fast-moving hydrocarbon fraction thus obtained was rechromatographed on silica gel with hexane/ethyl acetate (30:1) as the eluant: yield 15 mg; bright yellow, needle-shaped crystals; mp 226–229 °C. Anal. Calcd for $C_{30}H_{20}$ (mol wt 380.49): C, 94.70; H, 5.30. Found: C, 94.50; H, 5.30.

Photochemical Isomerization of Dianthrylpropenone 1l To Give 11. A solution of **1l** (300 mg) in benzene (175 mL) was irradiated under argon for 90 min (450-W Hanovia medium-pressure mercury lamp, 30 °C). Vacuum evaporation of the solvent gave a solid residue which was washed with ether and then recrystallized from a mixture of methylene chloride and ether to give colorless crystals: 210 mg (70%); mp 275–277 °C dec. Anal. Calcd for $C_{31}H_{20}O$ (mol wt 408.50): C, 91.15; H, 4.93. Found: C, 91.13; H, 4.96.

Photochemical Isomerization of Dianthrylpropene 1m To Give 12. A solution of **1m** (100 mg) in methylene chloride (150 mL) was irradiated at 20 °C under nitrogen for 1.5 h (125-W high-pressure mercury lamp, Philips HPK 125W; cutoff filter; $\lambda > 340$ nm). Vacuum evaporation of the solvent from the pale yellow solution gave a crystalline residue which was washed with benzene and recrystallized from methylene chloride by precipitation with methanol: yield 40 mg (40%); colorless crystals; mp 252 °C. After resolidification, the substance melts at 270 °C. Anal. Calcd for $C_{31}H_{22}$ (mol wt 394.52): C, 94.38; H, 5.62. Found: C, 94.00; H, 5.55.

Photochemical Isomerization of *trans,trans*-1,5-Bis(9-anthryl)penta-1,4-dien-3-one (1o) To Give 13. A solution of **1o** (50 mg) in methylene chloride (550 mL) was irradiated under nitrogen (125-W Philips high-pressure mercury lamp HPK 125W; cutoff filter, $\lambda > 360$ nm).[24] At 10-min intervals, 50 mg samples of **1o** were added. After 105 min, when a total of 500 mg of **1o** had been irradiated, the solvent was removed by vacuum evaporation. The residue thus obtained was purified by column chromatography on silica gel/CH_2Cl_2 to give 375 mg (75%) of pale yellow crystals, which were recrystallized from methylene chloride solution by addition of diethyl ether; mp 220–223 °C dec. Anal. Calcd for $C_{33}H_{22}O$ (mol wt 434.54): C, 91.22; H, 5.10. Found: C, 90.89, H, 5.07.

Photochemical Isomerization of 1,3-Bis(9-anthryl)-propan-1-one To Give 14. A solution of **3** (150 mg) in benzene (175 mL) was irradiated under nitrogen for 30 min (Philips high-pressure mercury lamp, HPK 125W; cutoff filter; $\lambda > 360$ nm; 20 °C). Vacuum evaporation of the solvent gave a solid residue which was washed with ether to remove a yellow byproduct. The remaining colorless solid was recrystallized from a warm benzene solution by precipitation with *n*-hexane: yield 140 mg (93%); colorless crystals; mp 265–270 °C dec. Anal. Calcd for $C_{31}H_{22}O$ (mol wt 410.52): C, 90.70; H, 5.40. Found: C, 90.87; H, 5.42.

Photochemical Isomerization of 4 To Give 15. A solution of **4** (50 mg) in methylene chloride (65 mL) was irradiated for 30 min at 10 °C under argon (Philips HPK 125W mercury lamp). The workup by vacuum evaporation of solvent left a colorless crystalline residue which was recrystallized from methylene chloride/cyclohexane: yield 38 mg (76%); mp ~245 °C dec. Anal. Calcd for $C_{31}H_{24}O$ (mol wt 412.54): C, 90.26; H, 5.86. Found: C, 90.00; H, 5.86.

Acknowledgment. We are gratefully indebted to Dr. Kjell Sandros for recording the emission spectra of **1d** and **1e** and to Gunnar Svensson for skillful technical assistance.

Registry No. **1a**, 2444-68-0; **1b**, 38080-19-2; **1c**, 84599-88-2; **1d**, 84599-89-3; **1e**, 84599-90-6; **1f**, 42196-97-4; **1g**, 87337-00-6; **1h**, 53744-36-8; **1i**, 87337-01-7; **1j**, 87337-02-8; **1k**, 87337-03-9; **1l**, 84599-77-9; **1m**, 84599-76-8; **1n**, 87337-04-0; **1o**, 84599-83-7; **1p**, 87337-05-1; **1q**, 87337-06-2; **2**, 87337-07-3; **3**, 84599-75-7; **4**, 84599-73-5; **5**, 84599-74-6; **6**, 68975-25-7; **7**, 87337-08-4; **8**, 87337-09-5; **9**, 69469-61-0; **10**, 28641-52-3; **11**, 84599-81-5; **12**, 84599-80-4; **13**, 87337-10-8; **14**, 84599-79-1; **15**, 84599-78-0.

(24) The use of a cutoff filter is essential. Product **13** upon photoexcitation undergoes an isomerization which we have not yet investigated.

Optical Rotatory Dispersion Studies. 136.[1] Enzymatic Reduction of 2-Methyl-2-(trideuteriomethyl)cyclohexane-1,3-dione. Unusual Conformation of 2,2-Dimethyl-3-hydroxycyclohexanone

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Received May 9, 1983

The enzymatic reduction of 2-methyl-2-(trideuteriomethyl)cyclohexane-1,3-dione with Kloeckera magna is not stereospecific with respect to the α center. The reaction product, 2-methyl-2-(trideuteriomethyl)-3-hydroxycyclohexanone, was shown to possess the 3*S* configuration. The circular dichroism and X-ray crystallographic data lead to the unexpected conclusion that the reduction product assumes the conformation with an axially oriented hydroxyl group.

The enzymatic reduction of 2,2-dialkyl-substituted cyclopentane-1,3-diones has been investigated in considerable detail by Kosmol et al.[3] and has found application as the chirality-introducing step in the industrial total synthesis of estradiol. With the appropriate choice of the microbiological system, the reduction can be carried out with nearly complete stereoselectivity; i.e., only one of the four possible stereoisomers **2–5** (Scheme I) is obtained. In a more recent study, Brooks et al.[4] carried out a similar investigation designed to establish a relationship between stereoselectivity and size differences of both alkyl substituents. As anticipated, the stereoselectivity of the reaction was found to be strongly dependent on this pa-

(1) For the preceding paper in this series, see: Harris, R. N.; Sundararaman, P.; Djerassi, C. *J. Chem. Am. Soc.* **1983**, *105*, 2408.

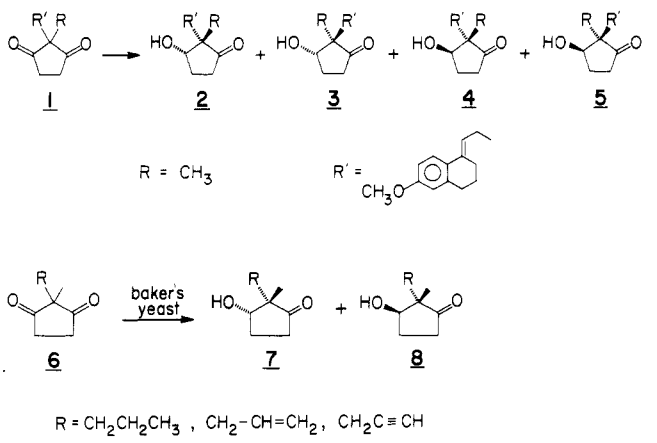
(2) (a) Stanford University. (b) Gesellschaft Für biotechnologische Forschung. (c) Medical Foundation of Buffalo.

(3) Kosmol, H.; Kieslich, K.; Vossing, R.; Koch, H.-J.; Petzold, K.; Gibian, H. *Liebigs Ann. Chem.* **1967**, *701*, 199.

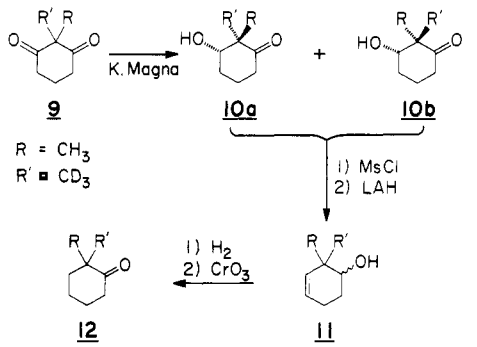
(4) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820.

0022-3263/83/1948-4549$01.50/0

Scheme I



Scheme II



rameter. Interestingly, only the 2*R*,3*S* (**7**) and 2*R*,3*R* (**8**) diastereoisomers were formed, their ratios being dependent on the type of alkyl substitution (Scheme I).

In the present study we attempted to investigate the stereoselectivity of the enzymatic reduction with Kloeckera magna (ATCC 20109) on a 1,3-dione in which both alkyl substituents differ in size only by virtue of their deuterium substitution, i.e., R = CH_3 and R′ = CD_3. In essence, we tried to determine whether the small steric size differences between a CH_3 and CD_3 group would be recognized by the active site of the enzyme.

Results and Discussion

The reduction was carried out on 2-methyl-2-(trideuteriomethyl)cyclohexane-1,3-dione (**9**, Scheme II), yielding 2-methyl-2-(trideuteriomethyl)-3-hydroxycyclohexanone (**10a,b**). Elimination of the hydroxyl group via **11** and subsequent hydrogenation and oxidation yielded 2-methyl-2-(trideuteriomethyl)cyclohexanone (**12**). This compound, in its optically active form, had been synthesized previously by us,[5] its *S* enantiomer displaying a negative Cotton effect at 300 nm associated with the n–π^* transition of the carbonyl chromophore. Thus, the CD spectrum of **12** obtained via enzymatic reduction (see Scheme II) would permit a determination of the enantiomeric excess as well as the absolute configuration of the predominant enantiomer. However, measurements of the CD spectrum of **12** did not show any observable signal in the 250–350-nm wavelength region under conditions where an enantiomeric excess of >5% would have been detectable. Thus, it is concluded that the enzymatic reduction product is essentially racemic with respect to the α center and that no steric isotope effect is observable. This negative result would warrant only brief mention were it not

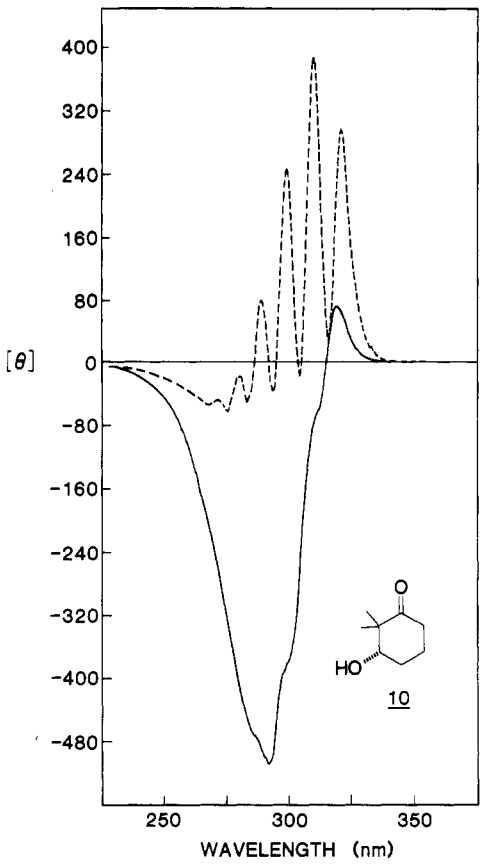
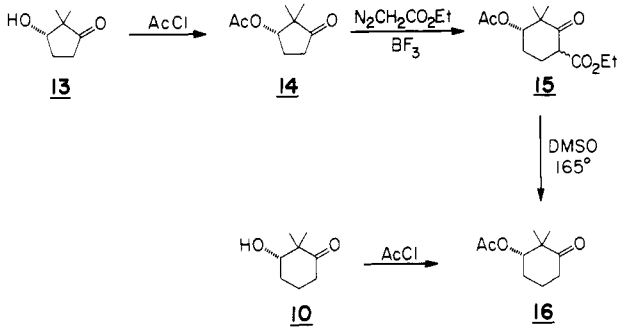


Figure 1. Circular dichroism spectra of (*S*)-2,2-dimethyl-3-hydroxycyclohexanone (**10**) in methanol (—) and methylcyclohexane (- - -).

Scheme III



for the interesting and unexpected observations dealing with the stereochemistry of the intermediate hydroxy ketone **10a,b**, which is discussed in the sequel.

In one of our previous studies[6] we utilized the same enzymatic reduction of 2,2-dimethylcyclopentane-1,3-dione to yield 2,2-dimethyl-3-hydroxycyclopentanone (**13**, Scheme III), which was the starting material for the synthesis of 2,2-dimethyl-3-deuteriocyclohexanone. The enantiomeric excess of this ketol was determined to be >95% and the configuration to be 3*S*. The enantiomeric excess of **10**[7] was also found to be >95% as determined by the Mosher method.[8] **13** was converted to **16** via the ring-expansion sequence outlined in Scheme III to establish its absolute configuration. The product was found to have a CD spectrum nearly identical in sign and amplitude with

(5) Lee, S.-F.; Edgar, M.; Pak, C. S.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 4784.

(6) Lee, S.-F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1981**, *103*, 295.

(7) The conformational studies were carried out on (*S*)-2,2-dimethyl-3-hydroxycyclohexanone (**10**) rather than on the diastereoisomeric mixture **10a** and **10b**.

(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

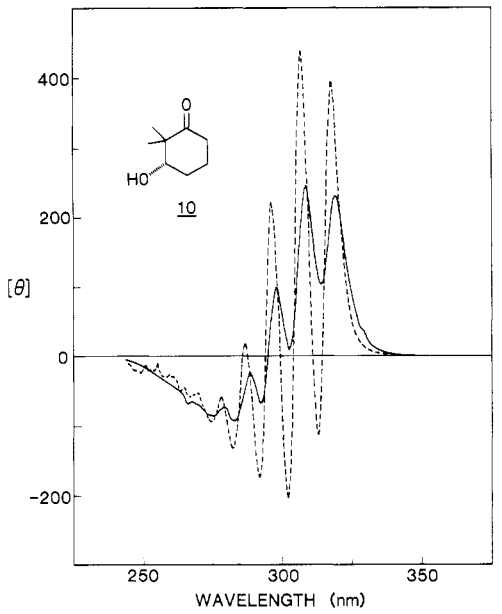


Figure 2. Circular dichroism spectra of (*S*)-2,2-dimethyl-3-hydroxycyclohexanone (**10**) in EPA (5:5:2 ether, pentane, ethanol) at room temperature (—) and 77 K (- - -).

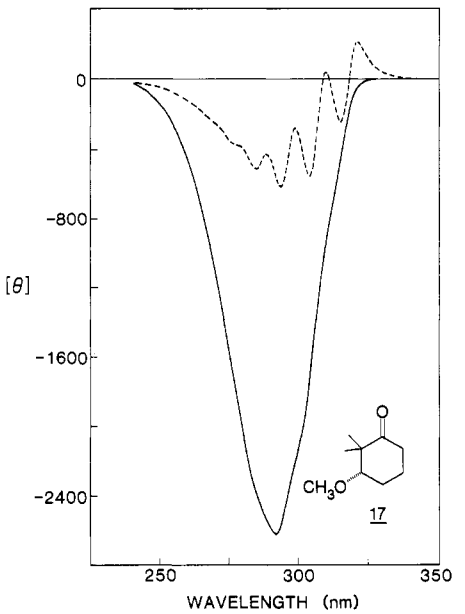
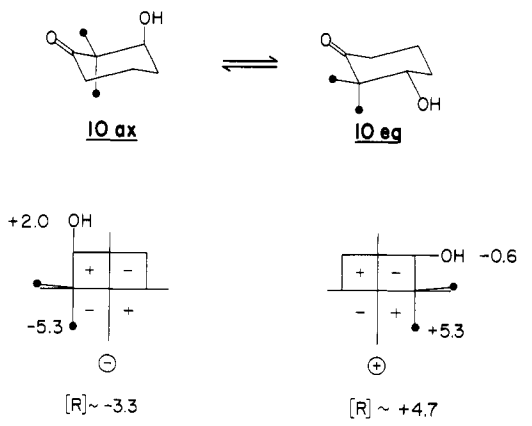


Figure 3. Circular dichroism spectra of (*S*)-2,2-dimethyl-3-methoxycyclohexanone (**17**) in methanol (—) and isooctane (- - -).

that derived from **10**. Thus both ketols **10** and **13** obtained by enzymatic reduction possess the 3*S* configuration as was expected. Difficulties, however, arose in the interpretation of the CD data shown in Figure 1. In a nonpolar solvent like methylcyclohexane the CD spectrum exhibits a bisignate Cotton effect, being positive at longer and negative at shorter wavelengths; in a polar solvent like methanol, the Cotton effect is predominantly negative in sign with only a small positive component at the long wavelength side.

Such solvent-dependent behavior is not at all uncommon and could indicate the presence of a conformational and/or solvational equilibrium. Low-temperature measurements in EPA (5:5:2 ether, pentane, ethanol, Figure 2) did not, however, reveal the anticipated amplitude variation; instead, only a sharpening of the vibrational fine structure was observed, but the overall rotational strength remained unchanged. Even more puzzling was the observation of the predominantly negative Cotton effect obtained in methanol (Figure 1). Numerous studies[9] on the conformational equilibrium position of cyclohexanols have shown that the conformation with the hydroxyl group in the equatorial position is ca. 0.5 kcal/mol more stable than the one with the axial hydroxyl group. Accordingly, at room temperature the conformational equilibrium is expected to be 70% equatorial:30% axial. From the octant diagram representation of both conformers (i.e., **10**-eq and **10**-ax, Scheme IV) and summation of the partial octant contributions of the α-*gem*-dimethyl[10] and hydroxyl groups,[11] one can estimate the anticipated rotational strength of each conformer as indicated in Scheme IV. Assuming the correctness of the above assumptions concerning the equilibrium position and estimates of the rotational strengths of each conformer, a positive Cotton effect with a rotational strength of +0.9 would have been expected to

Scheme IV



correspond to the preponderance of conformer **10**-eq. While this is partially the case in a hydrocarbon solvent including EPA, it is contrary to the observed methanol spectrum (Figure 1).

Since the absolute configuration of **10** was established beyond doubt as 3*S* by means of chemical correlation (Scheme III), the only alternative in the interpretation of the CD data was to assume that the preferred conformation in a hydroxylic solvent was not the one with the hydroxyl group in the equatorial but rather in the axial position. Since it was conceivable that intramolecular hydrogen bonding between the OH and C=O groups might stabilize the axial conformation, **10** was converted to its methyl ether derivative **17**, whose CD spectrum is shown in Figure 3. This molecule also exhibits a negative Cotton effect, even independent of solvent polarity, except for a small positive long wavelength component in isooctane. Hydrogen bonding is thus eliminated as a possible explanation.

At this point it was decided that only an X-ray crystallographic study would provide an unambiguous answer. The *p*-bromobenzenesulfonate derivative (**18**) of **10** was found to be a suitable crystalline compound, and its CD spectrum (in methanol), shown in Figure 4, again exhibits a negative Cotton effect, indicating that its conformation is the same as those of the ketol **10** and its methyl ether **17**. The molecular structure, as determined by X-ray

(9) (a) Mursakulov, I. G.; Ramazonov, E. A.; Guseinov, M. M.; Zefirov, N. S.; Samoshin, V. V.; Eliel, E. *Tetrahedron* **1980**, *36*, 1885. (b) Eliel, E. L. In "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 235.

(10) Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 2737.

(11) (a) Snatzke, G.; Eckhardt, G. *Tetrahedron* **1970**, *26*, 1143. (b) Kirk, D. N.; Klyne, W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1076. (c) Ripperger, H. *Z. Chem.* **1977**, *17*, 250.

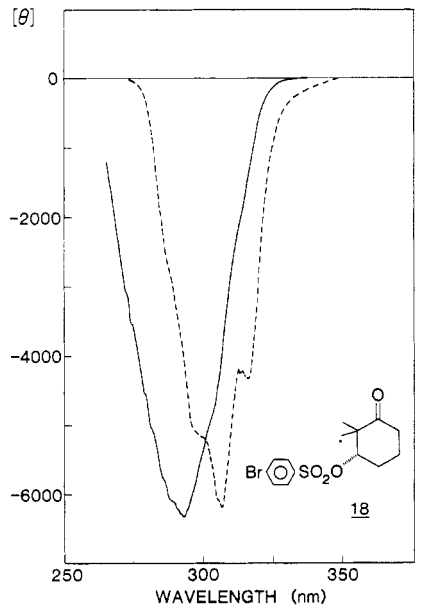


Figure 4. Circular dichroism spectra of 2,2-dimethyl-1-oxo-3-cyclohexanyl *p*-bromobenzenesulfonate (18) in methanol (—) and KBr (---). The ellipticity scale for the spectrum in KBr is arbitrary.

Table I. Crystal Data for 2,2-Dimethyl-1-oxo-3-cyclohexanyl *p*-Bromobenzenesulfonate (18)

molecular formula	$C_{14}H_{16}O_4SBr$
molecular weight	373.27
crystal system	orthorhombic
space group	$P2_12_12_1$
Z	4
cell dimensions, Å	
a	12.087 (1)
b	20.911 (2)
c	6.045 (?)
volume, Å^3	1527.8
density, g/cm^3	1.623
crystal size, mm	0.18 × 0.20 × 0.80
λ, Å	1.54184 (Cu Kα)

crystallography is given in Figure 5 (for relevant crystallographic data see Tables I and II (supplementary material)) and shows that the conformation of this molecule is the one with the OSO_2R group in the axial position. The CD spectrum of 18 was also measured in a solid phase (KBr), to eliminate the possibility that conformational differences exist between the solid and liquid phase, where it was also found to be negative (Figure 4).

Thus, the X-ray data confirm what had been suspected from the CD spectral data, namely, that the ketol 10 and its derivatives 17 and 18 preferentially assume the conformation with the OR (R = H, CH_3, and SO_2PhBr) group in the axial position. It should be noted that the above conclusions concerning the molecular conformation could not be decided clearly on the basis of the ^{1}H NMR coupling constants of the *H*COR proton. The observed signal consisted of a multiplet having a width of ca. 8–10 Hz whereas a doublet of doublets of 12, 5 Hz and 3, 5 Hz would have been expected[12] for an axial and equatorial proton, respectively.

In order to rationalize this deviation from the normal conformational behavior of an OR group in a cyclohexane ring, one has to assume the existence of an interaction (electrostatic?) between the carbonyl and β-OR groups.

(12) Bhacca, N. S.; Williams, D. H. In "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, 1964; p 51.

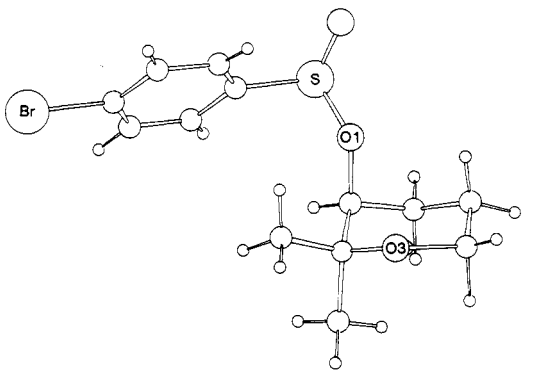


Figure 5. Molecular structure of 2,2-dimethyl-1-oxo-3-cyclohexanyl *p*-bromobenzenesulfonate (18) as determined by X-ray crystallography.

Hydrogen bonding as a stabilizing force can be ruled out on the basis of the observation that the ether and *p*-bromobenzenesulfonate derivatives of 10 (i.e., 17 and 18) are found to be present predominantly in conformations with the OR groups in the axial position. Molecular mechanics force field and quantum mechanical calculations as well as experimental studies on similar molecular systems with β substituents such as halogens and sulfur may shed some light on the questions posed in this investigation. We hope to perform such studies in the future.

Experimental Section

Crystal data for 2,2-dimethyl-1-oxo-3-cyclohexanyl *p*-bromobenzenesulfonate (18) are given in Table I. The integrated intensities for 1258 independent reflections having $\theta < 58°$ were measured on a Nicolet-Syntex P_3 diffractometer using Cu Kα radiation. The structure was solved by using the direct methods programs MULTAN[13] and NQEST[14] and refined by full-matrix least-squares procedures. All 17 hydrogen atoms were located in a difference Fourier map and were assigned isotropic thermal parameters equivalent to the carbon to which they were attached, but not refined.

The quantities $1/\sigma_F^2$ were used to weight the least-squares differences; data having $F < 2.0\sigma_F$ were given zero weight and not included in the refinement. The refinement converged at a residual ($R = \sum(F_o - F_c)/\sum F_o$) of 0.045 and 0.046 for all data; the weighted residual $R_w = [\sum w(F_o - F_c)^2/\sum wF_o^2]^{1/2}$ was calculated to be 0.057 and the standard deviation of an observation of unit weight [$S^2 = \sum w\Delta^2/(m-n)$ where m is the number of observations and n is the number of parameters] was found to be 3.9.

Positional parameters for the compound are given in Table II (supplementary material).

Optical rotations were determined on a Perkin-Elmer 141 polarimeter. A Varian Aerograph Series 2700 thermal-conductivity instrument equipped with 10 ft × 0.25 in. columns of 15% Carbowax 20 M on Chromosorb W (column A) or 10% SE-30 on Chromosorb W (column B) was used for preparative GC. Infrared spectra were recorded on a Beckman Model 710 infrared spectrophotometer. Low-resolution ^{1}H NMR spectra were obtained on a Varian T-60 (60 MHz) spectrometer, and the high-resolution ^{1}H spectra for coupling constants study were measured with the Bruker HXS 360 (360 MHz) spectrometer of the Stanford Magnetic Resonance Laboratory. Mass spectra were determined either on a Varian MAT-711 or MAT-44 spectrometer, both operated at 70eV with a direct inlet system. The CD spectra were measured on a JASCO J-40 circular dichrometer using a previously described[15] cell for the variable-temperature measurements.

2-Methyl-2-(trideuteriomethyl)cyclohexane-1,3-dione (9). A solution of 2-methylcyclohexane-1,3-dione (12.6 g, 0.1 mol) in

(13) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

(14) De Titta, G. T.; Edmonds, J. W.; Langs, D. A.; Hauptman, H. *Acta Crystallogr., Sect. A* **1975**, *A31*, 472.

(15) Barth, G.; Dawson, J. H.; Dollinger, P. M.; Linder, R. E.; Bunnenberg, E.; Djerassi, C. *Anal. Biochem.* **1975**, *65*, 100.

anhydrous methanol (160 mL) was treated with Triton B (42 mL) followed by CD_3I (16 g, 0.11 mol) and heated in a sealed tube at 70 °C (oil bath) for 16 h.[16] After evaporation to remove most of the methanol, the residue was treated with water and extracted with chloroform. The organic layer was washed with aqueous $NaHCO_3$ (5%), dried over anhydrous $MgSO_4$, and evaporated, yielding 15 g of crude product. Further purification was accomplished by distillation to give 9.8 g (68.5%) of **9**: bp 48–50 °C (0.5 mmHg); mp 38–39 °C; IR (neat) 2240, 1730, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 2.01 (q, 2 H), 2.71 (t, 4 H); MS, m/z (relative intensity) 143 (M^+, 7), 129 (17), 100 (18), 97 (11), 85 (11), 73 (8), 70 (b), 55 (35), 43 (100). Anal. Calcd for $C_8H_9D_3O_2$: C, 67.09; H + D, 8.44. Found: C, 66.80; H + D, 8.3.

(*S*)-3-Hydroxy-2-methyl-2-(trideuteriomethyl)cyclohexanone (10a,b). A 500-mL fermentation medium consisting of 50 g/L of cornsteep liquor in a 2-L Erlenmeyer flask was inoculated with Kloeckera magna (ATCC 20109) rinsed off with 3 mL of physiological NaCl solution. The mixture was shaken for 48 h at 30 °C at 140 rpm; 250 mL of this culture was used as seed for a 20-jar fermentor filled with 15 L of the same medium. The fermentor was stirred at 200 rpm under aeration. After a 24-h germination time, 900 mL of the culture was transferred to a second fermentor started under the same conditions. After 6 h, 17.5 g of **9** dissolved in 50 mL of DMF was added and the aeration rate reduced. After an addition 14 h the fermentation was terminated and the biomass removed by centrifugation. The broth was extracted three times with 5 L of ethyl acetate, and the combined extracts were concentrated under reduced pressure at 35 °C. The oily residue was purified by column chromatography on silica gel to yield 7.34 g (66%) of **10a,b**: $[\alpha]^{20}_D$ +12.3° (*c* 1.7, $CHCl_3$); IR (neat) 3450, 2870–2940, 2220, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14, 1.18 (2 s, 3 H), 1.5–2.6 (m, 7 H), 3.65 (m, 1 H); MS, m/z (relative intensity) 145 (M^+, 33), 127 (15), 122 (15), 101 (42), 92 (27), 91 (41), 85 (100), 72 (42), 71 (52), 70 (29), 57 (22), 55 (16); isotopic purity >98%.

(*S*)-2,2-Dimethyl-3-hydroxycyclohexanone (10). This compound was synthesized by the identical enzymatic reduction as described for **10a,b**, using 2,2-dimethylcyclohexane-1,3-dione instead of **9**: $[\alpha]^{20}_D$ +11.5° (*c* 0.9, $CHCl_3$); IR (neat) 3420, 2865–2940, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.18 (s, 3 H), 1.98 (m, 4 H), 2.42 (m, 3 H), 3.65 (m, 1 H); MS, m/z (relative intensity) 142 (M^+, 32), 124 (15), 98 (43), 86 (39), 82 (100).

2-Methyl-2-(trideuteriomethyl)cyclohex-3-enol (11). To a stirred solution of **10a,b** (300 mg, 2.07 mmol) in dry methylene chloride (25 mL) containing triethylamine (600 μL) was added dropwise methanesulfonyl chloride (300 μL) at 0 °C. After 1 h, the mixture was diluted with $CHCl_3$, washed with cold water, aqueous $NaHCO_3$ (5%), 1 N HCl, and brine, and then dried over anhydrous $MgSO_4$. After solvent evaporation, the residue was chromatographed on a column (silica gel, 30% ethyl acetate/benzene), yielding 415 mg (90%) of the mesylate, which was immediately used in the next step. To a slurry of $LiAlH_4$ (400 mg) in dry ether (30 mL) was added dropwise a solution of the mesylate (400 mg, 1.79 mmol) at −10 °C (1 h). The mixture was stirred at −5–0 °C for 0.5 h followed by 18 h at room temperature. Excess $LiAlH_4$ was decomposed with wet ether/water. After filtration and evaporation, the crude product was purified by GC (SE-30, 160 °C): IR (neat) 3380, 3020, 2875–2940, 2220, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95, 1.02 (2 s, 3 H), 1.45–2.28 (m, 5 H), 3.56 (m, 1 H), 5.39 (m, 2 H); MS, m/z (relative intensity) 129 (M^+, 3), 111 (21), 93 (3), 93 (5), 86 (8), 85 (100), 70 (20), 69 (19), 68 (13), 67 (12), 55 (7), 53 (3); isotopic purity 98%.

2-Methyl-2-(trideuteriomethyl)cyclohexanone (12). The hydrogenation of **11** (150 mg, 1.16 mmol) was carried out in a solution of ethyl acetate (15 mL) and absolute methanol (10 mL) with Pd/$BaCO_3$ (5%, 100 mg) at room temperature overnight. After filtration through Kieselguhr, the solvent was removed and the residue purified by GC (SE-30, 160 °C). To a solution of the hydrogenation product (80 mg, 0.6 mmol) in acetone (5 mL) was added dropwise Jones reagent (180 μL) over a period of 1 h at 0 °C, followed by stirring for 0.5 h at room temperature. The excess chromic acid was destroyed with isopropyl alcohol and $NaHCO_3$ (100 mg) by gradual addition with stirring. After filtration, the solution was carefully concentrated by distillation and the residue purified by GC (Carbowax, 150 °C) to yield **12** (58 mg, 82%) for which no CD could be detected: IR ($CHOl_3$) 2220, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.68 (m, 6 H), 2.30 (t, 2 H); MS, m/z (relative intensity) 129 (M^+, 21), 85 (100), 72 (25), 59 (49), 58 (26), 55 (21).

(3*S*)-2,2-Dimethyl-3-acetoxycyclopentanone (14). Compound **13**[6] (900 mg) was treated with acetyl chloride (8 mL) at −5 °C and the mixture stirred for 2 h. Excess acetyl chloride was removed at reduced pressure and the residue diluted with ether (30 mL), washed with 5% aqueous $NaHCO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by GC (SE-30, 170 °C) to yield 720 mg of **14**: $[\alpha]^{20}_D$ +55.5° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.10 (s, 3 H), 2.10 (s, 3 H), 1.87–2.75 (7, 4 H), 5.17 (m, 1 H); MS, m/z 170 (M^+, 6), 128 (57), 101 (43), 95 (32), 85 (29), 82 (64), 72 (32), 69 (49), 43 (100).

Ethyl (3*S*)-2,2-Dimethyl-3-acetoxy-1-oxocyclohexane-6-carboxylate (15). To a solution of **14** (550 mg, 3.24 mmol) in anhydrous ether (30 mL) containing BF_3 etherate (0.9 mL) at 0 °C was added dropwise ethyl diazoacetate[17] (737.6 mg, 6.48 mmol), and the solution was stirred at room temperature for 1 week. The reaction mixture was diluted with ether, washed with 5% aqueous $NaHCO_3$ and water, dried, and evaporated to yield the β-keto ester **15** (772 mg, 93%): $[\alpha]^{20}_D$ +9.5° (*c* 0.8, $CHCl_3$); IR (neat) 1770, 1740, 1710 cm^{-1}; MS, m/z (relative intensity) 256 (M^+, 18), 196 (54), 181 (100), 150 (14), 125 (39), 109 (15), 83 (33), 82 (37), 69 (42), 55 (37).

(3*S*)-2,2-Dimethyl-3-acetoxycyclohexanone (16). A solution of **15** (420 mg, 1.64 mmol) and NaCl (92 mg) in Me_2SO (1.85 mL) containing 81 μL of water was heated to 180–5 °C (oil bath) for 3.5 h.[18] Thereafter the reaction mixture was cooled, diluted with ether (20 mL), washed with water, and dried over Na_2SO_4. Removal of the solvent gave a crude product (280 mg) as a brown oil, which was purified by GC (SE-30, 170 °C), yielding 238 mg (78.8%) of **16**: $[\alpha]^{20}_D$ +8.62° (*c* 0.58, $CHCl_3$); IR (neat) 1745, 1715, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.19 (s, 3 H), 1.55–2.00 (m, 4 H), 2.05 (s, 3 H), 2.28 (m, 2 H), 4.99 (m, 1 H); MS, m/z (relative intensity) 184 (M^+, 12), 142 (18), 124 (34), 98 (27), 95 (22), 84 (100), 71 (29), 55 (44). Alternatively, compound **16** was obtained from **10** by the same procedure described for the preparation of **14** and showed identical physical data (IR, ^1H NMR, MS, GC retention time, R_f on TLC, $[\alpha]^{20}_D$, and CD spectra).

(3*S*)-2,2-Dimethyl-3-methoxycyclohexanone (17). A mixture of (3*S*)-2,2-dimethyl-3-hydroxycyclohexanone (**10**) (60 mg, 0.45 mmol), ethylene glycol (0.12 mL), and *p*-TsOH (1.5 mg) in dry benzene was refluxed for 2 h. Additional benzene (10 mL) was added, and the cooled mixture was washed with aqueous $NaHCO_3$ (10%) and brine and dried (Na_2SO_4). After evaporation, the crude ketal (68 mg) was dried overnight under vacuum. In a 25-mL flask was placed NaH (30 mg, 55% w/w dispersion in oil), and the oil was removed with two successive washes of dry pentane. Dry THF (5 mL) was added and the suspension heated to 45–50 °C (oil bath). To the suspension was added dropwise a solution of the above ketal (68 mg) and CH_3I (50 μL) in dry THF (3 mL), and the mixture was stirred for 40 min.[19] The cooled reaction mixture was hydrolyzed by dropwise addition of sufficient water, the aqueous layer was separated and extracted with ether, and then the combined organic solutions were washed with brine and cold water. The ether solution was stirred with 2 N HCl at room temperature overnight. After usual workup, the crude product was purified by GC (SE-30, 170 °C) to give **17** (45 mg): $[\alpha]^{20}_D$ +25.1° (*c* 0.5, CH_3OH); IR ($CHCl_3$) 1700, 1450, 1090 cm^{-1}; MS, m/z (relative intensity) 156 (M^+, 8) 124 (3), 82 (9), 71 (100), 55 (40).

3(*S*)-Hydroxy-2-methyl-2-(trideuteriomethyl)cyclohexanone *p*-Bromobenzenesulfonate (18). To a solution of **10a,b** (411 mg, 2.85 mmol) in dry pyridine (15 mL) was added *p*-bromobenzenesulfonyl chloride (1 g) and the mixture stirred at room temperature for 2 days. The mixture was then poured into ice–water containing $KHCO_3$ (1 g) and the precipitate collected by filtration. Two recrystallizations from ethanol–benzene

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gave colorless needles (560 mg), which were further recrystallized from benzene–isopropy alcohol for X-ray measurements: $[\alpha]^{20}_D$ +10.43° (c 0.3, $CHCl_3$); IR ($CHCl_3$) 2220, 1710, 1580, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.12 (2 s, 3 H), 2.10 (m, 4 H), 2.46 (m, 2 H), 4.72 (q, 1 H), 7.78 (s, 4 H); MS, m/z (relative intensity) 365 (M^+, 0.4), 363 (0.4), 323 (0.9), 321 (0.9), 239 (3.7), 236 (3.6), 221 (5.4), 219 (5), 157 (11.5), 155 (12), 144 (39), 127 (50), 98 (34), 85 (100), 55 (25); mol wt calcd for $C_{14}H_{14}D_3O_4S^{79}Br$ 363.01416, found 363.02545; mol wt calcd for $C_{14}H_{14}D_3O_4S^{81}Br$ 365.01416, found 365.02052.

Acknowledgment. Financial assistance by the National Science Foundation (Grant No. CHE 80-25733) is gratefully asknowledged, as is support by NIH Grant No. RR-0711 and NSF Grant No. GP-23633 for the Stanford Magnetic Resonance Laboratory. The X-ray work was supported by NIH Grant No. RR-05716 and the Margaret L. Wendt Foundation of Buffalo, NY. We thank F. Elaine DeJarnette (Buffalo) and Ruth Records (Standord) for technical assistance.

Supplementary Material Available: Table II, nonhydrogen atomic coordinates and isotropic thermal parameters for 18 (1 page). Ordering information is given on any current masthead page.

Proximate Charge Effects. 5.[1] Enthalpies of Solvent Transfer of Reactants and Transition States in the Saponification of Betaine Ethyl Ester

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Received May 23, 1983

The rates and activation enthalpies of the alkaline hydrolysis of betaine ethyl ester [(carbethoxymethyl)-trimethylammonium chloride] were measured in water, in 60 mol % ethanol–water, and in 60 mol % dimethyl sulfoxide–water. Unlike the alkaline hydrolysis of ethyl acetate which exhibits a large increase in $\Delta H^{\ddagger}$ on going from water as the solvent to 60 mol % ethanol–water, no such solvent effect was observed in the present case. Calorimetric determination of the enthalpies of solvent transfer revealed that, whereas there was a large desolvation of the ethyl acetate saponification transition state on transfer into aqueous ethanol, no such desolvation of the betaine ethyl ester transition state took place, an observation which had been made earlier about the saponification of acetylcholine. In 60 mol % dimethyl sulfoxide–water, a polar, poor hydrogen bond donor solvent, the $\Delta H^{\ddagger}$ for betaine ethyl ester and ethyl acetate saponification were nearly the same as in water as the solvent. Calorimetric determination of the enthalpies of solvent transfer of the saponification transition states of betaine ethyl ester and ethyl acetate from aqueous dimethyl sulfoxide to hydrogen bond donor solvents revealed that the increase in solvation on going to the better solvent was about the same for both esters.

The enthalpy of transfer of the transition state in the saponification of ethyl acetate from water to a less polar solvent, 60 mol % aqueous ethanol, was found[2] to be highly endothermic as can be expected from the desolvation of its highly localized negative charge on transfer to the poorer solvent. By contrast, the enthalpy of transfer of the acetylcholine saponification transition state between the same two solvents was found[2] to be isothermic. This observation was taken as evidence that this latter transition state has a coiled conformation and is internally solvated.

The purpose of the present work was to determine whether this conclusion is justified, that is, whether a saponification transition state which has a proximate positive charge positioned close to the negatively charged carbonyl oxygen will indeed lack the characteristic[2,3] endothermic enthalpy of transfer into a solvent of inferior solvating power. The system chosen for study was betaine ethyl ester which serves this purpose because (1) the principal conformation of its saponification transition state in a poorly solvating solvent (I, Figure 1) has a distance between the two oppositely charged groups which is very close to that found in the coiled transition state in the acetylcholine saponification and (2) it is a "reversed" system compared to acetylcholine, its positive charge being on the acyl rather than on the alkyl side of the ester group, thus eliminating any possible effect which may be due to such positioning.

Table I. Rate Constants[a] for the Alkaline Hydrolysis of Betaine Ethyl Ester

$^+(CH_3)_3NCH_2CO_2C_2H_5 + OH^- \rightarrow {}^+(CH_3)_3NCH_2CO_2^- + C_2H_5OH$

solvent[b]	temp, K	k_2, L mol^{-1} s^{-1}
H_2O	291.16	36.6 ± 4.5
H_2O	323.16	126.6 ± 21.1
0.60 aqueous ethanol	291.16	10.7 ± 1.5
0.60 aqueous ethanol	323.16	39.4 ± 4.2
0.60 aqueous Me_2SO	291.16	12.2 ± 3.1
0.60 aqueous Me_2SO	323.16	38.8 ± 1.1

[a] Extrapolated to zero ionic strength (log k_2 vs. $I^{1/2}$) by using six to ten kinetic runs at concentrations giving ionic strengths of 0.9×10^{-5}–1.5×10^{-4}. The uncertainties are given as the standard deviation of the extrapolated value. [b] Composition of mixed solvents indicated as the mole fraction of the organic component.

Saponification Rates

The rate of the alkaline hydrolysis of betaine ethyl ester (eq 1) was measured at two temperatures in three solvents:

$$^+(CH_3)_3NCH_2CO_2CH_2CH_3 + OH^- \rightarrow {}^+(CH_3)_3NCH_2CO_2^- + C_2H_5OH \quad (1)$$

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