear function of $(\delta_{\text{obsd}}^{5\text{eq}} + \delta_{\text{obsd}}^{5\text{ax}})$ over the entire range of ketone and Eu(fod)₃ concentrations. The slopes of these lines were therefore assumed to be the average induced shift ratios, $[\Delta_{\text{B}}^{5\text{eq}}/(\Delta_{\text{B}}^{5\text{eq}} + \Delta_{\text{B}}^{5\text{ax}})]_{av}$, for the 5-equatorial protons in these alkylcyclohexanone-Eu(fod)₃ complexes. The induced shift ratios for 4-*tert*-butylcyclohexanone were assumed to be the characteristic relative shifts for the 5-position protons in the absence of conformational averaging. These characteristic induced shift ratios were used together with the average induced shift ratios for the 2-alkylcyclohexanones to determine the mole fractions of equatorial, n'_{eq} , and axial, n'_{ax} , conformers of the complexed ketone. The observed induced shift ratios, the per cent 2-alkyl equatorial isomer and the conformational free-energy difference between the 2-alkyl equatorial and 2-alkyl axial isomers are collected in Table IX. For comparison, the conformational free-energy differences between the *cis* and *trans* isomers of 2-alkyl-4-*tert*-butylcyclohexanones and of 2,6-dialkylcyclohexanones are included.^{10,11}

Conformational analysis using induced shift ratios, and all other methods using lanthanide induced shifts, provides no direct information on the conformation of the uncomplexed substrate. If the complexation equilibrium constants, $K_{5,7}$ and $K_{6,8}$ were known, the conformational equilibrium constant, $K_{5,6}$, could of course be calculated. The reported free-energy differences for 2-alkyl-4-*tert*-butylcyclohexanones and 2,6-dialkylcyclohexanones are nearly identical with the conformational free-energy differences that we have determined for the 2-alkylcyclohexanone-Eu(fod)₃ complexes. The agreement between the free energies obtained by the induced shift ratio method and those obtained by the base equilibration methods is as good as the two base equilibration methods. This agreement strongly implies that the conformational preference of a 2-alkyl group is nearly the same in the free ketone and in the complexed ketone. If the conformational preferences in the free ketone and the complexed ketone are indeed identical, then the two complexation equilibrium constants must also be identical.

In order to derive eq 4, the induced shifts for the 5-position protons were assumed to be independent of the axial or equatorial location of the 2-alkyl group. The validity of this assumption could be checked by comparing the induced shifts of the 5-position protons of the *cis* and *trans* isomers of the 2-alkyl-4-*tert*-butylcyclohexanones. Each of these

Table X, Shift Ratios for the 3- and 5-Position Protons of the 2-Alkyl-4-*tert*-butylcyclohexanone

	2-Alkyl groups							
	H	Cis			Trans			
		Me	Et	<i>i</i> -Pr	<i>t</i> -Bu	Me	Et	<i>i</i> -Pr
$\Delta^{\delta_{\text{eq}}}$	0.393	0.402	0.379	0.365	0.333	0.410	0.391	0.388
$\Delta^{\delta_{\text{eq}}} + \Delta^{\delta_{\text{ax}}}$	± 0.003	± 0.01	± 0.002	± 0.001	± 0.01	± 0.004	± 0.003	± 0.007
$\Delta^{\delta_{\text{ax}}}$	0.393	0.413	0.394	0.419	0.405	0.464	0.434	0.403
$\Delta^{\delta_{\text{ax}}} + \Delta^{\delta_{\text{ax}}}$	± 0.003	± 0.05	± 0.004	± 0.008	± 0.001	± 0.003	± 0.002	± 0.005

molecules would be expected to be conformationally homogeneous since the 4-*tert*-butyl group should remain in the equatorial position. While determination of the absolute induced shifts is not convenient, the induced shift ratios are easily obtained.²⁰ A study of the induced shift ratios for all protons of the *cis* and *trans* isomers of 2-alkyl-4-*tert*-butylcyclohexanones has been completed using Yb(dpm)₃. The induced shift ratios for the 5-position and the 3-position protons are collected in Table X. Although the induced shift ratios are largely independent of the 2-axial or 2-equatorial location of the 2-alkyl group, the values for different alkyl groups differ by more than the standard deviations of the determinations in the case of the *cis*-2-isopropyl- and the *cis*-2-*tert*-butyl-4-*tert*-butylcyclohexanones. With these two exceptions, the assumed constancy of $\Delta_B^{\delta_{\text{eq}}}/(\Delta_B^{\delta_{\text{eq}}} + \Delta_B^{\delta_{\text{ax}}})$ appears to be adequately justified. An uncertainty as large as 0.01 in the induced shift ratios would lead to a 5% uncertainty in the conformational equilibrium data reported in Table IX.

The source of the apparent discrepancies for the *cis*-2-isopropyl and the *cis*-2-*tert*-butyl derivatives is not clear. For these compounds, the 5-position protons are among the least shifted of the ring protons and because of line broadening by Yb(dpm)₃ are among the most difficult to assign. The presence of bulky groups at both the 2- and 4-positions may also be responsible for the observed differences. Based on optical rotatory dispersion studies, the 2,4-substitution pattern has been suggested to distort the geometry of the cyclohexanone ring.²¹ Since ring geometry distortion should be larger in the *trans*-2,4-disubstituted cyclohexanones, one might have expected any deviations to appear in the *trans* series rather than in the *cis* series as observed.

In contrast to the conformational preferences in alkylcyclohexanes (Table IX), the conformational preference in the 2-alkylcyclohexanones decreases in the order 2-*tert*-butyl > 2-methyl > 2-ethyl > 2-isopropyl. Several explanations have been offered for this observed trend in cyclohexanones. The elimination of the interaction of a methyl group of an axial ethyl or isopropyl substituent with an adjacent equatorial hydrogen upon replacement of the ring methylene group by a carbonyl group has been suggested.¹⁰ Since no such effect is possible when the alkyl group is equatorial, the axial conformer would be stabilized. Cotterill and Robinson have suggested that the interaction of a methyl group of a 2-ethyl or 2-isopropyl substituent with the nonbonded electrons of the carbonyl oxygen is less favorable when the substituent group is in the equatorial rather than the axial position.²²

The energy difference between the rotational conformers of 2-alkylacetaldehydes have also been reported (Table XI). The effect of changing the alkyl group from methyl to ethyl to isopropyl is nearly the same for both the 3-alkyl-2-propanones and the 2-alkylcyclohexanones. The 2-alkyl ketone effect can be considered as being composed of two parts: one part which is identical for all the alkyl groups and is representative of a basic axial-equatorial energy difference for a cyclohexanone and a second part which is different for each alkyl group but for each particular alkyl group is the

Table XI, Alkyl Group Dependence of Conformational Energy Differences

2-Alkylacetaldehyde

2-Alkylcyclohexanones

R	ΔH_a° , kcal/mol	ΔG_c° , kcal/mol	$\Delta G_c^\circ - \Delta H_a^\circ$
-CH ₃	-0.90 ^a	-1.3	-0.4
-CH ₂ CH ₃	-0.70 ^b	-1.1	-0.4
-CH(CH ₃) ₂	-0.40 ^b	-0.7	-0.3
-C(CH ₃) ₃	0.25 ^b	-1.6	-1.8

^a S. S. Butcher and E. B. Wilson, Jr., *J. Chem. Phys.*, **40**, 1671 (1964). ^b G. J. Karabutsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965).

same for all 2-alkyl ketones. With an axial *tert*-butyl group, a methyl group is necessarily forced under the ring leading to an additional destabilization of the axial form. The difference between the observed conformational energy difference (-1.6 kcal/mol) and that expected based on the above model (-0.1 kcal/mol) suggests that the under-the-ring methyl interaction is at least 1.5 kcal/mol.²³

Experimental Section

All melting and boiling points are uncorrected. Analytical vapor phase chromatograms were obtained using a Perkin-Elmer Model 800 flame ionization chromatograph with support coated open tubular column (OV 225, 50 ft × 0.020 in.) or on an F&M Model 700 chromatograph. Infrared spectra were obtained on a Perkin-Elmer Model 337 spectrometer. Proton nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian Associates T-60 and at 100 MHz on a Varian Associates HA-100 spectrometer.

4-*tert*-Butylcyclohexanone. This compound was synthesized by dichromate oxidation of 4-*tert*-butylcyclohexanol (*cis* and *trans* mixture; Aldrich Chemical Co.) using the procedure of Warnhoff, Martin, and Johnson.²⁴ Work-up of the reaction and sublimation of the resulting green solid gave a white solid, mp 47.5–49° (lit.²⁵ 47–48°).

2-Methylcyclohexanone. Dichromate oxidation of 2-methylcyclohexanol using the procedure of Warnhoff, Martin, and Johnson²⁴ gave 2-methylcyclohexanone, bp 162–162.5° (760 mm) [lit.²⁶ 162–163° (760 mm)]. The ketone was further purified by vapor phase chromatography using a 20% FFAP column packing on Chromosorb P (5 m × 0.25 in.).

2-Ethylcyclohexanone. This ketone was synthesized by alkylation of the pyrrolidine enamine of cyclohexanone.²⁷ Cyclohexanone (147 g, 1.5 mol), pyrrolidine (130 g, 1.8 mol), and *p*-toluenesulfonic acid (1.5 g) in toluene were refluxed with continuous removal of water for 24 hr. Distillation of the enamine gave a pale yellow liquid, bp 103° (10 mm) [lit.²⁷ 105–107° (13 mm)].

A mixture of 30 g (0.20 mol) of the enamine and 62.5 g of ethyl

iodide in 200 ml of benzene was refluxed for 24 hr, after which time 50 ml of 10% sulfuric acid was added. After work-up and removal of the solvent, the residue was distilled. The fraction boiling between 180 and 190° (760 mm) was collected. The 2-ethylcyclohexanone was purified by preparative vpc using 20% TCEP on Chromosorb P at 140°. The ir showed a strong band at 1710 cm⁻¹ (C=O stretch). The nmr in CDCl₃ was ambiguous because of overlapping signals. Enough Eu(fod)₃-d₂₇ was added to the solution to shift the ring and side-chain methylene protons away from the methyl group of the side chain. Integration of the methyl group against the ring and side-chain methylene protons gave a relative area of 11:3.

2-Isopropylcyclohexanone. To 35 g (1.4 mol) of magnesium in 100 ml of ether was added 40 g (0.32 mol) of isopropyl bromide. After addition was complete, the reaction was refluxed for 30 min; then 70 g (0.71 mol) of cyclohexanone in 400 ml of ether was slowly added to the Grignard reagent. After refluxing for 1 hr, the reaction was quenched with 10% hydrochloric acid. Work-up and removal of the solvent gave 65.5 g (65%) of 1-isopropylcyclohexanone. The ir showed a strong band at 3400 cm⁻¹ (O-H stretch).

The alcohol was dehydrated using the procedure of Traynelis, Hergenrother, Hanson, and Valicenti.²⁸ A solution of 65.5 g of the alcohol in 250 g of dimethyl sulfoxide was refluxed for 24 hr, after which time the reaction was cooled and extracted with petroleum ether. Removal of the petroleum ether and distillation of the residue gave 35.3 g (65%) of isopropylcyclohexene, bp 148° (760 mm). The ir showed the absence of an O-H stretch. The nmr (neat) had signals at δ 5.4 (vinylic proton) and 1.0 (d, *J* = 7 Hz, isopropyl group).

The olefin was oxidized to the ketone using the procedure of Brown and Garg.²⁹ To a mixture of isopropylcyclohexene (9 g, 0.072 mol) and sodium borohydride (1.8 g, 0.048 mol) in 100 ml of tetrahydrofuran, maintained at 25–28°, was added 1.8 ml of boron trifluoride etherate in 5 ml of tetrahydrofuran. After the reaction was stirred for 2 hr, the excess hydride was destroyed by adding 5 ml of water. A mixture of 14.1 g (0.47 mol) of sodium dichromate dihydrate, 40 ml of water, and 10 ml of concentrated sulfuric acid was slowly added to the alkylborane, while the temperature was maintained at 25–30°. After addition was complete, the reaction was heated to 35° and stirred for 2 hr. After work-up, the 2-isopropylcyclohexanone was purified by preparative vpc using DC-QFI (5 m × 0.25 in.) at 120°. The nmr of the purified material showed an envelope between δ 1.4 and 2.4 (ring and side-chain methine protons) and a signal at δ 1.0 (d, *J* = 7 Hz, methyl groups of isopropyl side chain). The ir showed a strong band at 1710 cm⁻¹ (C=O stretch).

2-tert-Butylcyclohexanone. To 30 g (0.22 mol) of tert-butylbenzene were added 200 ml of morpholine and 100 ml of ethylenediamine. To this mixture was added 7.8 g (1.1 mol) of freshly cut lithium wire. An ice bath was used to cool the solution. After all the lithium had reacted, water was added. The residue after work-up was distilled to give 65.5 g (50%) of tert-butylcyclohexene, bp 170° (760 mm) [lit.³⁰ 170° (760 mm)].

To a mixture of 12.2 g (0.088 mol) of 2-tert-butylcyclohexene and 2.49 g (0.066 mol) of sodium borohydride in 100 ml of tetrahydrofuran was added 2.7 ml of boron trifluoride etherate. The reaction was allowed to stir for 5 hr, at which time the excess hydride was destroyed with 10 ml of water. A solution of 19.7 g (0.066 mol) of sodium dichromate dihydrate, 14.5 ml of concentrated sulfuric acid, and 100 ml of water was slowly added to the alkylboron. After the reaction mixture was stirred for 2 hr at 30°, the organic and aqueous phases were separated. After work-up, the residue was distilled. The fraction boiling at 170–175° was collected. 2-tert-Butylcyclohexanone was purified by preparative vpc on DC-QFI (5 m × 0.25 in.) at 150°.

Eu(fod)₃-d₂₇. These shift reagents were obtained from Merck Sharp and Dome. They were kept in a vacuum desiccator over phosphorus pentoxide. All transferring operations were performed in a drybox under dry, oxygen-free nitrogen.

In a typical experiment, a weighed amount of ketone was diluted with chloroform-*d* to 2 ml in a 2-ml volumetric flask. The shift reagent was transferred to a clean, dry, air-tight vial in a drybox. The shift reagent was then diluted with a small volume (generally 0.2 ml) of the ketone solution while still in the drybox. Once the reagent had dissolved, the solution was syringed into a 5-mm nmr

tube and the tube capped. The tube was removed from the drybox and the nmr spectrum taken. Another aliquot of the ketone solution (generally about 0.05 ml) was added to the nmr tube. After thorough shaking, another spectrum was taken. This dilution procedure was then repeated.

Acknowledgments. The nmr spectrometers used in this research were purchased through National Science Foundation departmental instrumentation grants. The authors wish to thank Professor M. R. Willcott, III, for valuable discussions. K.L.S. gratefully acknowledges the receipt of a John Simon Guggenheim Memorial Fellowship.

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Conformational Analysis Using Lanthanide Shift Reagents. Determination of Alkyl Group Conformations in 2-Alkyl-4-*tert*-butylcyclohexanones

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Abstract: The induced shift ratios for 4-*tert*-butylcyclohexanone, the *cis* and *trans* isomers of 2-methyl-, 2-ethyl- and 2-isopropyl-4-*tert*-butylcyclohexanone, and *cis*-2,4-di-*tert*-butylcyclohexanone have been determined using tris(dipivaloyl-methanato)ytterbium at 100 MHz. The induced shift data have been analyzed to give the rotamer populations for the ethyl and isopropyl groups in the *cis* and *trans* isomers of the 2-ethyl and 2-isopropyl derivatives. Extensive calculations based on the induced shift data have been used to obtain structures for the ketone-lanthanide chelate complexes which give the best fit between calculated and observed induced shifts for all the ring and side-chain protons.

Although a great deal is known about the conformations of six-membered ring compounds,² very little is known about the rotational conformations of alkyl chains attached to these rings. This dearth of information is partly due to the lack of simple yet reliable methods for obtaining information on side-chain conformations. In the preceding paper,³ lanthanide shift reagents were applied to the study of the ring inversion process in 2-alkylcyclohexanones (alkyl = Me, Et, *i*-Pr, and *tert*-Bu). In the course of that study, it was observed that, in the LIS spectrum of 2-ethylcyclohexanone, the methylene protons of the ethyl side chain exhibit very different lanthanide induced shifts, as shown in Figure 1. Irradiation of the methyl group resonances caused the two septets to collapse to give a pattern characteristic of the AB part of an ABX spin system. These two methylene protons are adjacent to an asymmetric carbon and are diastereotopic. Nonetheless, if all three rotamers were equally populated, the lanthanide induced shifts for the two methylene protons would be expected to be equal. The observed inequality in the induced shifts, therefore, indicates that the three rotamers are not equally populated in the complexed ketone. A similar result was observed for the 2-isopropylcyclohexanone, where now the methyl groups give different induced shifts.

In the previous paper,³ it was shown that the observed ratio of the characteristic induced shifts of a proton in two equilibrating isomers was the weighted average of the ratio of the characteristic induced shifts of that proton in each isomer. A simple graphical technique was also derived whereby this ratio could be simply and accurately obtained.⁴ For a freely rotating alkyl group, the observed induced shift ratio of a proton on that side chain should be a weighted average of the induced shift ratios of that proton in each of the three possible rotamers, the weightings being the populations of each rotamer. It appeared feasible, therefore, to attempt to determine these rotamer populations for the 2-ethyl and 2-isopropyl side chains by a procedure similar to that outlined in the previous paper. The 2-alkylcyclohexanones themselves are not suitable for the determination

of the rotational populations of the alkyl side chains because of the concurrent conformational averaging between R-equatorial and R-axial forms.³ Therefore, *cis*- and *trans*-2-alkyl-4-*tert*-butylcyclohexanone (alkyl = Me, Et, and *i*-Pr) and *cis*-2,4-di-*tert*-butylcyclohexanone were prepared and studied. We now report on the use of lanthanide induced shift ratios to determine the populations of the rotamers of the 2-alkyl side chains in these compounds.

Results

The *cis* and *trans* isomers of the 2-alkyl-4-*tert*-butylcyclohexanones were synthesized using adaptations of reported procedures. Nmr studies in the presence of Eu(fod)₃-d₂₇ were used to confirm the structural assignments. The nmr spectra of these compounds in the presence of Eu(fod)₃-d₂₇ were assigned by using the observed spin-spin coupling constants and by analogy with the shifted spectra of 4-*tert*-butylcyclohexanone and the 2-alkylcyclohexanones.³

Multiplet assignments of *cis*-2-methyl-4-*tert*-butylcyclohexanone in the presence of Eu(fod)₃-d₂₇ are as follows: (5% v/v TMS in CDCl₃) δ 14.5 (d, *J* = 14 Hz, 6-equatorial); 13.5 (m, 2-axial); 13.2 (t, *J* = 13 Hz, of d, *J* = 6 Hz, 6-axial); 9.6 (d, *J* = 7 Hz, methyl group); 8.1 (q, *J* = 12 Hz, 3-axial); 7.2 (br q, *J* = 12 Hz, 5-axial); 6.5 (m, 3-equatorial); 6.3 (t, *J* = 13 Hz, of t, *J* = 4 Hz, 4-axial); 5.8 (m, 5-equatorial); 2.6 (s, 4-*tert*-butyl group).

Multiplet assignments of *trans*-2-methyl-4-*tert*-butylcyclohexanone in the presence of Eu(fod)₃-d₂₇ are as follows: (5% v/v TMS in CDCl₃) δ 14.2 (m, 2-equatorial); 13.9 (d, *J* = 14 Hz, 6-equatorial); 13.4 (t, *J* = 13 Hz, of d, *J* = 6 Hz, 6-axial); 7.4 (d, *J* = 7 Hz, methyl group); 6.5 (m, 3- and 5-axial); 5.9 (m, 3-equatorial and 4-axial); 5.3 (m, 5-equatorial); 2.4 (s, 4-*tert*-butyl group).

Multiplet assignments for *cis*-2-ethyl-4-*tert*-butylcyclohexanone in the presence of Eu(fod)₃-d₂₇ are as follows: (5% v/v TMS in CDCl₃) δ 12.1 (d, *J* = 14 Hz, 6-equatorial); 10.9 (m, 6-axial and one of the methylene hydrogens of the ethyl side chain); 7.9 (septet, *J* = 7 Hz, methylene hydrogen of ethyl side chain); 6.5 (q, *J* = 12 Hz, 3-axial); 5.8