Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 162.
(25) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).
(26) "Aldrich Handbook of Chemicals," Aldrich Chemical Co., San Leardro, Calif., 1972.
(27) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(28) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).
(29) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).
(30) R. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, **29**, 1313 (1964).

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

Kenneth L. Servis*[1] and Donald J. Bowler

Contribution from the Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007. *Received May 25, 1974*

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(dipivaloylmethanato)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)$_3$-d_{27} were used to confirm the structural assignments. The nmr spectra of these compounds in the presence of Eu(fod)$_3$-d_{27} 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)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) 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)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) 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)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) 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

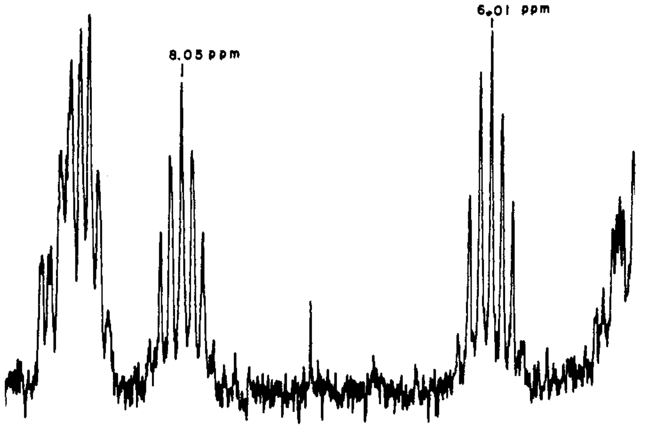


Figure 1. The 100-MHz nmr spectrum of 2-ethylcyclohexanone, (0.55 *M*) in the presence of Eu(fod)$_3$-d_{27} (0.29 *M*) in CDCl$_3$.

(m, 5-axial and 3-equatorial); 5.2 (br, t, *J* = 12 Hz, 4-axial); 4.8 (m, 5-equatorial); 4.5 (t, *J* = 7. Hz, methyl group of ethyl side chain); 2.2 (s, 4-*tert*-butyl group).

Multiplet assignments for *trans*-2-ethyl-4-*tert*-butylcyclohexanone in the presence of Eu(fod)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) δ 14.1 (br m, 2-equatorial); 13.5 (d, *J* = 14 Hz, 6-equatorial); 13.1 (t, *J* = 13 Hz, of d, *J* = 6 Hz, 6-axial); 8.9 (septet, *J* = 7 Hz, methylene hydrogen of ethyl side chain); 6.9 (septet, *J* = 7 Hz, methylene hydrogen of ethyl side chain); 6.6 (t, *J* = 13 Hz, of d, *J* = 4 Hz, 3-axial); 6.1 (q, *J* = 13 Hz, of d, *J* = 4 Hz, 5-axial); 5.9 (m, 3-equatorial and 4-axial); 5.1 (m, 5-equatorial); 4.9 (t, *J* = 7 Hz, methyl group of ethyl side chain); 2.3 (s, 4-*tert*-butyl group).

Multiplet assignments for *cis*-2-isopropyl-4-*tert*-butylcyclohexanone in the presence of Eu(fod)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) δ 11.1 (d, *J* = 14 Hz, 6-equatorial); 9.8 (m, 6-axial and methine proton of the isoropyl side chain); 9.3 (d, *J* = 13 Hz, of t, *J* = 6 Hz, 2-axial); 5.7 (q, *J* = 13 Hz, 3-axial); 4.9 (m, 5-axial and 3-equatorial); 4.7–4.2 (m, 5-equatorial and 4-axial); 4.7 (d, *J* = 7 Hz, methyl group of isopropyl side chain); 4.2 (d, *J* = 7 Hz, methyl group of isopropyl side chain); 1.9 (s, 4-*tert*-butyl group).

Multiplet assignments for *trans*-2-isopropyl-4-*tert*-butylcyclohexanone in the presence of Eu(fod)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) δ 15.1 (br m, 2-equatorial); 13.4 (m, 6-equatorial and 6-axial); 8.9 (m, methine proton of isopropyl side chain); 7.3 (t, *J* = 13 Hz, of d, *J* = 5 Hz, 3-axial); 6.6 (d, *J* = 7 Hz, methyl group of isopropyl side chain); 6.3 (m, 5-axial and 3-equatorial); 6.0 (t, *J* = 12 Hz, of t, *J* = 4 Hz, 4-axial); 5.3 (m, 5-equatorial); 4.2 (d, *J* = 7 Hz, methyl group of isopropyl side chain); 2.3 (s, 4-*tert*-butyl group).

Multiplet assignments for *cis*-2,4-di-*tert*-butylcyclohexanone in the presence of Eu(fod)$_3$-d_{27} are as follows: (5% v/v TMS in CDCl$_3$) δ 14.1 (d, *J* = 14 Hz, 6-equatorial); 13.3 (d, *J* = 13 Hz, of d, *J* = 4 Hz, 2-axial); 13.1 (t, *J* = 12 Hz, of d, *J* = 6 Hz, 6-axial); 8.9 (q, *J* = 13 Hz, 3-axial); 7.4 (s, 2-*tert*-butyl group); 7.3–6.7 (m, 5-axial and 3-equatorial); 6.3 (br, t, *J* = 12 Hz, 4-axial); 5.2 (m, 5-equatorial); 2.4 (s, 4-*tert*-butyl group).

The dependence of the chemical shifts of all the protons of the *cis*- and *trans*-2-alkyl-4-*tert*-butylcyclohexanones on the concentration of Yb(dpm)$_3$ was determined by diluting a weighed amount of shift reagent with a deuteriochloroform solution of the ketone. Since Yb(dpm)$_3$ increases nmr line width, spin–spin coupling constants could not, in general, be used for multiplet assignments. The assignments for each ketone in presence of Yb(dpm)$_3$ were made by analogy to the Eu(fod)$_3$-d_{27} assignments. The only major difference in the spectral changes produced by the two shift reagents occurs for the 2- and 6-axial protons. The induced shifts for these two protons are nearly identical for Eu(fod)$_3$-d_{27} but quite different for Yb(dpm)$_3$. The proton chemical shifts determined for each of the solutions with different Yb(dpm)$_3$ concentration are reported in Tables I–VII. Induced shift ratios were obtained as least-squares slopes of plots of the observed chemical shifts of the *i*th proton, δ_i, *vs.* the sum of all the identified proton chemical shifts for that molecule, $\Sigma_i\delta_i$, for each of the different solutions[3] and are included in Tables I–VII. It is convenient to normalize the induced shift ratios by setting the induced shift ratio of the proton with the largest slope for a particular compound equal to 10.00; these relative induced shift ratios are also included in Tables I–VII.

Table I. Chemical Shift Data for *cis*-2-Methyl-4-*tert*-butylcyclohexanone in the Presence of Yb(dpm)$_3$

[Yb(dpm)$_3$], mol/l.	[C=O], mol/l.	δ								
		2H$_{ax}$	3H$_{ax}$	3H$_{eq}$	4H$_{ax}$	5H$_{eq}$	6H$_{ax}$	6H$_{eq}$	CH$_3$	4-*t*-Bu
0.359	0.143	14.62	9.64	8.11	7.31	6.11	13.32	17.04	11.98	2.95
0.288	0.143	12.29	8.03	6.95	6.29	5.36	11.23	14.27	9.89	2.56
0.240	0.143	10.67	6.89	6.13	5.49	4.81	9.73	12.35	8.41	2.27
0.250	0.143	9.43	6.05	5.53	4.91	4.43	8.59	10.87	7.33	2.09
0.180	0.143	8.46	5.44	5.18	4.50	4.12	7.82	9.78	6.50	1.94
Induced shift ratio[a]		0.1641	0.1125	0.0793	0.0757	0.0532	0.1478	0.1939	0.1464	0.0271
Rel induced shift ratio[b]		8.46	5.80	4.09	3.90	2.74	7.62	10.00	7.55	1.39

[a] The average of the standard deviations is 0.002. [b] The induced shift for 6H$_{eq}$ has been set equal to 10.0.

Table II. Chemical Shift Data for *trans*-2-Methyl-4-*tert*-butylcyclohexanone in the Presence of Yb(dpm)$_3$

[Yb(dpm)$_3$], mol/l.	[C=O], mol/l.	δ									
		2H$_{eq}$	3H$_{ax}$	3H$_{eq}$	4H$_{ax}$	5H$_{ax}$	5H$_{eq}$	6H$_{ax}$	6H$_{eq}$	CH$_3$	4-*t*-Bu
0.371	0.286	19.14	9.39	8.49	8.03	6.69	8.49	15.77	17.86	10.72	3.11
0.298	0.286	16.16	7.92	7.26	6.80	5.81	7.26	13.34	15.04	8.94	2.69
0.248	0.286	13.93	6.93	6.29	5.89	5.18	6.29	11.53	12.93	7.65	2.40
0.212	0.286	12.39	6.19	5.71	5.27	4.71	5.71	10.25	11.45	6.71	2.19
0.186	0.286	11.08	5.62	5.14	4.78	4.34	5.14	9.18	10.40	5.99	2.02
0.165	0.286	10.15	5.17	4.73	4.14	4.09	4.73	8.40	9.41	5.41	1.89
Induced shift ratio[a]		0.1826	0.0852	0.0735	0.0761	0.0761	0.0530	0.1496	0.1716	0.1075	0.0246
Rel induced shift ratio[b]		10.00	4.67	4.03	4.17	4.17	2.90	8.19	9.40	5.89	1.35

[a] The average of the standard deviations is 0.0007. [b] The induced shift for 2H$_{eq}$ has been set equal to 10.0.

Table III. Chemical Shift Data for *cis*-2-Ethyl-4-*tert*-butylcyclohexanone in the Presence of $Yb(dpm)_3$

$[Yb(dpm)_3]$, mol/l.	[C=O], mol/l.	δ											
		$2H_{ax}$	$3H_{ax}$	$3H_{eq}$	$4H_{ax}$	$5H_{ax}$	$5H_{eq}$	$6H_{ax}$	$6H_{eq}$	H[a]	H′[a]	CH_3	4-*t*-Bu
0.401	0.293	16.94	11.48	8.39	9.09	9.43	6.65	15.28	19.52	18.77	13.88	8.43	3.33
0.267	0.293	11.66	7.78	6.00	6.42	6.83	5.05	10.66	13.42	12.70	9.36	5.78	2.45
0.229	0.293	10.13	6.73	5.29	5.53	6.07	4.56	9.31	11.65	10.97	8.07	4.97	2.19
0.200	0.293	9.08	6.01	4.82	5.08	5.56	4.24	8.40	10.43	9.76	7.18	4.44	2.06
0.178	0.293	8.21	5.39	4.49	4.34	5.19	3.99	7.63	9.41	8.73	6.41	3.99	1.91
0.160	0.293	7.48	4.78	4.08	4.24	4.78	3.68	6.98	8.54	7.90	5.78	3.62	1.76
0.114	0.293	5.91	3.65	3.31	3.65	3.91	3.27	5.65	6.75	6.01	4.45	2.83	1.53
0.089	0.293	4.99	3.09	2.95	2.95	3.55	2.95	4.79	5.67	4.99	3.67	2.33	1.36
Induced shift ratio[b]		0.1220	0.0861	0.0557	0.0627	0.0603	0.0378	0.1069	0.1414	0.1408	0.1043	0.0622	0.0200
Rel induced shift ratio[c]		8.63	6.10	3.94	4.43	4.26	2.67	8.63	10.00	9.96	7.38	4.40	1.63

[a] H and H′ are the two methylene protons of the ethyl group. [b] The average of the standard deviations is 0.0004. [c] The induced shift for $6H_{eq}$ has been set equal to 10.0.

Table IV. Chemical Shift Data for *trans*-2-Ethyl-4-*tert*-butylcyclohexanone in the Presence of $Yb(dpm)_3$

$[Yb(dpm)_3]$, mol/l.	[C=O], mol/l.	δ										
		$2H_{eq}$	$3H_{ax}$	$3H_{eq}$	$5H_{ax}$	$5H_{eq}$	$6H_{ax}$	$6H_{eq}$	H[a]	H′[a]	CH_3	4-*t*-Bu
0.338	0.160	19.63	10.05	8.05	8.47	6.25	15.07	17.07	12.79	9.63	7.21	3.05
0.196	0.160	11.10	5.78	4.76	5.24	4.10	8.82	9.80	7.34	5.64	4.10	1.97
0.157	0.160	9.43	4.97	4.11	4.59	3.75	7.59	8.35	6.27	4.87	3.49	1.73
0.131	0.160	8.23	4.35	3.69	4.15	3.51	6.75	7.31	5.53	4.35	3.07	1.59
0.112	0.160	7.35	3.91	3.35	3.85	3.35	6.11	6.57	4.93	3.91	2.75	1.49
0.098	0.160	6.69	3.59	3.11	3.59	3.11	5.65	6.03	4.51	3.59	2.49	1.40
Induced shift ratio[b]		0.1761	0.0879	0.0673	0.0665	0.0422	0.1284	0.1505	0.1126	0.0820	0.0641	0.0225
Rel induced shift ratio[c]		10.00	4.99	3.82	3.77	2.39	7.29	8.54	6.39	4.65	3.68	1.27

[a] H and H′ are the two methylene protons of the ethyl group. [b] The average of the standard deviations is 0.0005. [c] The induced shift for $2H_{eq}$ has been set equal to 10.0.

Table V. Chemical Shift Data for *cis*-2-Isopropyl-4-*tert*-butylcyclohexanone in the Presence of $Yb(dpm)_3$

$[Yb(dpm)_3]$, mol/l.	[C=O], mol/l.	δ										
		$2H_{ax}$	$3H_{ax}$	$3H_{eq}$	$5H_{ax}$	$5H_{eq}$	$6H_{ax}$	$6H_{eq}$	H[a]	CH_3[a]	CH_3'[a]	4-*t*-Bu
0.339	0.278	15.44	10.42	8.62	7.86	5.90	13.80	18.14	17.08	8.42	7.82	2.98
0.272	0.278	12.63	8.49	7.29	6.57	5.11	11.39	14.83	13.99	6.81	6.35	2.57
0.226	0.278	10.67	7.12	6.30	5.84	4.56	9.71	12.43	11.85	5.72	5.36	2.28
0.194	0.278	9.27	6.15	5.59	5.05	4.17	8.47	10.75	10.29	4.90	4.62	2.07
0.170	0.278	8.23	5.43	5.05	4.59	3.89	7.57	9.53	9.17	4.32	4.08	1.87
0.151	0.278	7.40	4.86	4.72	3.92	3.66	6.84	8.44	8.22	3.88	3.66	1.74
0.123	0.278	4.99	3.15	3.51	2.65	2.85	4.81	5.61	5.55	2.49	2.41	1.37
0.113	0.278	4.29	2.55	3.17	2.55	2.64	4.21	4.81	4.81	2.09	2.05	1.25
Induced shift ratio[b]		0.1355	0.0951	0.0665	0.0667	0.0396	0.1167	0.1626	0.1493	0.0768	0.0701	0.0212
Rel induced shift ratio[c]		8.33	5.85	4.09	4.10	2.43	7.18	10.00	9.18	4.72	4.31	1.56

[a] H, CH_3, CH_3' are the protons of the isopropyl group. [b] The average of the standard deviations is 0.0005. [c] The induced shift for $6H_{eq}$ has been set equal to 10.0.

Table VI. Chemical Shift Data for *trans*-2-Isopropyl-4-*tert*-butylcyclohexanone in the Presence of $Yb(dpm)_3$

$[Yb(dpm)_3]$, mol/l.	[C=O], mol/l.	δ											
		$2H_{eq}$	$3H_{ax}$	$3H_{eq}$	$4H_{ax}$	$5H_{ax}$	$5H_{eq}$	$6H_{ax}$	$6H_{eq}$	H[a]	CH_3[a]	CH_3'[a]	4-*t*-Bu
0.348	0.197	18.27	10.91	8.07	6.91	6.91	5.41	13.17	14.91	8.97	8.31	5.41	2.57
0.279	0.197	15.23	9.19	6.88	5.85	5.85	4.70	11.09	12.45	7.53	6.88	4.54	2.21
0.232	0.197	12.92	7.96	6.02	5.12	5.12	4.28	9.58	10.76	6.46	5.84	3.94	1.98
0.199	0.197	11.32	7.08	5.40	4.56	4.56	3.94	8.50	9.52	5.68	5.04	3.46	1.82
0.174	0.197	10.03	6.35	5.05	4.19	4.19	3.69	7.65	8.45	5.05	4.51	3.13	1.67
0.155	0.197	9.01	5.83	4.62	3.87	3.87	3.45	7.01	7.73	4.51	4.03	2.83	1.59
Induced shift ratio[b]		0.1802	0.0989	0.0667	0.0592	0.0512	0.0375	0.1200	0.1396	0.0864	0.0833	0.0500	0.0191
Rel induced shift ratio[c]		10.00	5.49	3.70	3.28	3.28	2.08	6.66	7.75	4.73	4.62	2.77	1.05

[a] H, CH_3, and CH_3' are the protons of the isopropyl group. [b] The average of the standard deviations is 0.0005. [c] The induced shift for $2H_{eq}$ has been set equal to 10.0.

Table VII. Chemical Shift Data for *cis*-2,4-Di-*tert*-butylcyclohexanone in the Presence of Yb(dpm)$_3$

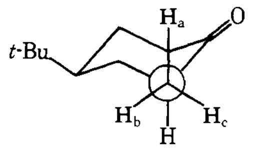
[Yb(dpm)$_3$], mol/l.	[C=O], mol/l.	δ 2H$_{ax}$	3H$_{ax}$	3H$_{eq}$	4H$_{ax}$	5H$_{ax}$	5H$_{eq}$	6H$_{ax}$	6H$_{eq}$	2-*t*-Bu	4-*t*-Bu
0.406	0.165	16.89	12.39	9.32	9.32	10.88	6.50	13.71	19.43	12.39	3.32
0.325	0.165	14.23	10.26	7.86	7.86	9.24	5.68	11.41	16.31	10.26	2.88
0.271	0.165	12.34	8.78	6.88	6.88	8.12	5.12	9.80	14.08	8.78	2.55
0.232	0.165	10.94	7.66	6.10	6.10	7.26	4.68	8.54	12.40	7.66	2.31
0.203	0.165	9.85	6.79	5.51	5.51	6.59	4.33	7.69	11.11	6.79	2.15
0.181	0.165	8.94	6.08	5.04	5.04	5.92	4.06	6.92	10.04	6.08	2.00
Induced shift ratio[a]		0.1529	0.1168	0.0793	0.0823	0.0908	0.0452	0.1308	0.1807	0.1168	0.0255
Rel induced shift ratio[b]		8.46	6.71	4.56	4.56	5.22	2.60	7.24	10.00	6.71	3.41

[a] The average of the standard deviations is 0.0006. [b] The induced shift for 6H$_{eq}$ has been set equal to 10.0.

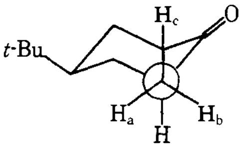
Discussion

For a conformationally mobile compound, the average induced shift ratios have been applied to the determination of the population of each of the conformers present at equilibrium in the substrate-lanthanide chelate complex.[4] For a cyclohexanone, the observed induced shift ratio for a pair of ring protons was shown to be the population weighted average of the characteristic induced shift ratios for that pair of protons in a conformationally homogeneous model compound. Although this method was applied to a case in which only two conformers were in rapid equilibrium, it should be equally applicable to cases in which three (or more) conformers are in equilibrium provided that suitable conformationally homogeneous model compounds are available.

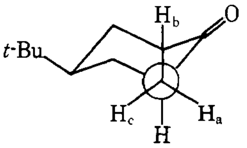
For the 2-alkyl-4-*tert*-butylcyclohexanones, three side chain rotamers might be expected to contribute to the rotational equilibrium (**1–3**). The observed induced shift ratio for a side-chain proton, $[\Delta_B{}^{H_a}/(\Delta_B{}^{H_a} + \Delta_B{}^{H_b} + \Delta_B{}^{H_c})]_{av}$, would be expected to be the weighted average of the characteristic induced shift ratios of that proton in each of the three rotamers in the absence of rotation; see eq 1 where n_1, n_2, and n_3 are the mole fractions of rotamers **1**, **2**, and **3**.



1



2



3

$$\left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b} + \Delta_B{}^{H_c}}\right)_{av} = n_1\left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b} + \Delta_B{}^{H_c}}\right)_1 + n_2\left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b} + \Delta_B{}^{H_c}}\right)_2 + n_3\left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b} + \Delta_B{}^{H_c}}\right)_3 \quad (1)$$

Since conformationally homogeneous model compounds are not available, there is no feasible method of directly determining the characteristic induced shift ratios for each of the rotamers in the absence of rotational averaging. We have instead calculated theoretical values for these induced shift ratios and used the theoretical values to determine the population of each of the rotamers contributing to the rotational equilibrium.

Quantitative techniques for the analysis of lanthanide induced shift data have been developed by several groups.[5-9] The shifts are usually assumed to arise from a dipolar field which is either axially symmetric or effectively axially symmetric.[10] When the principal magnetic axis of the lanthanide is taken to be collinear with the lanthanide base bond, the dipolar (pseudocontact) contribution[11] to the lanthanide induced shift of nucleus i is given by the McConnell-Robertson relationship[13]

$$\text{pseudocontact contribution} = k[(3\cos^2\theta_i - 1)/r_i{}^3]$$

where r_i is the distance from the lanthanide to nucleus i, and θ_i is the angle between the nucleus i–lanthanide vector and the base-lanthanide bond. The computational methods differ in the method used to determine the "best-fit" location of the lanthanide and the criterion used to define the "best fit."[6,7] We have used the computer program of Willcott and Davis,[6] PARADIGM, in which the best-fit location is taken as the mininum of the normalized standard deviation between the observed shifts, obsd$_i$, and the calculated shifts, calcd$_i$; the R factor

$$R = \{[\Sigma w_i(\text{obsd}_i - \text{calcd}_i)^2]/\Sigma w_i(\text{obsd}_i)^2\}^{1/2}$$

where w_i is the weight applied to the observation for the ith nucleus.

The best-fit location of the lanthanide was determined for each of 2-alkyl-4-*tert*-butylcyclohexanone complexes using the relative induced shift ratios for only the protons attached to the cyclohexanone ring. Cartesian coordinates of each of the ring protons as calculated by a modified Westheimer method[14,15] energy minimization procedure were used as input for the calculations. The lanthanide was then moved incrementally over the surface of a sphere whose radius was the assumed oxygen-lanthanide distance; then the oxygen-lanthanide distance was incremented and the process repeated. For each location, relative induced shift ratios and R factors were calculated. We have assumed that the lanthanide location which produces the smallest R factor best describes the lanthanide-ketone complex.[16] The best-fit location of the lanthanide together with the observed and calculated relative induced shift ratios are presented in Table VIII. The R factors were found to be relatively insensitive to the lanthanide location over the oxygen-lanthanide distance of 2.4–2.8 Å and over the C-O-Ln bond angle range of 140–220°. Minimum R factors were usually found for the oxygen-lanthanide distance

Table VIII. Experimental and Calculated Relative Induced Shift Ratios of the 2-Alkyl-4-*tert*-butylcyclohexanone[a]

2-Alkyl group	Relative lanthanide induced shifts ratios[b] 2H_{eq}	2H_{ax}	3H_{eq}	3H_{ax}	4H_{ax}	5H_{eq}	5H_{ax}	6H_{eq}	6H_{ax}	*R* factor
-H	10.0	7.86	3.18	4.81	3.70	3.18	4.81	10.0	7.86	1.7
	(10.0)	(7.83)	(3.32)	(4.63)	(3.79)	(3.32)	(4.63)	(10.0)	(7.83)	
Equatorial $-CH_3$	—	8.46	4.09	5.80	3.90	2.74	*c*	10.0	7.62	3.0
		(8.29)	(3.93)	(5.54)	(3.97)	(3.18)	(4.82)	(9.86)	(7.89)	
Axial $-CH_3$	10.0	—	4.17	4.67	4.03	2.90	4.17	9.40	8.19	3.9
	(10.4)		(3.51)	(4.73)	(3.76)	(2.91)	(4.05)	(9.46)	(7.79)	
Equatorial $-CH_2CH_3$	—	8.67	3.94	6.06	4.29	2.69	4.41	10.0	7.62	3.6
		(8.64)	(4.23)	(5.93)	(4.02)	(2.81)	(4.61)	(9.71)	(7.74)	
Axial $-CH_2CH_3$	10.0	—	3.82	4.98	*c*	2.40	3.73	8.62	7.29	2.6
	(9.95)		(3.50)	(4.76)	(3.52)	(2.51)	(3.70)	(8.64)	(7.17)	
Equatorial $-CH(CH_3)_2$	—	8.39	*c*	5.93	*c*	2.34	4.07	10.0	7.22	5.5
	—	(8.38)	(4.00)	(5.54)	(3.89)	(2.71)	(4.25)	(9.57)	(7.81)	
Axial $-CH(CH_3)_2$	10.0	—	3.70	5.49	3.78	2.08	3.28	7.75	6.66	2.0
	(9.81)	—	(3.78)	(5.30)	(3.43)	(2.10)	(3.80)	(7.73)	(6.70)	
Equatorial $-C(CH_3)_3$	—	8.46	4.56	6.71	4.56	5.22	2.60	10.0	7.24	2.3
		(8.47)	(4.44)	(6.42)	(3.90)	(5.32)	(2.73)	(9.99)	(7.44)	

[a] Calculated values in parentheses. [b] Scaled so that the largest induced shift ratio is 10.0. [c] Could not be determined.

of 2.5 or 2.6 Å and for the oxygen-lanthanide vector 20-30° off of the C=O bond axis.[17]

The agreement between the calculated and the observed induced shift ratios is, in general, excellent; the average standard deviation is of the order of 2-5%. The least-squares standard deviations in the induced shift ratios are of approximately the same magnitude. For these cyclohexanone-lanthanide chelate complexes, the lanthanide appears to be located sufficiently well to reproduce the observed induced shift ratios using the calculational procedure employed.

Since the induced shift ratios for the ring protons can be accurately reproduced by calculations using the derived lanthanide-chelate models, the induced shift ratios for the 2-alkyl group protons should also be accurately calculated using the same model structures. A comparison of the observed induced shift ratios with the calculated induced shift ratios for the 2-alkyl group protons in each of the three staggered rotamers should then yield the population of each of the rotamers present at equilibrium.

The best-fit lanthanide location was used to calculate induced shift ratios for each of the three methyl group protons in both *cis-* and *trans-*2-methyl-4-*tert-*butylcyclohexanone (Figure 2). Since the three methyl group rotamers are energetically equivalent in each of these compounds, the calculated induced shift ratio for the methyl group can be obtained by averaging the calculated induced shift ratios for each of the protons in any one rotamer. Alternatively, the averaged induced shift ratio for the methyl group proton can be included in the computer calculations by comparison of the observed average shift ratio with the average of the calculated shift ratios for the methyl group protons. The relative induced shift ratios calculated using these two procedures are presented in Table IX.

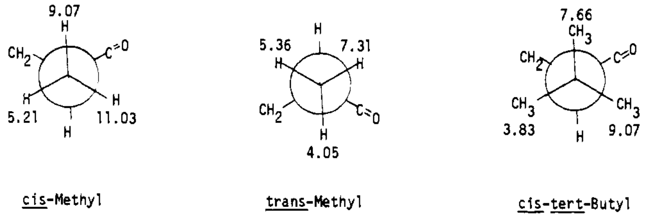


Figure 2. Calculated relative shift ratios for *cis*-2-methyl, *trans*-2-methyl, and *cis*-2-*tert*-butyl side chains in the absence of rotation.

For *cis*-2,4-di-*tert-*butylcyclohexanone, the induced shift ratio for each of the 2-*tert-*butyl methyl groups has been calculated using an average methyl group proton location rather than averaging the induced shift ratios for all three protons of a particular methyl group. The average methyl proton location was assumed to lie at the center of the circle described by the protons in a freely rotating methyl group. The calculated relative induced shift ratio for the 2-*tert-*butyl group was then obtained by averaging the calculated relative shift ratios (Figure 2) for the three average methyl proton locations. In addition, the averaged induced shift ratio for the 2-*tert*-butyl group protons were included in a full search of the best-fit location of the lanthanide by comparing the observed average shift ratio with the average of the calculated shift ratios for the average methyl protons. The observed and calculated induced shift ratios for the 2-*tert-* butyl group are included in Table IX.

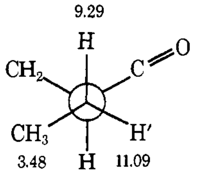
Table IX. Comparison of Observed and Calculated Relative Induced Shift Ratios for the 2-Alkyl Group Protons of 2-Alkyl-4-*tert*-butylcyclohexanones

2-Alkyl group		Relative induced shift ratios Obsd[a]	Calcd[b]	Calcd[c]
cis-2-Methyl		7.55	7.65	8.43
trans-2-Methyl		5.89	5.68	5.57
cis-2-*tert*-Butyl		6.71	6.81	6.85
cis-2-Ethyl	-CH	9.99	10.07,[d] 9.97[e]	10.58,[e] 10.49[d]
	-CH′	7.39	7.38,[d] 7.43[e]	8.17,[e] 7.18[d]
	$-CH_3$	4.40	4.46,[d] 4.40[e]	4.76,[e] 5.20[d]
trans-2-Ethyl	-CH	6.39	6.27[f]	6.06[f]
	-CH′	4.65	4.87[f]	4.72[f]
	$-CH_3$	3.64	3.50[f]	3.61[f]
cis-Isopropyl	-CH	9.20	9.69[g]	9.99[g]
	$-CH_3$	4.75	4.79[g]	5.17[g]
	$-CH_3'$	4.32	4.35[g]	4.52[g]
trans-Isopropyl	-CH	4.73	4.79[h]	4.87[h]
	$-CH_3$	4.62	5.01[h]	5.31[h].
	$-CH_3'$	2.77	2.90[h]	2.98[h]

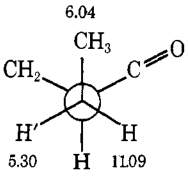
[a] Using $Yb(dpm)_3$. [b] Side-chain protons included in *R*-factor calculations. [c] Ring protons only used for *R*-factor calculations. [d] Using rotamer populations of Table X, footnote *a*. [e] Using rotamer populations of Table X, footnote *b*. [f] Using rotamer populations of Table XI. [g] Using rotamer populations of Table XII, footnote *a*. [h] Using rotamer populations of Table XIII, footnote *b*.

For the cis and trans isomers of 2-ethyl- and 2-isopropyl-4-*tert-*butylcyclohexanones, there is no reason to expect that all the side-chain rotamers will be equally populated. For these compounds, the lanthanide location which provided the best fit for the ring proton shifts was used to calculate relative induced shift ratios for each of the side-chain protons in each of three staggered rotamers. The calculated relative induced shift ratios for each of the 2-ethyl rotamers of *cis*-2-ethyl-4-*tert-*butylcyclohexanone are listed in Table

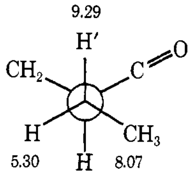
Table X. Comparison of Experimental with Calculated Shift Ratios for *cis*-2-Ethyl-4-*tert*-butylcyclohexanone



I



II



III

	I	II	III	Obsd	Calcd[a]	Calcd[b]
Δ_B^H/Σ^c	0.389	0.494	0.234	0.454 or 0.341	0.459	0.345
$\Delta_B^{H'}/\Sigma$	0.465	0.236	0.410	0.341 or 0.454	0.310	0.449
$\Delta_B^{CH_3}/\Sigma$	0.146	0.269	0.356	0.203	0.228	0.204

[a] Based on 67.3% II and 32.6% I. Exact solution is 70.0% II, 34.0% I, and −9.79% III. [b] Based on 72.0% I and 28:0% III. Exact solution is 73.7% I, 28.7% III, and −2.60% II. [c] $\Sigma = \Delta_B^H + \Delta_B^{H'} + \Delta_B^{CH_3}$.

X. To simplify the determination of the rotamer populations, the induced shift ratios were expressed relative to the ethyl group protons only. The three linear equations 2a–c,

$$\left(\frac{\Delta_B{}^H}{\Sigma\Delta_B}\right)_{av}^{obsd} = n_I\left(\frac{\Delta_B{}^H}{\Sigma\Delta_B}\right)_I^{calcd} + n_{II}\left(\frac{\Delta_B{}^H}{\Sigma\Delta_B}\right)_{II}^{calcd} + n_{III}\left(\frac{\Delta_B{}^H}{\Sigma\Delta_B}\right)_{III}^{calcd} \tag{2a}$$

$$\left(\frac{\Delta_B{}^{H'}}{\Sigma\Delta_B}\right)_{av}^{obsd} = n_I\left(\frac{\Delta_B{}^{H'}}{\Sigma\Delta_B}\right)_I^{calcd} + n_{II}\left(\frac{\Delta_B{}^{H'}}{\Sigma\Delta_B}\right)_{II}^{calcd} + n_{III}\left(\frac{\Delta_B{}^{H'}}{\Sigma\Delta_B}\right)_{III}^{calcd} \tag{2b}$$

$$\left(\frac{\Delta^{CH_3}}{\Sigma\Delta_B}\right)_{av}^{obsd} = n_I\left(\frac{\Delta_B{}^{CH_3}}{\Sigma\Delta_B}\right)_I^{calcd} + n_{II}\left(\frac{\Delta_B{}^{CH_3}}{\Sigma\Delta_B}\right)_{II}^{calcd} + n_{III}\left(\frac{\Delta_B{}^{CH_3}}{\Sigma\Delta_B}\right)_{III}^{calcd} \tag{2c}$$

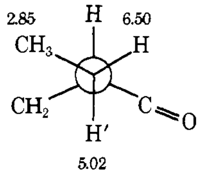
where $\Sigma\Delta_B = \Delta_B{}^H + \Delta_B{}^{H'} + \Delta_B{}^{CH_3}$, can then be solved to give the mole fractions of each of the rotamers (n_I, n_{II}, and n_{III}) present at equilibrium. Based on the shift results, there is no way to know which of the two observed induced shift ratios should be assigned to which of the two methylene protons. One assignment yields rotamer populations of n_I = 32.6% and n_{II} = 67.4%, while the other assignment yields rotamer populations of n_I = 72.0% and n_{III} = 28.0%. The calculated induced shift ratios using these rotamer populations are included in Table X.

The rotamer populations of *trans*-2-ethyl-4-*tert*-butylcyclohexanone have been determined in a similar manner. The calculated and observed induced shift ratios for the protons of the 2-ethyl group in this compound are presented in Table XI. One assignment for the methylene protons yields rotamer populations of n_{IV} = 70.5% and n_{VI} = 29.5%. If the methylene proton assignments are reversed, a good fit between the observed and calculated induced shift ratios can only be obtained if the rotamer with the methyl group under the ring, V, is the predominant rotamer: n_{IV} = 23.1%, n_V = 70.8%, n_{VI} = 4.1%. Since the methyl under the ring interaction appears to be highly unfavorable,[2] the solution with a predominance of V does not appear to be reasonable.

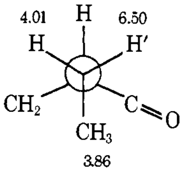
For *cis*-2-isopropyl-4-*tert*-butylcyclohexanone, the calculated rotamer populations together with the observed and calculated induced shift ratios are listed in Table XII. In this case, an uncertainty arises for the methyl group assignments. One assignment for the methyl group protons yields rotamer populations of n_{VII} = 62.4% and n_{VIII} = 37.6%, while reversal of the assignments yields rotamer populations of n_{VII} = 67.2%, n_{VIII} = 24.7%, and n_{IX} = 8.1%. In this case, the alternate methyl group assignments yield very similar population ratios, because the induced shift ratios for the methyl groups are very similar. For *trans*-2-isopropyl-4-*tert*-butylcyclohexanone, the calculated rotamer populations together with the observed and calculated induced shift ratios are listed in Table XIII. By use of one set of methyl group assignments, rotamer populations of n_X = 12.2% and n_{XI} = 88.8% are obtained. Reversal of the methyl group assignments leads to a large negative population[19] of rotamer XI (−18%). Since, on energetic grounds, rotamer XI would be expected to be the favored form,[3] this alternate solution to the rotamer populations has not been considered further.

The reasonableness of the derived rotamer populations for each of the different 2-alkyl groups can be verified by several methods. In the solution of the rotational population equations, no *a priori* limitation was placed on the values which the populations could assume. Of course, to be chemically reasonable, the individual populations would have to be positive, and the sum of the populations must be equal to

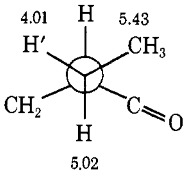
Table XI. Comparison of Experimental with Calculated Shift Ratios for *trans*-2-Ethyl-4-*tert*-butylcyclohexanone



IV



V

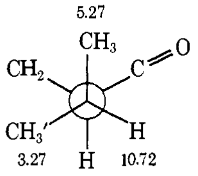


VI

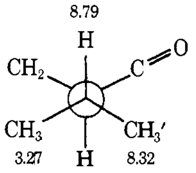
	IV	V	VI	Obsd	Calcd[a]
Δ_B^H/Σ^b	0.452	0.279	0.347	0.435	0.420
$\Delta_B^{H'}/\Sigma$	0.349	0.452	0.277	0.316	0.327
$\Delta_B^{CH_3}/\Sigma$	0.198	0.269	0.375	0.248	0.250

[a] Based on 70.5% IV and 29.5% VI. Exact solution is 77.4% IV, 32.5% VI, and −9.9% V. [b] $\Sigma = \Delta_B^H + \Delta_B^{H'} + \Delta_B^{CH_3}$.

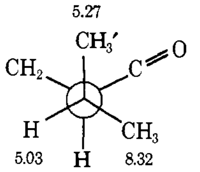
Table XII. Comparison of Experimental with Calculated Shift Ratios for *cis*-2-Isopropyl-4-*tert*-butylcyclohexanone



VII



VIII

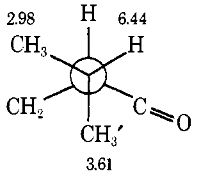


IX

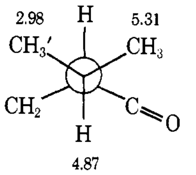
	VII	VIII	IX	Obsd	Calcd[a]	Calcd[b]
$\Delta_{\mathrm{B}}^{\mathrm{H}}/\Sigma$[c]	0.557	0.431	0.270	0.503	0.509	0.503
$\Delta_{\mathrm{B}}^{\mathrm{CH_3}}/\Sigma$	0.274	0.160	0.447	0.238 or 0.260	0.231	0.260
$\Delta_{\mathrm{B}}^{\mathrm{CH_3'}}/\Sigma$	0.170	0.408	0.283	0.260 or 0.238	0.259	0.238

[a] Based on 62.4% VII and 37.6% VIII. Exact solution is 60.0% VII, 36.5% VIII, and 3.0% IX. [b] Based on 67.2% VII, 24.7% VIII, and 8.1% IX. [c] $\Sigma = \Delta_{\mathrm{B}}^{\mathrm{H}} + \Delta_{\mathrm{B}}^{\mathrm{CH_3}} + \Delta_{\mathrm{B}}^{\mathrm{CH_3'}}$.

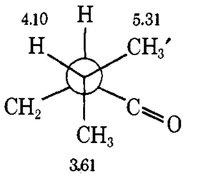
Table XIII. Comparison of Experimental with Calculated Shift Ratios for *trans*-2-Isopropyl-4-*tert*-butylcyclohexanone



X



XI



XII

	X	XI	XII	Obsd	Calcd[a]	Calcd[b]
$\Delta_{\mathrm{B}}^{\mathrm{H}}/\Sigma$[c]	0.494	0.370	0.315	0.388	0.389	0.370
$\Delta_{\mathrm{B}}^{\mathrm{CH_3}}/\Sigma$	0.229	0.403	0.277	0.379	0.385	0.403
$\Delta_{\mathrm{B}}^{\mathrm{CH_3'}}/\Sigma$	0.277	0.226	0.408	0.227	0.234	0.226

[a] Based on 12.2% X and 88.8% XI. Exact solution is 14.7% X, 87.7% XI, and −3.0% XII. [b] Based on 100% XI. [c] $\Sigma = \Delta_{\mathrm{B}}^{\mathrm{H}} + \Delta_{\mathrm{B}}^{\mathrm{CH_3}} + \Delta_{\mathrm{B}}^{\mathrm{CH_3'}}$.

1.0. In each case, the sum of the derived rotamer populations is indeed nearly 1.0, and no large negative populations for any individual rotamer are found.[20] An alternate procedure is to use the derived rotamer populations together with the relative induced shift ratios for both the ring and side-chain protons as input to the computer calculations and redetermine new *R* factors and a new optimized lanthanide location. The rotamer populations can then be varied and the calculation repeated. The best set of rotamer populations should then also have the smallest computed *R* factor in each case. For *cis*-2-ethyl-4-*tert*-butylcyclohexanone, the dependence of the computed *R* factor on the assumed rotamer populations is given in Table XIV. For an alternate structure to be rejected at the 0.10 significance level, the *R* factor ratio[21,22] would have to be greater than 1.448. The *R* factor does increase when the best-fit rotamer population is varied but not dramatically.

Table XIV. Dependence of *R* Factors on Rotamer Populations for *cis*-2-Ethyl-4-*tert*-butylcyclohexanone

	Rotamer populations, %		
R factor, %	I	II	III
4.37	0	60	40
3.60	0	70	30
4.54	0	80	20
4.07	50	50	0
3.15	60	40	0
4.42	70	30	0

Although the *R*-factor calculation method does provide for more straightforward statistical testing, the method is considerably more cumbersome and does not lead to obviously improved results. Direct solution of the three simultaneous equations to yield the rotamer populations is considerably more straightforward and does not lead to obviously inferior results.

Vicinal spin–spin coupling constants exhibit a well-known dihedral angle dependence[23] and can, in favorable cases, be used to determine rotamer populations.[24] The observed spin–spin coupling constants between the 2-position proton on the ring and the proton on the side-chain carbon attached to the 2 position will be population weighted averages of the coupling constants for a gauche, J_g, and a trans, J_t, relationship of these protons. The observed values are listed in Table XV. Using the observed values for the *cis*-methyl derivative and the *trans*-isopropyl derivative, values of J_g = 4.6 Hz and J_t = 11.7 Hz were obtained.[25] These coupling constant values together with the proposed rotamer populations can then be used to calculate rotationally averaged coupling constants for the *cis*-ethyl, *trans*-ethyl, and *cis*-isopropyl compounds.[26] The calculated values obtained by this method are included in Table XV.

Table XV. Vicinal Proton–Proton Spin Coupling Constants for 2-Alkyl-4-*tert*-butylcyclohexanones

	$^{3}J_{\mathrm{2H,C\alpha H}}$, Hz	
R	Obsd	Calcd[a]
cis-Me	7.0	7.0
trans-Me	7.0	7.0
cis-Et, Δ_{B} = 7.39[b]		4.6,[c] 9.7[d]
Δ_{B} = 9.99[b]		6.9,[c] 6.6[d]
trans-Et	7.0	6.7[e] 8.2[e]
cis-*i*-Pr	6.0	6.0[f]
trans-*i*-Pr	11.0	11.0

[a] Using J_g = 4.6 Hz and J_t = 11.7 Hz. [b] See ref 26. [c] Using the populations of Table X, footnote *a*. [d] Using the population of Table X, footnote *b*. [e] Using the population of Table XI, footnote *a*. [f] Using the population of Table XII, footnote *a*.

The rotamer populations obtained by the induced shift ratio method apply only to the substrate–lanthanide chelate complex. Since the vicinal coupling constants were obtained at low concentrations of $Eu(fod)_3$-d_{27}, the coupling constants apply predominantly to the uncomplexed form of the ketone. The fact that the averaged coupling constants are consistent with the rotamer populations in the complexed ketones suggests that the rotamer populations are not radically different in the free and complexed ketone. Several reports have recently appeared on the use of lanthanide shift reagents for structural determinations. These include the structures of lactams,[27] amides and diamides,[28] six-membered ring phosphorus heterocycles,[29] and 3-arylcyclohexanones.[30] In each of these cases, shift reagents have been used to determine conformations with no apparent effect on the conformational equilibrium being studied. Our previous results for the ring inversion of 2-alkylcyclohexanones show no apparent effect on the chair–chair equilibrium constants on complexation with the lanthanides.[4] However, Bentrude, Tan, and Yee have presented evidence that $Eu(dpm)_3$ perturbs the conformations of 2-substituted 5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinanes.[31] Until further studies have been reported, conformational analysis using lanthanide shift reagents must proceed with due caution.

The relative stabilities of the rotamers for the equatorial and axial isopropyl groups are consistent with those deduced by Wellman, Briggs, and Djerassi[32] based upon variable-temperature circular dichroism studies of 2α-isopropyl-19-nor-5α-androstan-3-one and 2β-isopropyl-19-nor-5α-androstan-3-one. For equatorial ethyl and isopropyl groups, the relative stabilities of the rotamers are not in agreement with those proposed by Cotterill and Robinson.[33] The expectation[33b] of a correlation of the rotamer populations with the cyclohexanone conformational preferences for these alkyl groups does not appear to be borne out.

Experimental Section

cis-**2-Methyl-4-***tert***-butylcyclohexanone.** The silyl enol ether of 4-*tert*-butylcyclohexanone was prepared using the procedure of House, *et al.*[34] To 30.0 g (0.19 mol) of 4-*tert*-butylcyclohexanone were added 27.1 g (0.25 mol) of distilled trimethylchlorosilane, 50.5 g (0.50 mol) of triethylamine, and 100 ml of dimethylformamide. The solution was refluxed for 24 hr, during which time a large quantity of precipitate formed. After cooling, the reaction was extracted with Skelly A. The organic extracts were rapidly washed in succession with cold 1.5 *M* hydrochloric acid and cold, saturated sodium bicarbonate. This procedure was repeated twice more. The residue left after removal of the solvent was distilled to give 35.8 g (82%) of the silyl enol ether of 4-*tert*-butylcyclohexanone, bp 94–101° (2.8 mm) [lit.[34] 98° (4.2 mm)]. The ir showed the absence of the carbonyl stretching band. A band was observed at 1670 cm^{-1} (C=C stretch).

The alkylation procedure of House, *et al.*,[35] was used. To 12.3 g (0.054 mol) of the silyl enol ether in 70 ml of dry ether was added 26 ml of methyllithium (0.059 mol of a 2.3 *M* solution in ether) with a syringe. The reaction was stirred for 30 min at room temperature after which time the ether was removed, and 100 ml of dry 1,2-dimethoxyethane was added. To this was added 9.9 g (0.07 mol) of methyl iodide. This mixture was stirred for 30 min and then partitioned between hexane and saturated sodium bicarbonate. After removal of the solvent, the residue was distilled, bp 114–120° (17 mm), to give 2-methyl-4-*tert*-butylcyclohexanone [lit.[36] 110–113° (14 mm)]. The cis isomer was purified by preparative vpc using 10% Silar 5 CP at 165°. The nmr spectrum was consistent with the cis conformer: δ 1.0 (d, J = 6.5 Hz, methyl group).[37]

trans-**2-Methyl-4-***tert***-butylcyclohexanone.** The procedure of House, *et al.*,[34,35] was again used except that 61.3 g (0.43 mol) of methyl iodide was used. The reaction was quenched 25 sec after addition of the methyl iodide to the silyl enol ether. The trans isomer was purified by preparative vpc on 10% Silar 5 CP at 165°. To keep the trans isomer from epimerizing, a glass lined injection port was used. The nmr spectrum was consistent with the trans isomer: δ 1.19 (d, J = 7.0 Hz, methyl group). The literature indicated that the methyl group of the trans isomer lies 0.19 ppm downfield from the cis isomer.[37]

cis-**2-Ethyl-4-***tert***-butylcyclohexanone.** To 15 g (0.066 mol) of the silyl enol ether of 4-*tert*-butylcyclohexanone in 70 ml of dry benzene was added 32 ml of *n*-butyllithium (0.074 mol of a 2.2 *M* solution in hexane). The reaction was refluxed for 2.5 hr, after which time 12.4 g (0.079 mol) of ethyl iodide in dry 1,2-dimethoxyethane was added. After an additional 1.5 hr of refluxing, the reaction was cooled and partitioned between Skelly A and saturated sodium bicarbonate. The residue left upon removal of the solvent was distilled to give 2-ethyl-4-*tert*-butylcyclohexanone, bp 76–90° (0.5 mm) [lit.[37] 88° (2.7 mm)]. The cis isomer was purified by spinning band distillation. Vpc analysis (OV 225, 50 ft × 0.020 in., 125°) on the purified cis isomer showed the purity to be better than 90%.

trans-**2-Ethyl-4-***tert***-butylcyclohexanone.** The pyrrolidine enamine of 4-*tert*-butylcyclohexanone was prepared in an analogous manner to that described in the synthesis of 2-ethylcyclohexanone.[3] The enamine was purified by distillation, bp 150° (20 mm) [lit.[36] bp 110–115° (0.03 mm)]. The ir showed a strong band at 1650 cm^{-1} [C=C stretch (lit.[36] 1640 cm^{-1})]. To 17.5 g (0.083 mol) of the enamine in 150 ml of dry benzene at 60° was added 18.5 g (0.11 mol) of ethyl iodide. The solution was refluxed for 24 hr, at which time the enamine was hydrolyzed with water. The residue left after work-up and removal of the solvent was distilled to give 2-ethyl-4-*tert*-butylcyclohexanone, bp 96–101° (3 mm) [lit.[37] bp 88° (2.7 mm)]. The trans isomer was purified by vpc using 10% Silar 5 CP at 180°. The injection port was glass lined to prevent epimerization of the ketone on the metal wall.

cis-**2-Isopropyl-4-***tert***-butylcyclohexanone.** To 40 g (0.29 mol) of 2-isopropylphenol (Aldrich Chemical Co.) were added 48 g (0.52 mol) of *tert*-butyl chloride and 3.3 g of aluminum chloride. The reaction was stirred for 2.5 hr at room temperature. Then an additional 16 g of *tert*-butyl chloride was added and the solution heated to 55° for an additional 2.5 hr. Then, an additional 16 g of *tert*-butyl chloride was added, and, after 12 hr, another 20 g was added. After stirring for 12 hr, the reaction was cooled and quenched with 250 ml of water. The residue left after work-up was distilled to give 30 g (50%) of 2-isopropyl-4-*tert*-butylphenol, bp 141–145° (20 mm) [lit.[35] bp 139.5° (28 mm)].

To 100 ml of 95% ethanol in a Parr shaker bottle were added 10 g (0.052 mol) of 2-isopropyl-4-*tert*-butylphenol, 1 ml of glacial acetic acid, and 5.0 g of rhodium on alumina (5%). The solution was hydrogenated in a Parr shaker for 14 hr, after which time, the solution was filtered and the solvent evaporated. The residue was distilled giving 5.5 g (54%) of a colorless liquid, bp 94–100° (2.0 mm) [lit.[37] bp 89° (2.7 mm)]. Infrared analysis showed that the ketone had been obtained instead of the alcohol (C=O stretching band at 1710 cm^{-1}). The cis isomer was purified by spinning band distillation.

trans-**2-Isopropyl-4-***tert***-butylcyclohexanone.** The procedure of Opitz, Mildenberger, and Suhr[38] was used. This procedure involves alkylation of the pyrrolidine enamine of 4-*tert*-butylcyclohexanone with isopropyl iodide in the presence of ethyldicyclohexylamine in acetonitrile. The enamine was prepared by the procedure given for *trans*-2-ethyl-4-*tert*-butylcyclohexanone. Ethyldicyclohexylamine was prepared using the procedure of Stodola.[39] Acetonitrile was purified by distilling the reagent grade material (Mallinckrodt AR) from phosphorus pentoxide immediately before use. To a refluxing solution of 14 g (0.06 mol) of the enamine in 100 ml of acetonitrile were added 7.0 g (0.041 mol) of isopropyl iodide and 14 g (0.06 mol) of ethyldicyclohexylamine dropwise. After the solution was refluxed for 12 hr, an additional 7 g of isopropyl iodide and 14 g of the amine were added. After another 24 hr of refluxing, an additional 7 g of isopropyl iodide and 14 g of ethyldicyclohexylamine were added. The reaction was refluxed for another 24 hr. After cooling the solution was partitioned between ether and water. The residue after removal of the ether was dissolved in hexane and washed with acetic acid and then with water. After removal of the hexane, the residue was bulb-to-bulb distilled. The trans ketone was purified by preparative vpc on 10% Silar 5 CP at 185°. As a check on the stereochemistry at the C_2 carbon, a small amount of the ketone was dissolved in methanol containing sodium methoxide. After 2 hr, vpc analysis (support coated open tubular column, OV 225, 50 ft × 0.020 in., 150°) showed that the cis isomer had appeared.

***cis*-2,4-Di-*tert*-butylcyclohexanone.** 2,4-Di-*tert*-butylphenol (10 g, 0.048 mol, Aldrich Chemical Co.) was catalytically hydrogenated with 5% rhodium on alumina as outlined in the synthesis of *cis*-2-isopropyl-4-*tert*-butylcyclohexanone. The residue remaining after removal of the solvent was distilled to give *cis*-2,4-di-*tert*-butylcyclohexanone, bp 95° (2.5 mm) [lit.[37] bp 89° (23 mm)]. Again, the ir showed a strong band at 1710 cm^{-1} (C=O stretch).

Yb(dpm)$_3$. This shift reagent was obtained from Merck Sharp and Dome. Precautions and experimental procedures were the same as outlined for Eu(fod)$_3$-d_{27}.[3]

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.

References and Notes

(1) John Simon Guggenheim Fellow, 1973–1974.

(2) (a) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," Wiley, New York, N.Y., 1965; (b) W. A. Thomas, *Annu. Rep. NMR Spectrosc.*, **3**, 91 (1970); (c) H. Booth, *Prog. Nucl. Magn. Resonance Spectrosc.*, **5**, 149 (1969).

(3) K. L. Servis and D. J. Bowler, *J. Amer. Chem. Soc.*, **97**, 73 (1975).

(4) K. L. Servis and D. J. Bowler, *J. Amer. Chem. Soc.*, **95**, 3392 (1973).

(5) J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Commun.*, 1506 (1970).

(6) M. R. Willcott, III, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972); R. E. Davis and M. R. Willcott, III, *ibid.*, **94**, 1744 (1972).

(7) G. E. Hawkes, D. Leibfritz, D. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **95**, 1659 (1973).

(8) M. Ochiai, E. Mizata, O. Aki, A. Morimoto, and T. Okada, *Tetrahedron Lett.*, 3245 (1972).

(9) B. Bleaney, C. M. Dobson, B. A. Levine, R. B. Martin, R. J. P. Williams, and A. V. Xavier, *J. Chem. Soc., Chem. Commun.*, 791 (1972).

(10) Roberts and coworkers[7] have checked this assumption for borneol and isoborneol using Eu(fod)$_3$ and Pr(fod)$_3$. They find that for these two alcohols the assumption is valid. In this study, we will assume that it is valid for the ketones used.

(11) For proton shifts, the contact contribution appears to be minimized when Yb(dpm)$_3$ is used as a shift reagent.[12]

(12) (a) O. A. Ganson, P. A. Loefflar, R. E. Davis, M. R. Willcott, III, and R. E. Lenkinski, *J. Amer. Chem. Soc.*, **95**, 3390 (1973); (b) J. Reuben, *J. Magn. Resonance*, **11**, 103 (1973).

(13) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1363 (1958).

(14) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969), and references contained therein.

(15) Professor N. L. Allinger kindly supplied these coordinates.

(16) R. E. Davis, M. R. Willcott, III, R. E. Lenkinski, W. Von E. Doering, and L. Birladeanu, *J. Amer. Chem. Soc.*, **95**, 6846 (1973).

(17) The O–Ln distances are similar to what has been found by LIS studies[6,11] and by X-ray diffraction.[18]

(18) *Cf.* W. D. Horrocks, Jr., J. P. Sipe, III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258 (1971).

(19) Negative population is, of course, meaningless.

(20) The small negative populations which result from the exact solutions undoubtedly indicate the inaccuracies in this method. The rotamer populations have been adjusted to remove the small negative values.

(21) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(22) All the alternate structures can be rejected at the 0.25 significance level except for those two with *R* factors of 3.60 and 3.15% in Table XIV.

(23) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) E. Becker, "High Resolution NMR," Academic Press, New York, N.Y., 1969, p 104.

(24) J. W. Emsley, J. Feeney, and L. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1965.

(25) The relationships assumed were $^3J^{\mathrm{Me}} = \frac{1}{3}(2J_g + J_t)$ and $^3J^{i\mathrm{-Pr}} = 0.9J_t + 0.1J_g$.

(26) For the *cis*-ethyl compound, the coupling constants cannot be directly obtained. However, the width of the multiplet is smaller for the methylene proton with the larger induced shift. Except for the coupling constant with the 2-position ring proton, the coupling constants for the two methylene protons should be identical. Any difference in the width of the multiplets for the two methylene protons must arise from differences in the coupling constants to the 2-position ring proton. The greater width of the less shifted multiplet indicates that coupling to the less shifted methylene proton is greater than the coupling to the more shifted methylene proton. This is consistent only with the populations of Table X, footnote *b*. For the *trans*-ethyl compound, the coupling constant to only one of the methylene protons could be measured.

(27) (a) P. V. Demarco, B. J. Cerimele, R. W. Crane, and A. L. Thakkar, *Tetrahedron Lett.*, 3539 (1972); (b) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971); (c) H. L. Ammon, P. H. Mazzocchi, J. Kopedky, Jr., H. J. Tamburin, and P. H. Watts, Jr., *ibid.*, **95**, 1968 (1973).

(28) (a) G. Montaudo and P. Finocchiaro, *J. Org. Chem.*, **37**, 3434 (1972); (b) G. Montaudo, P. Finocchiaro, and C. G. Overberger, *J. Polym. Sci., Part B*, **11**, 619 (1973).

(29) W. G. Bentrude and J. H. Hargis, *J. Amer. Chem. Soc.*, **92**, 7136 (1970).

(30) (a) B. L. Shapiro, M. D. Johnston, and M. J. Shapiro, *Org. Magn. Resonance*, **5**, 21 (1973); (b) B. L. Shapiro, M. D. Johnston, and T. W. Proulx, *J. Amer. Chem. Soc.*, **95**, 520 (1973).

(31) W. G. Bentrude, H. Tan, and K. C. Yee, *J. Amer. Chem. Soc.*, **94**, 3264 (1972).

(32) K. M. Wellman, W. S. Briggs, and C. Djerassi, *J. Amer. Chem. Soc.*, 87, 73 (1965).

(33) (a) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 777 (1964); (b) M. J. T. Robinson, "Conformational Analysis," Butterworths, London, 1971, p 635.

(34) H. O House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(35) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

(36) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

(37) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

(38) G. Opitz, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 47 (1961).

(39) F. H. Stodola, *Microchem. J.*, 7, 389 (1963).