response factors of the two compounds into account.

The pentane was removed by distillation and the 2-nitropropane and 2-bromo-2-nitropropane were separated by preparative GLC on a $^1/_4$ in. × 12 ft column of SF-96 on Chromosorb W (column temperature 85 °C, detector temperature 180 °C, injector temperature 110 °C, flow rate 60 mL/min). The purity of the 2-bromo-2-nitropropane was checked by GLC. Analyses for radioactivity were conducted on a Beckman LS-100C liquid scintillation counter on 50-mg samples in 15 mL of scintillation cocktail (26.50 g of butyl-PBD scintillator in 8 pints of toluene). Three samples were counted for each run to ±0.2% (2σ) precision.

Isotope effects were calculated from the equation[33]

$$\frac{k_1}{k_2} = \frac{\log (1 - F_1)}{\log [1 - F_1(R_p/R_0)]} \quad (9)$$

where F_1 is the fraction of reaction, R_0 is the molar activity of the original 2-nitropropane, R_p is the molar activity of the 2-bromo-2-nitropropane isolated from the reaction mixture, and k_1/k_2 is k_{12}/k_{14}. The data and the derived isotope effects are listed in Table I.

(33) Melander, L.; Saunders, W. H., Jr. "Reaction Rates of Isotopic Molecules"; Wiley-Interscience: New York, 1980; p 100.

Optical Rotary Dispersion Studies. 129.[1] Conformational Isotope Effects and Octant Contributions of CD_3 and $^{13}CH_3$ Groups in Cyclohexanone

Shy-Fuh Lee, Mark Edgar, Chwang Siek Pak, Günter Barth, and Carl Djerassi*

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received December 21, 1979*

Abstract: Through the variable-temperature circular dichroism measurements of (2*S*)-2-methyl-d_3-2-methylcyclohexanone (**3**) and (2*S*)-2-methyl-^{13}C-2-methylcyclohexanone (**4**), quantitative values for the conformational isotope effect are obtained. The chair conformation with the heavier isotope in the equatorial position is found to be energetically preferred by 3.4 and 1.5 cal/mol for **3** and **4**, respectively, and empirical force-field calculations qualitatively confirm this view. The CD_3 and $^{13}CH_3$ groups act as weaker octant perturbers compared to CH_3.

Introduction

The investigation of steric isotope effects, i.e., the effect of differences in the "effective size" between different isotopes, has been investigated primarily through kinetic studies where this phenomenon is most easily measurable.[2] The conformation of the transition state has to be known to obtain quantitative values through this method, as for example the difference in van der Waals radii, information which is rarely available. A more direct approach to this question would be the determination of the effect which an isotopic substitution exerts on the composition of a dynamic conformational equilibrium. Experimental verification for the existence of this "conformational isotope effect" has only recently become available.

Using ^{13}C NMR chemical shifts, Baldry and Robinson[3] concluded that for *trans*-1-methyl-d_3-3-methyl substituted cyclohexanes (e.g., compound **1**, Scheme I) the conformation with the CD_3 substituent in the axial position is favored by ca. 11 cal/mol. This value corresponds to an equilibrium shift of 0.6% toward **1**-ax (Scheme I) at room temperature. Two other studies[4,5] have interpreted the unusually large NMR chemical shifts introduced through deuterium substitution in terms of conformational isotope effects but did not attempt to evaluate the conformational-energy differences.

From our studies,[6,7] using variable-temperature circular dichroism measurements, we have shown that for 2,2-dimethylcyclohexanones, substituted with deuterium in various ring positions (e.g., compound **2**, Scheme I), the conformer with the deuterium in the axial position is energetically more stable by 2 to 7 cal/mol, which corresponds to a 0.09 to 0.30% equilibrium shift towards **2**-ax (Scheme I). Therefore, the results of both these studies are consistent in that deuterium is found to occupy preferentially the position of higher strain (e.g., axial), which is in agreement with the results from the kinetic investigations that deuterium is of "smaller size" compared to hydrogen. The high sensitivity of the circular dichroism measurements toward such small changes in a conformational equilibrium was achieved by dimethylation of the α position. While the *gem*-dimethyl group does not contribute by itself to any preference of one conformer over the other, it causes the rotational strengths of both conformers to be large numbers of opposite sign (see Scheme I); therefore we have termed this group a "chiral probe".

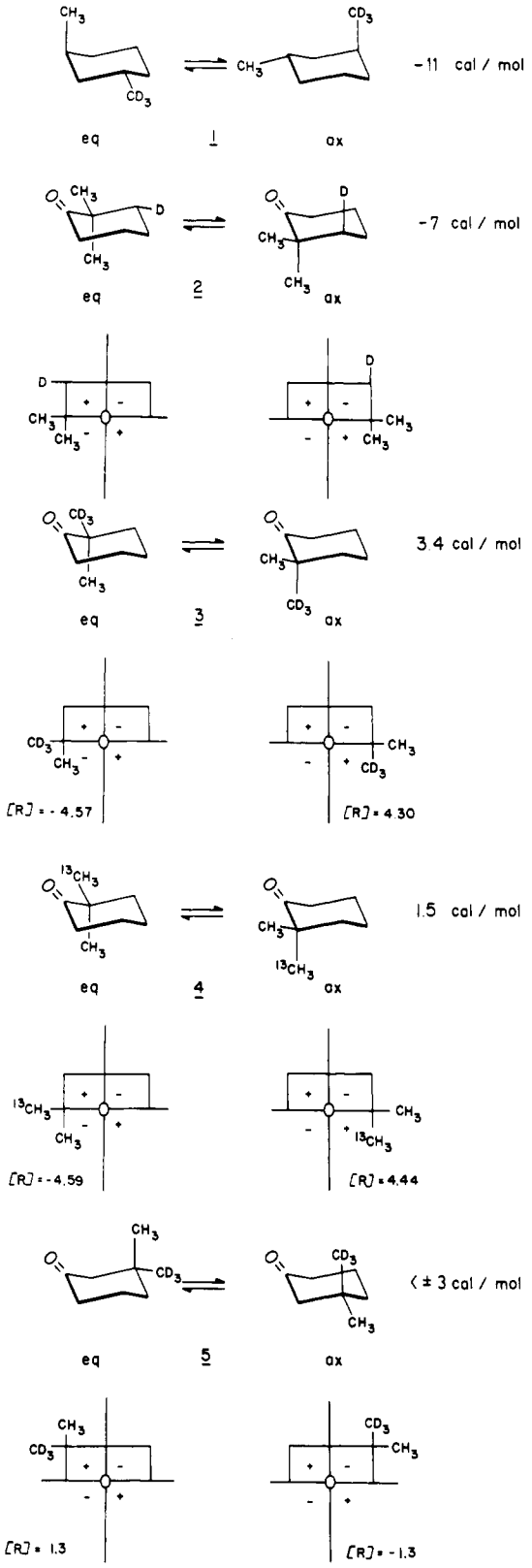
By applying the same principle, we report here the conformational isotope effects for the equilibria of (2*S*)-2-methyl-d_3-2-methylcyclohexanone (**3**), (2*S*)-2-methyl-^{13}C-2-methylcyclohexanone (**4**), and (3*R*)-3-methyl-d_3-3-methylcyclohexanone (**5**). These compounds can be assumed to exist exclusively in a dynamic equilibrium between two chair conformations, which are reproduced in Scheme I together with their octant representations. As has been observed for **1** and **2**, the isotopic "size difference" is expected to bias the equilibria of **3**–**5** slightly toward one or the other side. Quantitative evaluation of the energy differences from the temperature-dependent circular dichroism spectra requires a knowledge of the rotational strengths of the specific conformers. For **3** we obtained these values from conformationally rigid (2*S*,4*R*)-2-methyl-d_3-2-methyl-4-*tert*-butylcyclohexanone (**6**) and (2*R*,4*R*)-2-methyl-d_3-2-methyl-4-*tert*-butylcyclohexanone (**7**) with the CD_3 substituent in the axial and equatorial position, respectively. A comparison of the circular dichroism spectra of these two compounds with that of the previously reported[1] (4*R*)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**8**) allows us to obtain values for the relative octant contributions of the CD_3 group in various positions of the cyclohexanone ring—a subject which is discussed in detail in the present paper.

Synthesis. The synthesis of compounds **3** and **5**–**8** starting with (+)-nopinone (**10**) of known optical purity was achieved by the reaction steps outlined in Scheme II. Stepwise alkylation under

(1) For preceding paper see: Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.*, **1980**, *102*, 2737-45.
(2) For a recent review on this subject see: Carter, R. E.; Melander, L. *Adv. Phys. Org. Chem.* **1973**, *10*, 1-27.
(3) Baldry, K. W.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1663-1668.
(4) Calvert, R. B.; Shapley, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 7726-7727.
(5) Anet, F. A. L.; Dekmezian, A. H. *J. Am. Chem. Soc.* **1979**, *101*, 5449-5451.
(6) Lee, S.-F.; Barth, G.; Kieslich, K.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 3965-3966.
(7) Lee, S.-F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1978**, *100*, 8010-8012.

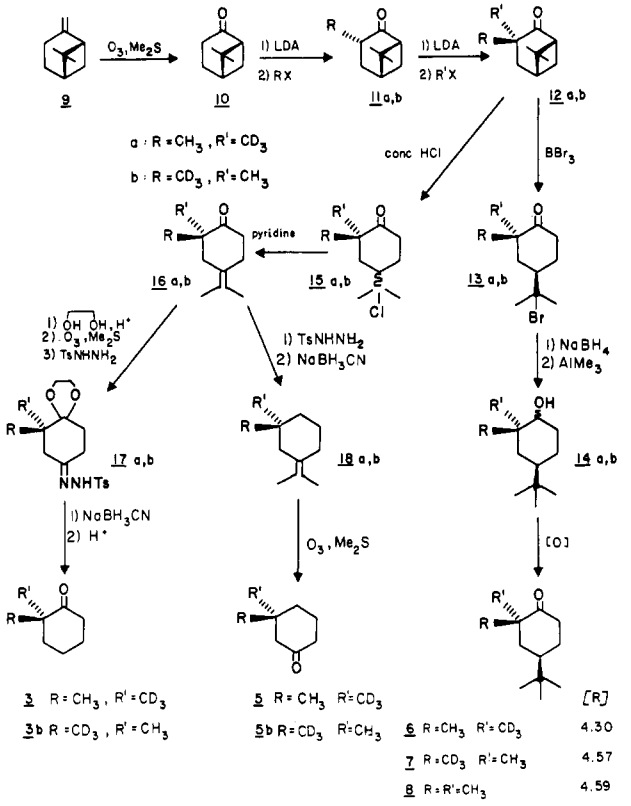
0002-7863/80/1502-4784$01.00/0

Scheme I

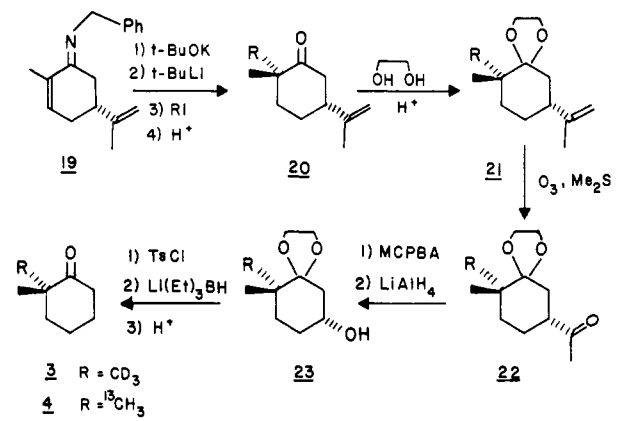


kinetic control[8] proceeds with high stereoselectivity from the sterically least hindered side opposite to the *gem*-dimethyl bridge leading to **12a** and **12b**. Ring opening can be carried out under conditions which lead to retention of configuration[7,9] or racemization[10] of the chiral center at C-4 (intermediates **13a,b** and

Scheme II



Scheme III



15a,b, respectively). Removal of the 2-chloroisopropyl substituent of **15** via dehydrochlorination (**16**), ketalization, ozonolysis, tosylhydrazone formation,[12] $NaBH_3CN$ reduction, and removal of the protective ketal group provided **3**. Removal of the ketone group of **16** via the tosylhydrazone and reduction with $NaBH_3CN$ led to **18a,b** which was converted to **5a,b** by ozonolysis. Compounds **6–8** were accessible through $NaBH_4$ reduction and alkylation with $Al(CH_3)_3$ of **13** followed by oxidation of the alcohols **14a,b**. By simple reversal of the alkylation sequence of (+)-nopinone (**10**), both enantiomers of **3** and **5** were synthesized which showed mirror-image circular dichroism spectra. An independent synthesis of **3** was accomplished through alkylation[11] of the Schiff base of (−)-carvone (**19**)[12] and removal of the isopropenyl group as shown in Scheme III. The degree of stereoselectivity of the methylation step was deduced from the ^1H NMR spectra (α-methyl resonance) of the various intermediates (**20** to **22**) and was determined to

(8) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50–52.
(9) Levine, S. G.; Gopalakrishnan, B. *Tetrahedron Lett.* **1979**, 699–702.
(10) Van Der Jen, A.; Van Der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1034–1044.
(11) Wender, P. A.; Eisenstat, M. A. *J. Am. Chem. Soc.* **1978** *100*, 292–294.
(12) Malhotra, S. K.; Moakley, D. F.; Johnson, F. *Chem. Abstr.* **1969**, *71*, 113112x (U.S. Patent 3 463 810).

be 74.1% *cis*-methyl-d_3 with respect to the C-5 substituent. As a result, compound **3** has an enantiomeric excess of 48.2%. The circular dichroism spectra of **3** as obtained by these two synthetic routes were found to be in excellent agreement with each other, thus establishing the absolute configuration and optical purity unambiguously. Synthesis of the corresponding $^{13}CH_3$ derivative **4** was accomplished in the same manner as for **3** (see Scheme III), using iodomethane-^{13}C instead of iodomethane-d_3.

Conformational Isotope Effects. The circular dichroism spectra of **3** and **4** in IPM (isopentane–methylcyclohexane 4:1) at room temperature and 77 K are shown in Figure 1a,b. In both cases, a negative Cotton effect is observed and the rotational strength decreases (i.e., becomes more negative) on lowering the temperature to 77 K. Before discussing these intensity changes in terms of shifts in the conformational equilibria, alternative possibilities should be considered. Temperature dependent solvation[13] or dimerization equilibria[14] have been observed for a variety of ketones even in such nonpolar solvent systems as hydrocarbons. The solvated and unsolvated species can have distinctly different rotational strengths. In a previous study,[1] we have investigated the circular dichroism spectrum of **8** in solvents of different polarity and at different temperatures. No intensity changes were observed in IPM and we concluded that in this solvent system solvational equilibria are not present. By analogy we infer that this also applies to **3** and **4**. Furthermore, the observed temperature-dependent changes ($\Delta[R] = -0.041$ for **3** and $\Delta[R] = -0.021$) are well outside the experimental error of measurement which is estimated to be $\Delta[R] = \pm 0.003$.

For these reasons, we feel confident that the observed intensity changes are associated with a temperature-dependent equilibrium shift, which leads to the conclusion that qualitatively the conformer with the negative rotational strength becomes more populated on lowering the temperature. From inspection of the octant diagrams of **3** and **4** (Scheme I), it is therefore the conformation with the CD_3 and $^{13}CH_3$ group in the equatorial position which is energetically preferred. Use of the estimates for the rotational strengths of these conformers as obtained from the conformationally "locked" compounds **6**–**8**[1] (see discussion below) gives conformational energy differences of 3.4 ± 0.7 and 1.5 ± 0.5 cal/mol[6,7] for equilibria of **3** and **4**, respectively (Scheme I). For **5** in the 3,3-dimethylcyclohexanone series, only a very small intensity change of $\Delta[R] = -0.006$ is observed (Figure 1c) on lowering the temperature to 77 K. This value is too close to the experimental error limit to be ascribed to a conformational change. Furthermore, it should be noted that, since the rotational strength ($[R] = \pm 1.3$) of the two chair conformers of **5** (Scheme I) amounts only to about 29% of the corresponding values ($[R] = 4.5$) for the conformers of **3** and **4**, the sensitivity of the circular dichroism measurements of **5** toward changes in the conformational equilibrium will be reduced by the same factor.[7] Therefore the only statement one can make from these measurements about equilibrium **5** is that the energy difference is less than ±3 cal/mol. We wish to point out that the above interpretation rests on the assumption that the equilibria are completely described by the two possible chain conformations (Scheme I), i.e., that other conformations like the twist forms do not participate.

Our results for **3** and **4** lead us to the conclusion that in contrast to the steric situation for *trans*-1-methyl-d_3-3-methylcyclohexane (**1**),[3] the α-axial methyl (rather than CD_3 or $^{13}CH_3$) substituent in cyclohexanone is sterically more favored than the equatorial position. This conclusion is in clear contradiction to the well-known observation that, for instance, in α-methylcyclohexanone the conformation with the methyl group in the equatorial orientation is energetically more stable by 1.6 kcal/mol[16,17] compared to the

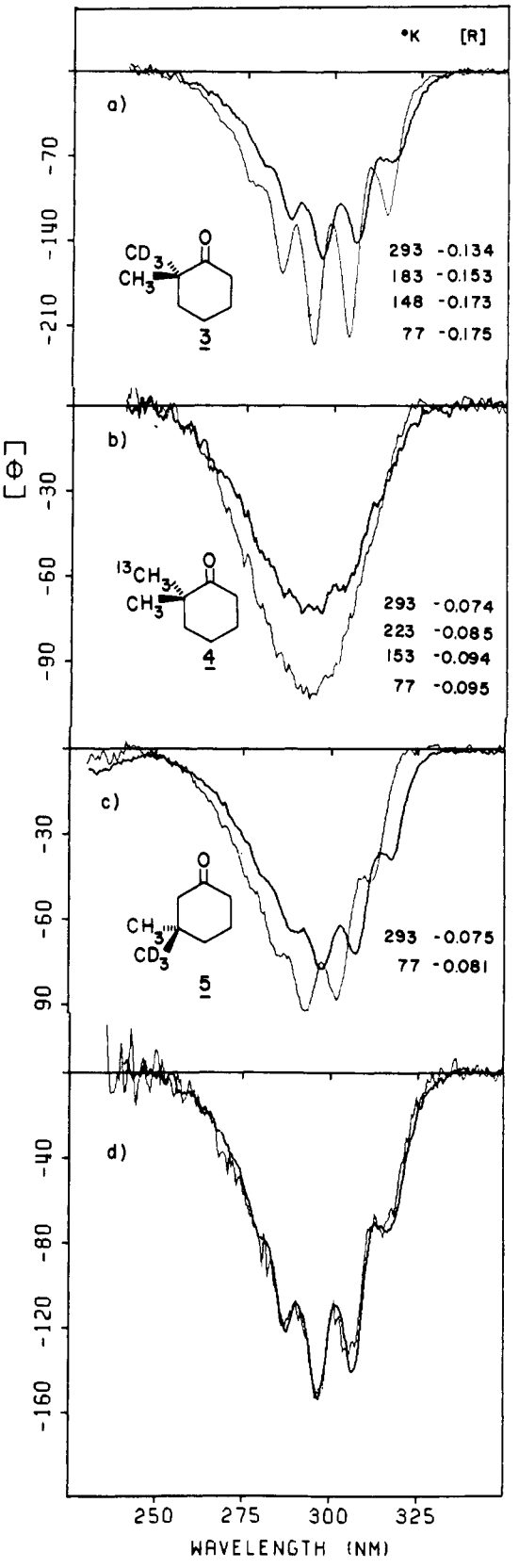


Figure 1. Circular dichroism spectra of (a) (2*S*)-2-methyl-d_3-2-methylcyclohexanone (**3**); (b) (2*S*)-2-methyl-^{13}C-2-methylcyclohexanone (**4**); and (c) (3*R*)-3-methyl-d_3-3-methylcyclohexanone (**5**) in IPM (isopentane–methylcyclohexane 4:1 v/v) at room temperature (heavy line) and 77 K (thin line). (d) Heavy line: (2*S*)-2-methyl-d_3-2-methylcyclohexanone (**3**) in IPM at room temperature. Thin line: difference of (2*R*,4*R*)-2-methyl-d_3-2-methyl-4-*tert*-butylcyclohexanone (**7**) and (2*S*,4*R*)-2-methyl-d_3-2-methyl-4-*tert*-butylcyclohexanone (**6**) divided by 2. All spectra are corrected to 100% enantiomeric excess and isotopic purity.

(13) Rassat, A. (pp 314–328); Moscowitz, A. (pp 329–334) in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry"; Snatzke, G., Ed.; Heyden & Son: London, 1967.
(14) Pennington, R. E.; Kobe, K. A. *J. Am. Chem. Soc.* **1957**, *79*, 300–305.
(15) The values were obtained by a linear least-squares fit to the data points at four different temperatures (see Figure 1) in an Arrhenius diagram.
(16) Beard, C.; Djerassi, C.; Sicher, J.; Sipos, F.; Tichy, M. *Tetrahedron* **1963**, *19*, 919–928.

Table I. Empirical Force Field Calculations of Conformational Energy Differences[a]

compd	energy difference, cal/mol $E_{ax} - E_{aq}$[b] calcd	exptl
1	−20	−11
2	41	3.4
5	9	<±3
1-methyl-d_3-1-methylcyclohexane	−38	

[a] The EFF calculations were carried out by using the program MOLBD2 from Boyd, R. H. *J. Chem. Phys.* **1968**, *49*, 2574–2853. The bond deformation parameters were taken from Wertz, D. H.; Allinger, N. L. *Tetrahedron* **1974**, *30*, 1579–1586, and those for the nonbond interactions from ref 20. Parameter B in the equation $U_{st} = 0.5A(R_{ij} - B)$ was set to 1.07 for C-D vs. 1.092 for the C-H bond to obtain a foreshortening of the C-D bond; R_{ij} is the internuclear distance and A the bond-stretch force constant. [b] E_{ax} and E_{eq} are the minimum energies for the conformers with the deuterated substitution in the axial and equatorial position, respectively (see Scheme I).

one with the methyl group in the axial one, i.e., the larger substituent (CH_3 vs. H) preferentially occupies the sterically less-hindered equatorial position. This last argument has generally been used to disclaim earlier suggestions for the existence of a "2-alkyl ketone effect"[17] which implied that, due to a possible severe eclipse–interaction between an equatorial substituent and the carbonyl group, the energy relationship between an equatorial and axial substituent is different in cyclohexanone as compared to a cyclohexane ring. At the same time, it has been shown experimentally[17] that for apparently bulkier substituents like α-ethyl (1.1 kcal/mol) and α-isopropyl (0.4 kcal/mol), the energy difference is considerably less than that for a methyl group. Although such an investigation has not been carried out yet, one would predict from these data that, for example, 2-methyl-2-isopropropylcyclohexanone would exist in a conformational equilibrium shifted toward the conformation with the isopropyl group in the axial position, the reverse situation as compared to the corresponding cyclohexane derivative. In light of these arguments, the results obtained for **3** and **4** are not as unusual as they might appear at first sight.

To obtain further insight into this steric situation, we have carried out empirical force field (EFF)[18] calculations which have been shown[19–21] to predict quite accurately energy differences of conformational equilibria. Since, to our knowledge, no specific force constants for deuterium have been reported in the literature, we have chosen to foreshorten the C–D bond distance by 0.02 Å while leaving all other parameters the same as for hydrogen. From electron diffraction studies[22] it has been shown that the equilibrium bond distance of C–D is shorter by ca. 0.002 Å due to unharmonicity of the stretch potential. Probably a more important factor, however, is the difference in the mass-dependent vibrational amplitudes between the C–D and the C–H bond which has been determined[22] to be on the order of 0.01 Å. We also point out that Lightner et al.[23] have used a similar C–D bond shortening for their CNDO/S calculation of the rotational strengths of various ketones which owe their chirality to deuterium substitution and report generally good agreement with the experimental data.

The results of the EFF calculations for **1**, **3**, and **5** are summarized in Table I. Although no particular physical significance should be placed on the magnitude of the obtained data, their signs are in surprisingly good agreement with the experimental results. Table I also includes the calculated energy difference for 1-methyl-d_3-1-methylcyclohexane which is found to be −38 cal/mol in favor of the conformation with the CD_3 group in the axial position. This is a similar result as obtained for **1** but opposite to that of **3** (Table I). The EFF calculations therefore confirm that the vicinal relationship between the carbonyl and the *gem*-dimethyl groups is the determining factor for the differences between the cyclohexane **1** and the cyclohexanone **3**. For the 3,3-dimethyl analogue **5** the calculations predict again, although smaller in magnitude, an energetic preference for the equatorial CD_3 group. Because of the insufficient sensitivity of the variable-temperature circular dichroism measurements (see discussion above), this prediction is not amenable to experimental verification.

Table II. Relative Isotopic Octant Contributions $\delta[R]$ in Cyclohexanones[a]

position of substituent	CD_3	$^{13}CH_3$	CH_3 octant contributions[b]
α-equatorial	<±0.01	<±0.01	0.50–0.66
α-axial	−0.27	−0.15	3.94–6.54
β-equatorial[c]	−0.082	−0.013	1.66–1.99

[a] Values are expressed in terms of the difference of the reduced rotational strengths $\delta[R]$ between the contribution of the heavier isotope and the lighter one at the same or the mirror image position of the octant diagram. [b] Values taken from Kirk D. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1076–1103, and converted to $\delta[R]$ by using the empirical relationship $\delta[R] = 3.32 \times \delta\Delta\epsilon$. [c] Values taken from ref 26.

We also point to the remarkable difference in the resolution of vibronic fine structure between **3** and **4**. No vibronic sub-bands are discernable even at 77 K in the spectrum of **4** (Figure 1b) whereas the spectrum of **3** shows a clearly resolved progression of 5 bands (Figure 1a) with an almost equal spacing of 1136 ± 15 cm^{-1}, belonging to the carbonyl stretch mode in the excited state.

Isotope Octant Contributions. Since compounds **3**–**5** exist in a conformational equilibrium between their two chair conformations (see Scheme I), octant contributions for the CD_3 or $^{13}CH_3$ groups in the equatorial and axial position cannot be deduced directly from their circular dichroism spectra. Therefore, we have synthesized the conformationally rigid compounds **6** and **7** and compared them with 2,2-dimethyl-4-*tert*-butylcyclohexanone (**8**) which has been reported[1] previously. The $[R]$ values for **6**–**8** are given beneath their structures in Scheme II. Within experimental error (±0.005), compound **7**, with an equatorial CD_3 group, and **8** have identical rotational strengths, whereas **6**, with the CD_3 group in the axial position, has a 6% lower rotational strength compared to **8**. The relative octant contributions of a CD_3 group as obtained from these data are given in Table II. By subtraction (and division by two) of the circular dichroism spectrum of **7** and **6**, which represent conformationally fixed models for the chair conformations **3**-eq and **3**-ax (Scheme I), the circular dichroism spectrum (assuming a 50:50 equilibrium) is predictable, and this comparison is shown in Figure 1d. The excellent agreement between the computed and measured spectrum represents a confirmation of the quality of the circular dichroism data obtained for **6** and **7** and furthermore indicates that the introduction of the 4-*tert*-butyl group does not seem to influence the chiroptical properties of the cyclohexanone ring. It also justifies the above mentioned neglect of possible twist conformations in the energy calculation for the equilibria of **3** and **4**. Table II also includes relative octant contributions for an α-axial and α-equatorial $^{13}CH_3$ group. These values were obtained from **4**, assuming that as for CD_3 the relative contribution of an equatorial $^{13}CH_3$ group is negligibly small compared to its contribution in the axial position.

Consistent with the data obtained from other deuterium substituted ketones,[22–25] the C–D bond is found to be a weaker

(17) Eliel, L. E. "Stereochemistry of Carbon Compounds"; McGraw-Hill: London, 1962; p 240.
(18) For a recent review on this subject see: Altona, C.; Faber, D. H. *Fortschr. Chem. Forsch.* **1974**, *45*, 1–38.
(19) Engler, E. M.; Andose, J. D.; Schleyer, P. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005–8025.
(20) Fitzwater, S.; Bartell, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 5107–5115.
(21) Osawa, E.; Collins, J. B.; Schleyer, P. R. *Tetrahedron* **1977**, *33*, 2667–2675.
(22) Bartell, L. S.; Kuchitsu, K.; DeNeui, R. J. *J. Chem. Phys.* **1961**, *35*, 1211–1218.
(23) Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.*, **1980**, *102*, 1983–90.
(24) Lightner, D. A.; Chang, T. C.; Horwitz, J. *Tetrahedron Lett.* **1977**, 3019–3020. Errata: *Ibid.* **1978**, 696.

perturber than the C–H bond. The same conclusion applies for the substitution of ^{13}C vs. ^{12}C.[27,28] Therefore, the experimental evidence thus far accumulated leads to the conclusion that with few exceptions the heavier isotope is a weaker perturber concerning the octant contributions to the carbonyl n → π* transition Cotton effect. We also note (see Table II) that substitution of a CH_3 group vs. a CD_3 group causes a similar reduction of the rotational strength by a factor of ca. 1.06 when the methyl group is either α-axial or β-equatorial.[26] Although it would be premature to generalize this observation, we wish to point out that, if future data confirm this, it would lead to a useful application for obtaining estimates of methyl octant contributions in more complicated situations where the observed Cotton effect amplitude results from a larger number of other group contributions, especially since such a deuterium substitution will cause negligible conformational changes. In cases where an unusually large Cotton effect amplitude is suggestive of a deviation from the ideal chair conformation, a distinction between the contributions from the ring-twist and normal methyl contributions might be possible. Such an example was recently reported by us[1] for (2*R*,4*R*)-2-methyl-4-*tert*-butylcyclohexanone which showed a rotational strength of $[R] = -1.46$ (isooctane), whereas from application of the octant rule to the ideal chair form of this compound a rotational strength of close to zero would have been expected.

Experimental Section

Rotations were taken on a Perkin-Elmer 141 polarimeter in chloroform unless noted otherwise. A Varian Aerograph Series 2700 thermal-conductivity instrument equipped with 10 ft × 0.25 in. columns of 15% Carbowax 20M on Chromosorb W (column A), 20% Carbowax 20M on Chromosorb W (column B), or 10% SE-30 on Chromosorb W (column C) was used for preparative VPC. Circular dichroism spectra were recorded with a JASCO J-40 circular dichrometer and the low-temperature spectra were taken in a previously reported cell.[29] Nuclear magnetic resonance spectra were determined on a Varian T-60 or XL-100 instrument with deuteriochloroform as the solvent and tetramethylsilane as the internal strandard unless otherwise indicated. A Perkin-Elmer 700A infrared spectrophotometer was used to record the infrared spectra. Mass spectra were determined either on an AEI-MS-9 or a Varian MAT-44. Merck silica gel 60 (230–400 mesh) was used for column chromatography (wet-packed). Extracts were dried with anhydrous magnesium sulfate.

(+)-Nopinone (10). This compound was obtained from (−)-β-pinene (Aldrich) of known optical purity ($[\alpha]^{21}_D$ −21° (neat), 90% enantiomeric excess) as described earlier.[30]

3α-Methyl-d_3-nopinone (11b). To a solution of lithium *N*-isopropyl-*N*-cyclohexylamide, prepared from *N*-isopropyl-*N*-cyclohexylamine (5.7 g, 40 mmol) and *n*-butyllithium (14.4 mL, 34.6 mmol) in anhydrous THF (30 mL) at −78 °C, was added a solution of 4.0 g (29 mmol) of (+)-nopinone (**10**) in THF (5 mL). After being stirred for 2 h, the solution was warmed to 0 °C and iodomethane-d_3 (2.8 mL, 44 mmol) was introduced. The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The reaction mixture was poured into water and extracted with ether. The combined extracts were washed with 5% hydrochloric acid and brine, dried, and concentrated to give a pale yellow liquid composed of approximately 19% nopinone, 77% 3α-methyl-d_3-nopinone, and 4% 3,3-dimethyl-d_6-nopinone (column C, 140 °C). This mixture could be separated by high-performance liquid chromatography (Waters Association Inc. System 500, silica gel, 5% ethyl acetate–hexane) or by column chromatography (silica gel/compound 100 g/1 g, 5% ethyl acetate–hexane) to yield 3.2 g (71%) of methyl-d_3-nopinone (**11b**): $[\alpha]^{24}_D$ +58° (*c* 2.1); IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR δ 0.90 (s, 3 H), 1.33 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 155 (M^+, 35), 95 (60), 83 (100).

(+)-3α-Methylnopinone (11a). Employing the sequence as outlined above except replacing iodomethane-d_3 with iodomethane furnished methylnopinone (**11a**): $[\alpha]^{24}_D$ +58° (*c* 5.08); IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H NMR δ 0.90 (s, 3 H), 1.31 (d, 3 H, *J* = 6 Hz), 1.33 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 152 (M^+, 22), 83 (100).

(+)-3β-Methyl-3α-methyl-d_3-nopinone (12a). A solution of lithium *N*-isopropyl-*N*-cyclohexylamide in THF (25 mL) was prepared from *N*-isopropyl-*N*-cyclohexylamine (2.6 g, 18 mmol) and *n*-butyllithium (7.1 mL, 17 mmol) at −78 °C (nitrogen). To this solution was added (+)-3α-methylnopinone (2.0 g, 13 mmol) in THF (5 mL). After a period of 2 h, the solution was warmed to 0 °C and iodomethane-d_3 (1.5 mL) was slowly added. The temperature was maintained at 0 °C for 2 h followed by 12 h at 25 °C. Using an isolation procedure similar to that outlined for 3α-methyl-d_3-nopinone (**11b**) gave dimethyl-d_3-nopinone (**12a**) (1.5 g, 70%): $[\alpha]^{24}_D$ +69° (*c* 4.56); IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR δ 0.83 (s, 3 H), 1.23 (s, 3 H), 1.33 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 169 (M^+, 40), 95 (100).

(+)-3α-Methyl-3β-methyl-d_3-nopinone (12b). Using the experimental conditions (except iodomethane was used) listed above for **12a** in conjunction with (+)-3α-methyl-d_3-nopinone (**11b**) provided dimethyl-d_3-nopinone **12b**: $[\alpha]^{24}_D$ +76.8 ° (*c* 6.30); IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR δ 0.83 (s, 3 H), 1.31 (s, 3 H), 1.33 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 169 (M^+, 40), 95 (100).

(+)-(2*S*,4*R*)-2-Methyl-d_3-2-methyl-4-(2-bromo-2-propyl)cyclohexanone (13a). To a solution (−78 °C, argon) of (+)-3β-methyl-3α-methyl-d_3-nopinone (**12a**) (434 mg, 2.57 mmol) in methylene chloride (15 mL, distilled from P_2O_5) was added borontribromide (0.31 mL, 3.28 mmol).[9] After the pale yellow solution was stirred for 45 min, pyridine (0.78 mL, 10 mmol) and subsequently methanol (1.1 mL, 27 mmol) were added. The resulting colorless solution was poured into cold water (20 mL)/ether (20 mL). The isolated aqueous layer was extracted with ether and the combined organic extracts were washed with an oxalic acid solution (saturated) and brine, dried, and concentrated to an oil. Rapid (nitrogen pressure) separation by column chromatography (60 g of silica gel, 5% ethyl acetate-hexane) gave a colorless crystalline compound (426 mg, 66%) which could be further purified by sublimation [25 °C (0.5 mm)] to yield bromo ketone **13a**: mp 44–46 °C; $[\alpha]^{21}_D$ +74.8° (*c* 4.0); IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H NMR δ 1.08 (s, 3 H), 1.80 (s, 6 H); mass spectrum, m/z (relative intensity) 251 (M^+, 3), 249 (M^+, 3), 192 (5), 190 (4), 170 (20), 69 (100).

(+)-(2*R*,4*R*)-2-Methyl-d_3-2-methyl-4-(2-bromo-2-propyl)cyclohexanone (13b). Application of the procedure given above to (+)-3α-methyl-3β-methyl-d_3-nopinone (**12b**) gave bromo ketone **13b**: mp 42.5–44 °C; $[\alpha]^{21}_D$ +76.2° (*c* 8.9); IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H NMR δ 1.20 (s, 3 H), 1.80 (s, 6 H); mass spectrum (70 eV), *m/z* 251 (M^+, 4), 249 (M^+, 4), 192 (7), 190 (6), 170 (33), 69 (100).

(+)-(2*S*,4*R*)-2-Methyl-d_3-2-methyl-4-*tert*-butylcyclohexanone (6). Bromo ketone **13a** (426 mg, 1.70 mmol) was dissolved in methanol (8 mL) at 5 °C and then sodium borohydride (109 mg, 2.88 mmol) was introduced. The reaction mixture, after 25 min, was poured into cold (5 °C) hydrochloric acid (10 mL)/ether (15 mL). The aqueous phase was isolated and extracted with ether. The combined ether extract was washed with brine, dried, and concentrated to a gummy solid (453 mg). The crude hydroxy bromide (453 mg, 1.80 mmol) was placed in a 50-mL 3-necked round-bottom flask (the flask should only be filled to $^1/_3$ of the total volue due to foaming in the latter stages of the reaction) equipped with a gas inlet (with stopcock), dry ice condenser, and septum. An argon bubbler was attached to the dry ice condenser. The flask and condenser were cooled to −78 °C and then methyl chloride (bp −24 °C) was introduced through the gas inlet tube until a volume of ~9 mL was obtained. Trimethylaluminum (25% in hexane, 10 mL, 24 mmol) was added followed by removal of the cooling bath, thus causing the reaction mixture to reflux. After 2.5 h, the reaction flask was cooled to −78 °C and methanol (4.5 mL) was *slowly* introduced, followed by 10% hydrochloric acid (6 mL). The methyl chloride was removed (foaming) by allowing the dry ice condenser and the reaction flask to warm slowly to 25 °C. The reaction mixture was extracted with ether and the combined ether extracts were washed with brine, dried, and concentrated to a tarry residue. Chromatography (25 g of silica gel, 10% ethyl acetate–hexane) afforded *tert*-butylcyclohexanols **14a,b** (297 mg).

A solution of the *tert*-butylcyclohexanols **14a,b** (297 mg, 1.59 mmol) in ether (25 mL) was treated with a chromic acid solution[8] (250 drops). After 2.5 h, the reaction mixture was poured into water (30 mL) containing 1 g of sodium carbonate. Stirring was continued (~1 h) until the ether layer was colorless (more sodium carbonate was added when necessary). The isolated aqueous layer was extracted with ether and the combined organic extract was washed with brine, dried, and concentrated to a pale yellow liquid which was the pure (VPC, column B, 190 °C) *tert*-butylcyclohexanone **6** (247 mg, 78% yeild from bromo ketone **13a**). CD samples were further purified by preparative VPC (column B, 190 °C) and subsequent distillation: $[\alpha]^{18}_D$ +101° (*c* 4.6); IR (neat) 1710 cm^{-1}; ^{1}H NMR δ 0.90 (s, 9 H), 1.04 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 185 (M^+, 3), 170 (1.5), 126 (2), 57 (100).

(25) Numan, H.; Wynberg, H. *J. Org. Chem.* **1978**, *43*, 2232–2236.
(26) Sundararaman, P.; Djerassi, C. *Tetrahedron Lett.* **1978**, 2457–2460. Errata: *Ibid.* **1979**, 4120.
(27) Pak, C. S.; Djerassi C. *Tetrahedron Lett.* **1978**, 4377–4378.
(28) Sing, Y. L.; Numan, H.; Wynberg, H.; Djerassi, C. *J. Am. Chem. Soc.* **1979**, *101*, 5155–5158. Errata: Ibid. **1979**, *101*, 7439.
(29) Barth, G.; Dawson, J. H.; Dolinger, P. M.; Linger, R. E.; Bunnenberg, E.; Djerassi, C. *Anal. Biochem.* **1975**, *65*, 100–108.
(30) Konopelski, J. P.; Djerassi, C.; *J. Org. Chem.*, in press.

(+)-(2*R*,4*R*)-2-Methyl-d_3-2-methyl-4-*tert*-butylcyclohexanone (7). Use of the same reaction steps as for **6** but with reversal of the sequence of methylations gave ketone **7**: $[\alpha]^{18}_D$ +101° (*c* 3.5); IR (neat) 1710 cm^{-1}; ^1H NMR δ 0.90 (s, 9 H), 1.19 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 185 (M^+, 12), 170 (1.5), 126 (2), 57 (100).

(2*S*)-2-Methyl-d_3-2-methyl-4-isopropylidenecyclohexanone (16a). To a 1:1 solution (12 mL) of concentrated sulfuric acid–concentrated hydrochloric acid[10] at 0 °C was added (+)-3β-methyl-3α-methyl-d_3-nopinone (**12a**, 1.3 g 7.7 mmol); the resulting mixture was stirred at 25 °C for 6 h, poured onto ice, and extracted with ether. The ethereal extract was washed with brine, dried, and evaporated to dryness. Distillation [84 °C (4 mm)] provided 1.38 g (87%) of chloro cyclohexanone **15a** as a colorless semisolid: IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR δ 1.05 (s, 3 H), 1.16 (s, 3 H), 1.56 (s, 6 H); mass spectrum (70 eV), *m/z* (relative intensity) 169 (M^+ – HCl, 93).

A solution of chloro cyclohexanone **15a** (637 mg, 3.10 mmol) in pyridine (4 mL)[10] was refluxed for 8 h. The cool reaction mixture was diluted with ether, washed with 5% hydrochloric acid and brine, dried, and concentrated to afford 475 mg of a mixture of isopropylidene **16a** and isopropenyl compounds (9:1, column C, 140 °C). Pure isopropylidenecyclohexanone **16a** was isolated by preparative VPC: $[\alpha]^{24}_D$ −2.4° (*c* 4.2); IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR δ 1.06 (s, 3 H), 1.73 (br s, 6 H), 2.33 (br s, 2 H), 2.46 (br s, 4 H); mass spectrum (70 eV), *m/z* (relative intensity) 169 (M^+, 100), 154 (13), 110 (58).

Tosylhydrazone 17a. Isopropylidenecyclohexanone **16a** (550 mg, 3.25 mmol) was added to a mixture of ethylene glycol (0.8 mL), *p*-toluenesulfonic acid (6 mg), and dry benzene (20 mL), and the resulting solution was heated to reflux in a Dean–Stark apparatus for 2 h. The cool reaction mixture was diluted with ether, washed with saturated sodium bicarbonate and water, dried, and evaporated to give the ketal (650 mg). A small amount was purified by preparative VPC (column C, 160 °C): $[\alpha]^{24}_D$ −1.3° (*c* 4, $CHCl_3$); ^1H NMR δ 0.90 (s, 3 H), 1.68 (br s, 6 H), 3.93 (s, 4 H); mass spectrum (70 eV), *m/z* (relative intensity) 213 (M^+, 43), 198 (10), 167 (41), 153 (30), 99 (33), 86 (100).

The crude ketal from above (580 mg, 2.72 mmol) in methanol (10 mL) was treated at −78 °C with an excess of ozone. To this solution (purged of excess ozone with nitrogen) was added methyl sulfide (2 mL), and the resulting solution was allowed to stir at 25 °C for 15 h. The reaction mixture was diluted with ether, washed with brine, dried, and concentrated to give the keto ketal (520 mg) which was used without further purification. An analytical sample was prepared by preparative VPC (column C, 160 °C): $[\alpha]^{24}_D$ −1.8° (*c* 4.0); IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.00 (s, 3 H), 2.30 (s, 3 H), 4.03 (s, 4 H); mass spectrum (70 eV), *m/z* (relative intensity) 187 (M^+, 10), 172 (3), 169 (3), 129 (16), 100 (40), 99 (100), 85 (69).

To a solution of the unpurified keto ketal (450 mg, 2.41 mmol), from above, in absolute ethanol (1 mL) was added tosylhydrazine (580 mg, 3.12 mmol) and the resulting mixture was refluxed for 15 h. Solvent was removed and the residue was chromatographed on silica gel (5% ethyl acetate–benzene) to furnish the ketal tosylhydrazone **17a** (630 mg) as an oil: ^1H NMR δ 0.86 (s, 3 H), 2.41 (s, 2 H), 3.96 (s, 4 H), 7.26 (d, 2 H, *J* = 8 Hz), 7.80 (d, 2 H, *J* = 8 Hz); mass spectrum (70 eV), *m/z* (relative intensity) 355 (M^+, 5), 294 (2), 200 (14), 172 (77), 157 (29), 156 (20), 91 (100), 65 (32).

(2*S*)-2-Methyl-d_3-2-methylcyclohexanone (*3*). A mixture of the tosylhydrazone **17a** (624 mg, 1.75 mmol), sodium cyanoborohydride[31] (497 mg, 7.91 mmol), and *p*-toluenesulfonic acid (98 mg) in 9 mL of a 1:1 mixture of DMF–sulfolane was heated at 110 °C for 8 h. The reaction mixture was poured into water and extracted with ether. The combined organic extract was washed with 5% hydrochloric acid and water. After most of the ether was removed by distillation, the residue was treated with 10% hydrochloric acid (5 mL) for 15 h. The solution was extracted with ether and the ethereal extracts were washed with brine, dried, and concentrated by distillation. The resulting dimethylcyclohexanone **3** (~70%) was isolated by preparative VPC (column C, 110 °C): IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR δ 1.05 (s, 3 H), 1.68 (m, 6 H), 2.30 (t, 2 H); mass spectrum (70 eV), *m/z* (relative intensity) 129 (M^+, 22), 85 (100), 72 (32), 59 (20), 58 (18).

(2*R*)-2-Methyl-d_3-2-methylcyclohexanone (3b). The enantiomeric cyclohexanone **3b** was prepared as outlined for cyclohexanone **3**. Spectral data for intermediates **15b–3b** were identical with the corresponding compounds **15a–3** except that the $[\alpha]_D$ values had the opposite sign.

(3*R*)-3-Methyl-d_3-3-methyl-1-isopropylidenecyclohexane (18a). A solution of (2*S*)-2-methyl-d_3-2-methyl-4-isopropylidenecyclohexanone (**16a**, 510 mg, 3.02 mmol) and tosylhydrazine (750 mg, 4.03 mmol) in a minimum amount of absolute ethanol was refluxed (nitrogen) for 24 h. The tosylhydrazone (853 mg) was isolated after solvent removal and chromatography (2% ethyl acetate–benzene): ^1H NMR δ 0.98 (s, 3 H), 1.63 (s, 6 H), 2.10 (s, 2 H), 2.25 (s, 4 H), 2.40 (s, 3 H), 7.26 (d, 2 H, *J* = 8 Hz), 7.80 (d, 2 H, *J* = 8 Hz); mass spectrum (70 eV), *m/z* (relative intensity) 337 (M^+, 10), 334 (28), 298 (14), 182 (27), 169 (82), 167 (30), 152 (51), 122 (100), 112 (47), 110 (86).

The tosylhydrazone (490 mg, 1.45 mmol), sodium cyanoborohydride (411 mg, 6.54 mmol), and *p*-toluenesulfonic acid (82 mg) in 8 mL of a 1:1 mixture of DMF–sulfolane were heated at 110 °C for 8 h. The cool reaction mixture was poured into water and extracted with ether. The ethereal solution was washed with brine, dried, and concentrated by distillation. Isopropylidenecyclohexane **18a** (170 mg) was isolated by preparative VPC (column A, 110 °C): ^1H NMR δ 0.85 (s, 3 H), 1.61 (s, 3 H), 1.66 (s, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 155 (M^+, 55), 140 (45), 137 (22), 112 (52), 109 (28), 96 (26), 83 (100), 81 (50), 72 (46), 67 (27).

(3*R*)-3-Methyl-d_3-3-methylcyclohexanone (5). Ozone (excess) was passed through a solution of the isopropylidenecyclohexane **18a** (170 mg, 1.10 mmol) in methanol (2 mL). After the solution was purged with nitrogen, dimethyl sulfide (0.5 mL) was introduced and the resulting solution was stirred at 25 °C for 15 h. The reaction mixture was diluted with ether, washed with brine, dried, and concentrated by distillation. The cyclohexanone **5** (quantative) was isolated by preparative VPC (column C, 110 °C): IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR δ 0.96 (s, 3 H), 2.13 (br s, 2 H); mass spectrum (70 eV), *m/z* (relative intensity) 129 (M^+, 25), 114 (6), 111 (9), 86 (7).

(3*S*)-3-Methyl-d_3-3-methylcyclohexanone (5b). Preparation of cyclohexanone **5b** was accomplished in a manner similar to that described for cyclohexanone **5** (see compounds **18a** and **5**). Spectral properties for **18b** and **5b** were identical with those of **18a** and **5**.

(+)-(2*S*,5*R*)-2-Methyl-d_3-2-methyl-5-isopropenylcyclohexanone (20). The Schiff base of (−)-carvone[12] **19** (Fritzsche Brothers, Inc.; 2.15 g, 9.0 mmol) was added dropwise to a solution of *t*-BuOK (107 mg) in THF (29 mL).[11] After 30 min at 25 °C, the reaction mixture was cooled to −78 °C and *t*-BuLi (8.0 mL, 1.9 M in pentane) was introduced. After a 30-min stirring period, iodomethane-d_3 (3.1 g) was added and the reaction vessel was allowed to warm to 25 °C (ca. 30 min). The reaction mixture was quenched with 2 N hydrochloric acid (18 mL) and extracted with ether. The ether extract was washed with 5% hydrochloric acid and brine, dried, and concentrated to yield 985 mg of crude product. An analytical sample was prepared by preparative VPC (column C, 190 °C): $[\alpha]^{25}_D$ +83° (*c* 0.64); IR (CCl_4) 1705 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (s, 2.25 H), 1.10 (s, 0.75 H),[11] 1.73 (m, 7 H), 2.35 (m, 3 H), 4.60 (br s, 2 H); mass spectrum (70 eV), *m/z* (relative intensity) 169 (M^+, 28), 154 (3), 110 (25), 95 (52), 82 (41), 72 (100), 68 (60), 67 (81).

(+)-(2*S*,5*R*)-2-Methyl-d_3-2-methyl-5-isopropenylcyclohexanone Ethylene Ketal (21). A solution of *p*-toluenesulfonic acid (4 mg), ethylene glycol (331 mg), and isopropenylcyclohexanone **20** (435 mg, 2.57 mmol) in benzene (9 mL) was refluxed (Dean–Stark trap) for 12 h. The resulting reaction mixture was washed with saturated sodium bicarbonate and brine, dried, and concentrated to afford 528 mg of crude product. A sample was purified by preparative VPC (column A, 190 °C): $[\alpha]^{25}_D$ +29° (*c* 0.43); IR (CCl_4) 2212, 1645 cm^{-1}; ^1H NMR δ 0.88 (s, 2.25 H), 1.02 (s, 0.75 H),[11] 3.90 (s, 4 H), 4.65 (br s, 2 H); mass spectrum (70 eV), *m/z* (relative intensity) 213 (M^+, 2), 172 (5), 140 (9), 139 (100), 138 (8), 86 (20), 67 (13).

(+)-(2*S*,5*R*)-2-Methyl-d_3-2-methyl-5-acetylcyclohexanone Ethylene Ketal (22). Ozone (excess) was passed through a solution of ethylene ketal **21** (500 mg, 2.35 mmol) in methanol (10 mL) at −78 °C until the solution became blue. Dimethyl sulfide (0.5 mL) was added and the reaction mixture was stirred overnight at 25 °C. Solvent removal gave 620 mg of crude product which was purified by preparative VPC (column C, 190 °C) to furnish acetylcyclohexanone ethylene ketal **22**: $[\alpha]^{25}_D$ +14° (*c* 0.50); IR (CCl_4) 2220, 1710 cm^{-1}; ^1H NMR δ 0.90 (s, 2.25 H), 1.00 (s, 0.75 H),[11] 2.13 (s, 3 H), 3.93 (s, 4 H); mass spectrum (70 eV), *m/z* (relative intensity) 215 (M^+, 1), 173 (10), 172 (100), 171 (17), 155 (4), 113 (13), 99 (52), 86 (18).

(+)-(2*S*,5*R*)-2-Methyl-d_3-2-methyl-5-hydroxycyclohexanone Ethylene Ketal (23). To a solution of ethylene ketal **22** (370 mg, 1.72 mmol) in methylene chloride (15 mL) was added *m*-chloroperbenzoic acid (591 mg, 85% pure). The reaction mixture was stirred for 64 h in the dark at 25 °C and then washed with 10 mL of 5% sodium thiosulfate, saturated sodium bicarbonate, and brine. Subsequent drying and solvent removal resulted in 305 mg of (2*S*,5*R*)-2-methyl-d_3-2-methyl-5-acetoxycyclohexanone ethylene ketal: ^1H NMR δ 0.88 (s, 2.25 H), 1.02 (s, 0.75 H),[11] 2.01 (s, 3 H), 3.91 (s, 4 H), 4.83 (m, 1 H).

To a slurry of lithium aluminum hydride (113 mg, 2.98 mmol) in ether (10 mL) was added (2*S*,5*R*)-2-methyl-d_3-2-methyl-5-acetoxycyclohexanone ethylene ketal (260 mg, 1.13 mmol). After the solution was stirred at 25 °C for 4 h, water (100 μL), 15% NaOH (100 μL), and water (300 μL) were successively added. The filtered solution was con-

(31) Hutchins, R. O.; Milewski, C. A.; Marganoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668.

centrated to give hydroxycyclohexanone ethylene ketal **23** as a white solid (209 mg): mp 67-75 °C; $[\alpha]^{25}_D$ -15° (c 0.53); IR (CCl_4) 3544, 2210 cm^{-1}; ^1H NMR δ 0.93 (s, 3 H), 3.33 (br s, 1 H), 3.95 (s, 4 H); mass spectrum (70 eV), m/z (relative intensity) no M^+, 117 (5), 116 (8), 115 (100), 114 (6), 99 (4), 86 (31), 71 (10).

(2S)-2-Methyl-d_3-2-methylcyclohexanone (3). A solution of the 5-hydroxycyclohexanone ethylene ketal **23** (185 mg, 0.979 mmol) and p-toluenesulfonyl chloride (4.83 mg, 2.54 mmol) in pyridine (3.5 mL) was stirred at -10 °C for 18 h. The reaction mixture was poured onto ice and after 20 min the precipitate formed was isolated by filtration and dried under vacuum to give 313 mg of tosylate: ^1H NMR δ 0.82 (s, 2.25 H), 0.97 (s, 0.75 H),[32] 2.43 (s, 3 H), 3.88 (s, 4 H), 4.58 (m, 1 H), 7.36 (d, 2 H, J = 8 Hz), 7.78 (d, 2 H, J = 8 Hz).

The tosylate (266 mg, 0.776 mmol) in THF (3 mL) was treated with lithium triethylborohydride (1.8 mL, 1 M in THF) and the resulting solution was heated at reflux for 24 h. To the cool reaction mixture was added 3 N sodium hydroxide (2 mL) followed by 30% hydrogen peroxide (2 mL). After the mixture was stirred for 20 min, the aqueous layer was separated and extracted with ether. The combined ethereal extract was washed with water and brine, dried, and concentrated to produce (2S)-2-methyl-d_3-2-methylcyclohexanone ethylene ketal (234 mg).

The cyclohexanone ethylene ketal (50 mg, 0.289 mmol) in ether (2 mL) was treated with 10% hydrochloric acid (0.4 mL) for 11.5 h at 25 °C. A saturated sodium carbonate solution was added and the organic layer was isolated. The organic phase was washed with brine, dried, and concentrated to give 30 mg of cyclohexanone **3**. Purification was accomplished by preparative VPC (column A, 150 °C): IR (CCl_4) 2210, 1707 cm^{-1}; mass spectrum (70 eV), m/z (relative intensity) 129 (M^+, 15), 85 (100), 83 (17), 72 (38), 55 (42).

(2S)-2-Methyl-^{13}C-2-methylcyclohexanone (4). The title compound **4** was synthesized from (-)-carvone by the synthetic method outlined in Scheme III except that iodomethane-^{13}C (82% isotopic purity; Stohler Isotopic Chem.) was substituted for iodomethane-d_3: ^1H NMR (CCl_4) δ 1.03 (s, 1.08 H), 1.03 (d, 2.46 H, $J(^{13}C\text{-}C\text{-}C)$ = 5 Hz), 1.03 (d, 2.46 H, $J(^{13}C\text{-}H)$ = 127 Hz); mass spectrum (70 eV), m/z (relative intensity) 127 (M^+, 25), 83 (100), 70 (25), 57 (21).

(32) After removal of the C-5 substituent, the two separated methyl resonances merged into a singlet.

Acknowledgments. We acknowledge the valuable technical assistance of Ms. Ruth Records and thank Professor David Lightner (University of Nevada) for providing us with a preprint of ref 23. Partial financial support was provided by grants from the National Science Foundation (CHE 78-27413) and the National Institues of Health (GM 20276-06).

Heterogeneous Rates of Electron Transfer. Application of Cyclic Voltammetric Techniques to Irreversible Electrochemical Processes

R. J. Klingler and J. K. Kochi*

Department of Chemistry, Indiana University, Bloomington, Indiana 47401.
Received January 14, 1980

Abstract: The anodic peak potentials in the irreversible cyclic voltammograms of various homoleptic alkylmetals in acetonitrile show a striking linear correlation with their ionization potentials I_D determined in the gas phase. Application of various transient electrochemical techniques proves that the electrode process arises from a totally irreversible ECE sequence in which the peak potential is determined solely by the kinetics of heterogeneous electron transfer and diffusion—uncomplicated by any follow-up chemical reaction. As a result, the anodic peak potential E_p can be directly related to the activation free energy for electron transfer, and the correlation of E_p and I_D represents a linear free-energy relationship. The mechanism of heterogeneous electron transfer is described as an outer-sphere process, dependent only on the driving force for one-electron oxidation and independent of steric effects of the alkylmetal. The close relationship between the activated complexes for heterogeneous and homogeneous electron transfer is emphasized in a direct comparison of the electrochemical process with the oxidation of the same alkylmetals by a series of poly(pyridine)iron(III) complexes in solution.

Introduction

Many organometals are excellent electron donors by virtue of the powerful effect exerted by alkyl groups as σ-donor ligands.[1-4] Consequently, the ionization potential of a given alkylmetal is always lower than that of most other metal derivatives.[5] This property of alkyl ligands confers upon organometals a ubiquitous role as electron donors in a variety of electron-transfer and charge-transfer interactions with inorganic as well as organic electrophiles and oxidants.[6]

Ionization from the substitution-inert alkylmetals of the main-group elements such as Sn, Pb, Hg, etc., occurs from a carbon–metal bonding orbital (HOMO). As a result, the structure of the alkyl ligand strongly affects the ionization potential of the alkylmetal.[4,7] Coupled with the availability of a wide variety of alkyl ligands, the structures of alkylmetals can be finely tuned to cover a range of electron-donor and steric properties. Such a control over electronic and steric effects makes alkylmetals ideally suited for the study of electron-transfer mechanisms. Thus many alkylmetals are readily oxidized by the well-known oxidants, tris(phenanthroline)iron(III)[8,9] and hexachloroiridate(IV),[10-12] by a rate-limiting electron-transfer step (e.g., see eq 1-3).

(1) Jonas, A. E.; Schweitzer, G. K.; Grimm, F. A.; Carlson, T. A. *J. Electron Spectros. Relat. Phenom.* **1972**, *1*, 29.
(2) Evans, S.; Green, J. C.; Joachim, P. J.; Orchard, A. F.; Turner, D. W.; Maier, J. P. *J. Chem. Soc., Faraday Trans. 2* **1972**, *68*, 905.
(3) Boschi, R.; Lappert, M. F.; Pedley, J. B.; Schmidt, W.; Wilkins, B. T. *J. Organomet. Chem.* **1973**, *50*, 69.
(4) Fehlner, T. P.; Ulman, J.; Nugent, W. A.; Kochi, J. K. *Inorg. Chem.* **1976**, *15*, 2544.
(5) Kochi, J. K. "Organometallic Mechanisms and Catalysis"; Academic Press: New York, 1978; Table IV, p 454, and Table I, p 501.
(6) See ref 5, Chapters 16-18.
(7) (a) Beltram, G.; Fehlner, T. P.; Mochida, K.; Kochi, J. K. *J. Electron Spectros. Relat. Phenom.* **1980**, *18*, 153. (b) Wong, C. L.; Mochida, K.; Gin, A.; Weiner, M. A.; Kochi, J. K. *J. Org. Chem.* **1979**, *44*, 3979.
(8) Peloso, A. *J. Organomet. Chem.* **1974**, *67*, 423.
(9) Wong, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 5593.
(10) (a) Abley, P.; Dockal, E. R.; Halpern, J. *J. Am. Chem. Soc.* **1972**, *94*, 659. (b) Anderson, S. N.; Ballard, D. H.; Chrzastowski, J. Z.; Dodd, D.; Johnson, M. D. *J. Chem. Soc., Chem. Commun.* **1972**, 685.
(11) (a) Chen, J. Y.; Gardner, H. C.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 6150. (b) Gardner, H. C.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 1855.
(12) Chen, J. Y.; Kochi, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 1450.

0002-7863/80/1502-4790$01.00/0