case of pyrrolidine, for example, the dihedral angle between the lone-pair lobe and the C_α–C_β bond is nearly 120° and the protonation ^{13}C shift is the smallest of all of the four amines (in Figure 9), which corresponds well with the MO theoretical prediction given in Figure 8. However, in the case of α-picoline, where the dihedral angle between the lone-pair lobe and the C–CH_3 bond is 0°, the protonation causes the largest upfield ^{13}C shift for the β carbon. This example also corresponds with the theoretical results of the stereospecificity in the σ-inductive effect. For piperidine and quinuclidine, with the corresponding dihedral angle of 180°, the protonation-induced shifts for the β carbon are +4.8 and +4.4 ppm, respectively. For *N*-methylpiperidine and quinolizidine, with the dihedral angle of 60°, the protonation-induced shifts for the β carbon are +2.8 and +2.6 ppm, respectively. Hence the protonation-induced shifts of the β-carbon atoms fall in the order, $\theta = 0°$ (cis) > $\theta = 180°$ (trans) > $\theta = 60°$ > $\theta = 120°$. The change in the charge density obtained by the pseudo-atom approach falls in the order, $\theta = 0°$ (cis) > $\theta = 60°$ > $\theta = 180°$ (trans) > $\theta = 120°$ (Figure 8).

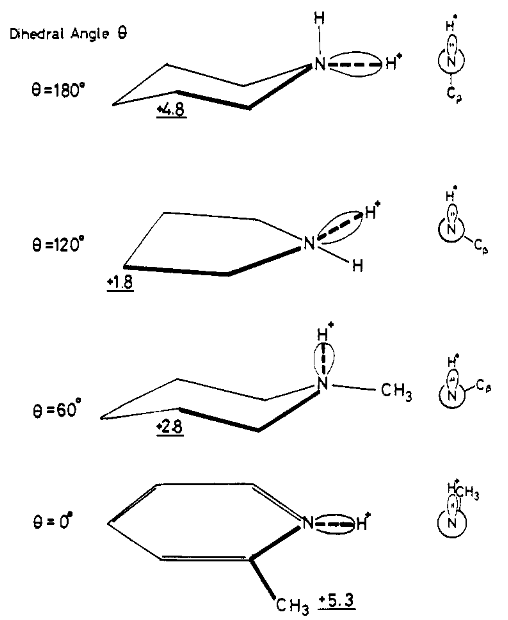
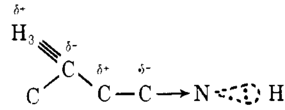


Figure 9. Stereospecific ^{13}C shifts induced by protonation for several cyclic N bases (ppm).

Conclusions

In summarizing the above results and discussion, the following conclusions may be drawn. (1) By the protonation of saturated amines the C–H bond is polarized to produce the C^-–H^+ structure and the electron on hydrogen atom is transmitted through the carbon skeleton onto the positively charged nitrogen atom. (2) The protonation ^{13}C shifts alternate and attenuate along the σ-carbon skeleton. These features of ^{13}C shifts can be interpreted in terms of charge density variation and correspond well with alternation in the σ-inductive effect predicted by Pople, *et al.*[3]

From (1) and (2), the σ-inductive effect induced by N protonation may be schematically represented as follows.



(3) The C–H bond is electronically polarized more readily than the C–C bond by the inductive effect and therefore the C–H carbon has more electron density than the C–C carbon by the protonation. This may be responsible for the observed trend of protonation-induced ^{13}C upfield shifts in the order of the secondary carbon > the tertiary carbon > the quaternary carbon. (4) The protonation ^{13}C shifts exhibit a marked conformational dependence, which can be interpreted in terms of stereospecificity of the σ-inductive effect.

Conformational Mobility of *cis*-Cyclooctene-*1,3,3-d*$_3$ Oxide

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Contribution from the Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007. *Received June 30, 1972*

Abstract: Ring inversion in *cis*-cyclooctene-*1,3,3-d*$_3$ oxide was studied by means of low-temperature nmr spectroscopy. A single process, with a free energy of activation of 8.0 kcal/mol at −120°, was observed. The results are interpreted in terms of a boat–chair conformation.

The transannular reactions of medium-ring compounds have been the subject of a number of investigations,[2,3] but frequently the presence of a specific ring conformation has not been included in the mechanistic considerations. One of the best known of these reactions is the formolysis of *cis*-cyclooctene oxide, which gives *cis*-1,4-cyclooctanediol (23–30%), *trans*-1,2-cyclooctanediol (5-19%), 3-cycloocten-1-ol (11%), 4-cycloocten-1-ol (4%), and traces of other compounds.[2b] We have carried out a study of the temperature dependence of the nmr spectrum of *cis*-cyclooctene-*1,3,3-d*$_3$ oxide in order to obtain information about the confor-

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[1] Alfred P. Sloan Research Fellow, 1969–1971.

[2] For reviews, see (a) V. Prelog and J. G. Traynham, in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 9; (b) A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev., Chem. Soc.*, **20**, 148 (1966).

[3] J. G. Traynham and DeWitt B. Stone, Jr., *J. Org. Chem.*, **35**, 2025 (1970), and references therein.

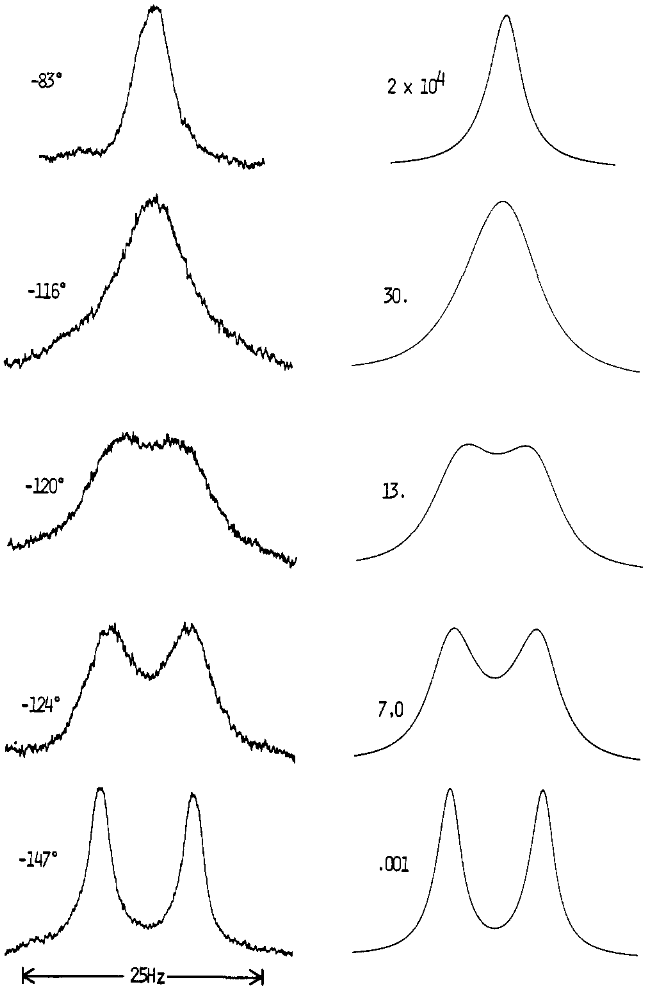


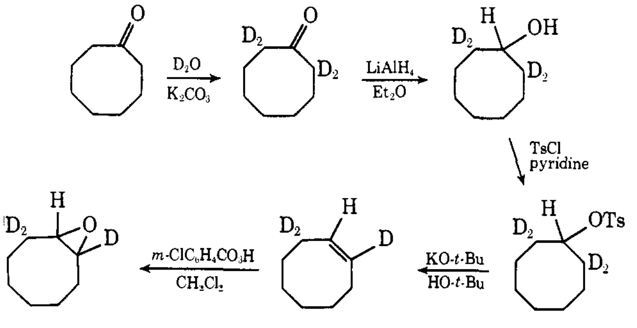
Figure 1. Experimental (left) and calculated (right) pmr spectra of *cis*-cyclooctene-*1,3,3*-d_3 oxide in vinyl chloride. The rate constants at −83 and −147° are arbitrary values for fast and slow exchange, respectively.

mations present and to determine the barrier to ring inversion.

Results

The deuterated epoxide was synthesized in five steps from cyclooctanone, as outlined in Scheme I. Refluxing the ketone with a 10% solution of potassium carbonate in D_2O (three exchanges) afforded cyclooctanone-*2,2,8,8*-d_4, and the cyclooctanone was reduced to the cyclooctanol with lithium aluminum hydride. The tosylate was prepared and converted to *cis*-cyclooctene-*1,3,3*-d_3 with potassium *tert*-butoxide in *tert*-butyl alcohol.[4] Treatment of the alkene with *m*-chloroperbenzoic acid in methylene chloride solution afforded the epoxide, which was purified by preparative vapor phase chromatography.[7] The deuterated *cis*-cyclooctene oxide, mp 54–55° (lit.[8] 56–57°), was identified by its nmr spectrum and by comparison of its vpc retention time with that of authentic cyclooctene oxide.

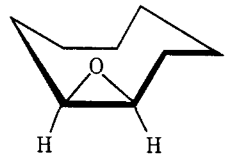
Scheme I



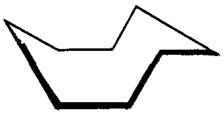
Experimental and calculated spectra for the proton on C-2 of the epoxide are shown in Figure 1. At +30°, the spectrum is a singlet[9] with a line width at half-height of 4.1 Hz and centered 278 Hz (2.78 ppm) downfield from internal TMS. As the temperature is lowered, the spectrum broadens and splits into two peaks of approximately equal areas. At −147°, the chemical shifts are 289.1 and 279.6 Hz, and the average line width is 3.0 Hz. The rate constant[14] of 13 sec^{-1} at −120° corresponds to a free energy of activation of 8.0 kcal/mol.

Interpretative Discussion

Hendrickson[15] has suggested that *cis*-cyclooctene oxide may have conformation **1**, which is derived from the preferred[16,17] boat–chair conformation (**2**) of cyclooctane by joining the three-membered ring to the boat–chair form at the position with the most favorable (smallest) C–C–C–C dihedral angle. A similar conformation has been reported[18] as the result of an X-ray diffraction study of **3**, which has a cis-fused three-membered ring. *cis*-Cyclooctene has been assigned a comparable conformation on the basis of low-temperature nmr studies of deuterated derivatives.[17,19]



1



2

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(4) The cis alkene predominates[5] in the reaction of cyclooctyl bromide with potassium *tert*-butoxide in *tert*-butyl alcohol. The crude deuterated cyclooctene in pentane was extracted with aqueous silver nitrate to remove any of the trans isomer present.[6]

(5) Z. Zavada, J. Krupicka, and J. Sicher, *Chem. Commun.*, 66 (1967).

(6) A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Amer. Chem. Soc.*, **75**, 3212 (1953); however, see also W. L. Waters, *J. Org. Chem.*, **36**, 1569 (1971).

(7) After preliminary purification at 120° on a 1/8 in. × 20 ft column of 20% SE-30 on Chromosorb P, the material was rechromatographed using a 1/8 in. × 6 ft glass column of 10% SE-52 on 60–80 Chromosorb WAW (column temperature, 85°).

(8) A. C. Cope, S. W. Swenton, and C. F. Spencer, *J. Amer. Chem. Soc.*, **74**, 5884 (1952).

(9) The signal is broadened by coupling to the adjacent deuterons and possibly by long-range coupling to some of the other ring protons. Line broadening from long-range proton–proton couplings has been observed[10–13] for a number of epoxides.

(10) P. Joseph-Nathan and E. Diaz, *Org. Magn. Resonance*, **3**, 193 (1971).

(11) L. J. T. Andrews, J. M. Coxon, and M. P. Hartshorn, *J. Org. Chem.*, **34**, 1126 (1969).

(12) R. G. Carlson and N. S. Behn, *Chem. Commun.*, 339 (1968).

(13) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

(14) The parameters used for calculation of the spectra at −116, −120, and −124° were $\Delta\nu$ = 9.5 Hz and T_2 = 0.0953 sec.

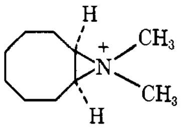
(15) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **86**, 4854 (1964).

(16) J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *ibid.*, **91**, 1386 (1969).

(17) F. A. L. Anet in "Organic Chemistry: A Series of Monographs," Vol. 21, G. Chiurdoglu, Ed., Academic Press, New York, N. Y., 1971, p 15, and references therein.

(18) L. M. Trefonas and R. Majeste, *Tetrahedron*, **19**, 929 (1963).

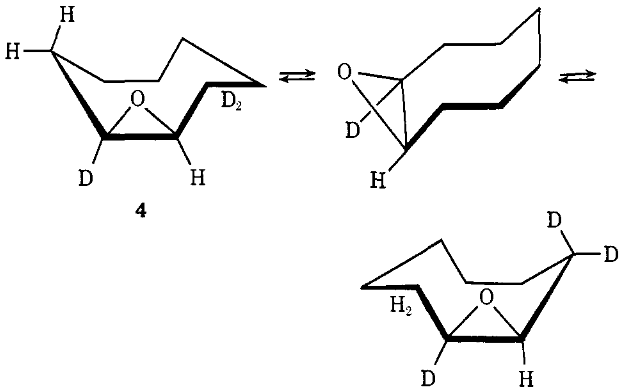
(19) M. St. Jacques, Ph.D. Thesis, University of California at Los Angeles, 1967.



3

The low-temperature nmr results for the deuterated cyclooctene epoxide indicate the presence of two equally probable epoxide hydrogen sites with nonidentical chemical shifts. This could be accommodated by two nonidentical conformations of equal energy in each of which the epoxide hydrogens are equivalent or by a single conformation with nonequivalent epoxide hydrogen positions. While the present data do not unequivocally rule out the first alternative, the second alternative appears much more likely in view of the known conformations of other cyclooctane derivatives.[16,17,19]

The nmr results for the deuterated epoxide are best interpreted in terms of a mixture of nearly equal amounts of conformations **4** and **5**. The barrier to interconversion of these forms (8.0 kcal/mol) is nearly equal to the free energy of activation for the corresponding process[20] in *cis*-cyclooctene-d_{13} (8.2 kcal/mol).[17,19] By analogy to a pathway described[19] for ring inversion in *cis*-cyclooctene, inversion of the epoxide may occur as shown above.



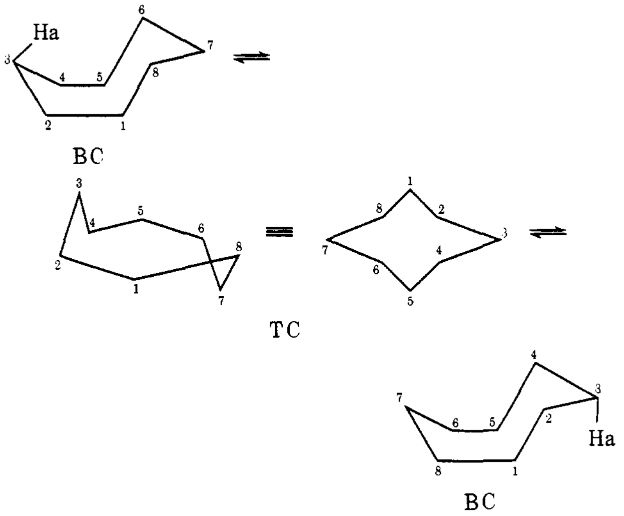
4

5

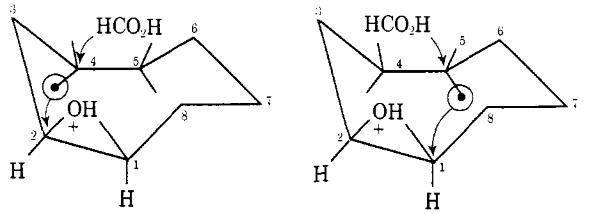
Studies of the conformation and barriers to conformational changes for a number of cyclooctane derivatives have been reported,[16,17,19,21] and the results for some compounds assigned a boat–chair conformation are summarized in Table I. The free energies of activation are found in the narrow range 7.3–8.5 kcal/mol. Inversion in cyclooctane could occur by a process similar to the one shown above for the epoxide. In a second possible pathway, the twist–chair conformation is an intermediate in the inversion process, as shown below. A third possibility, in which the BC form first pseudorotates to the TBC conformation, has been described by Roberts, *et al.*[16]

Table I. Free Energy Barriers of Some Cyclooctane Derivatives Possessing the Boat–Chair Conformation

Compd	Barrier (kcal/mol) Inversion	Pseudo-rotation	Ref
Cyclooctane	8.1	<5	17, 21a
1,1-Difluorocyclooctane	7.5	4.9	16
1,1,4-Tetrafluorocyclooctane		6.1	16
1,1-Ethylenedioxycyclooctane	7.6	5.3	17
1,1-Ethylenedithioxycyclooctane	8.5	6.6	17
Oxocane	7.4		21f
1,3-Dioxocane	7.3	5.7	21f
Cyclooctanone	7.5	6.3	17, 19
5-*tert*-Butylcyclooctanone		8.0	17, 19
Methylenecyclooctane	8.1		17
cis-Cyclooctene	8.2	5.8	17, 19
cis-Cyclooctene oxide	8.0		This work



Conformation **1** of *cis*-cyclooctene oxide provides a basis for understanding some of the transannular reactions of this compound. *cis*-1,4-Cyclooctanediol, the major product of transannular reaction in the formolysis of the epoxide, can be formed by hydride transfer and attack of formic acid as shown in **6a** and **6b**. Solvolysis of *cis*-cyclooctene-5,6-d_2 oxide with 90% formic acid showed[22] that 39% of the 1,4-diol was formed by a 1,3-hydride shift (corresponding to **6a**),[23] and the remainder of this diol was formed by a 1,5-hydride shift (corresponding to **6b**).[23] 3-Cycloocten-1-ol was found by the same deuterium-labeling experiment to arise from both a 1,5-hydride shift (94%) and a 1,3-hydride shift (6%); the predominant pathway pre-



6a **6b**

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[20] Two rate processes were detected for the deuterated *cis*-cyclooctene at low temperatures. At room temperature, the ring possesses a time-averaged plane and axis of symmetry. Slowing of the first process ($\Delta G^{\ddagger} = 8.2$ kcal/mol) removes the plane of symmetry, and slowing of the second process ($\Delta G^{\ddagger} = 5.8$ kcal/mol) results in loss of the axis of symmetry. It is the process with the higher barrier that corresponds to the process observed in the epoxide.

[21] (a) F. A. L. Anet and J. S. Hartman, *J. Amer. Chem. Soc.*, **85**, 1204 (1963); (b) F. A. L. Anet and M. St. Jacques, *ibid.*, **88**, 2585 (1966); (c) F. A. L. Anet and M. St. Jacques, *ibid.*, **88**, 2596 (1966); (d) G. Ferguson, D. D. Mac Nicol, W. Oberhansli, R. A. Raphael, and J. A. Zabkiewicz, *Chem. Commun.*, 103 (1968); (e) J. Dale, T. Ekeland, and J. Krane, *J. Amer. Chem. Soc.*, **94**, 1389 (1972); (f) F. A. L. Anet and P. J. Degen, *ibid.*, **94**, 1390 (1972).

[22] A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *J. Amer. Chem. Soc.*, **82**, 6366 (1960).

[23] Hydride shifts from C-7 to C-1 and from C-6 to C-2 of 6 appear less likely than the hydride shifts shown in 6a and 6b. The transannular reactions of *cis*-cyclooctene oxide are not necessarily concerted.

sumably involves hydride transfer from the 5-axial position of 6 to C-1, followed by loss of a proton on C-4, while the less favored route could involve hydride transfer from C-4 to C-2, followed by loss of a proton on C-3. The C-4 to C-2 hydride shift and subsequent removal of a proton on C-5 would rationalize the formation of 4-cycloocten-1-ol.

Experimental Section

Ambient-temperature pmr spectra were obtained with the Varian A-60 spectrometer. A Varian HA-100 spectrometer, equipped with a variable-temperature accessory, Model 4343, was used to record the low-temperature spectra. Temperatures were measured by replacing the sample tube with an nmr tube containing a thermocouple immersed in vinyl chloride.

The calculated spectra were obtained with an IBM 360/65 computer equipped with a University Computing Co. (UCC) plotter. The DNMR2 computer program of Binsch and Kleier[24] was used for the calculations.

Cyclooctanone-*2,2,8,8*-d_3. A mixture of 4.0 g of cyclooctanone, 3.0 g of anhydrous potassium carbonate, and 30 ml of D_2O (99.7% D) was refluxed for 1 hr and then cooled to room temperature and extracted with ether. The organic layer was separated, dried over Drierite, and concentrated at the rotary evaporator. The exchange reaction was repeated twice, using reflux times of 1 and 3.5 hr, respectively. A pmr spectrum of the deuterated cyclooctanone (3.65 g) showed the absence of α protons.

Cyclooctanol-*2,2,8,8*-d_4. A suspension of lithium aluminum hydride (1.6 g) in 25 ml of ether was stirred for 0.5 hr at room temperature, followed by dropwise addition of 3.65 g of cyclooctaone-d_4 in 25 ml of ether. The mixture was stirred at room temperature for 4.5 hr and was hydrolyzed by successive dropwise addition of 1.6 ml of water, 1.6 ml of 15% NaOH, and 4.8 ml of water. The solution was filtered, washed with 20 ml of saturated NaCl solution, and dried over Drierite. Removal of the solvent at the rotary evaporator afforded 3.60 g of cyclooctanol-d_4. The pmr spectrum showed peaks centered at δ 4.93 (OH), 3.75 (proton on C-1), and 1.55 ppm, relative to external TMS.

Tosylate of Cyclooctanol-*2,2,8,8*-d_4. The deuterated cyclooctanol (3.6 g, 0.0272 mol) was dissolved in 40 ml of pyridine and cooled to 0° in an ice–salt bath. *p*-Toluenesulfonyl chloride (10.4 g, 0.0544 mol) was added with stirring, and the solution was kept at 0° for 23 hr. The reaction mixture was poured into a two-phase mixture of ether and 300 ml of iced 2 *N* hydrochloric acid. The aqueous phase was extracted two more times with ether, and the combined ether portions were washed four times with 2 *N* hydrochloric acid, twice with saturated sodium bicarbonate solution, and twice with saturated sodium chloride solution. The ether solution was dried over Drierite, and most of the ether was removed at room temperature with the aid of the rotary evaporator.

***cis*-Cyclooctene-*1,3,3*-d_3.** The tosylate from the previous step was dissolved in 100 ml of *tert*-butyl alcohol, and 6.1 g of potassium *tert*-butoxide was added. The mixture was heated for 1 hr at 55° and at 40° for an additional 11 hr. *tert*-Butyl alcohol (35 ml) was added after 0.5 hr. After cooling to room temperature, the reaction mixture was poured into 500 ml of ice water and extracted five times with methylene chloride. The methylene chloride portions were combined, washed five times with water, dried over Drierite, and concentrated by distillation at atmospheric pressure until a volume of about 20 ml was reached. An nmr spectrum at this point showed absorption at δ 1.45, 2.40, 4.6, and 7.15–7.8 ppm (relative to internal TMS), indicating that the unchanged starting material was present.[25]

Most of the methylene chloride was removed at room temperature at the rotary evaporator. The residue was dissolved in 30 ml of *tert*-butyl alcohol and added to a solution of 6.1 g of potassium *tert*-butoxide in 100 ml of *tert*-butyl alcohol. The solution was heated to 83° and maintained at this temperature for 21 hr, then at 90° for 5 hr. The reaction mixture was cooled to room temperature, poured into 500 ml of ice water, and extracted four times with ether. The combined ether extracts were washed with water, dried over Drierite, and concentrated by distillation. An nmr spectrum showed absorption at δ 6.0, 2.3, and 1.6 ppm, relative to internal TMS, which could be assigned to the alkene.

Pentane (purified by permanganate) was added to the alkene, and the mixture was shaken five times with water to reduce the amount of *tert*-butyl alcohol present. The solution was then washed five times with 25-ml portions of 20% (by weight) aqueous silver nitrate, in order to remove any *trans*-cyclooctene-d_3 that might be present.[6] The combined silver nitrate portions were washed twice with 15-ml portions of pentane, and the combined pentane solutions were washed once with water, dried over Drierite, and concentrated by distillation. Methylene chloride was added, and most of the solvent was again removed by distillation.

***cis*-Cyclooctene-*1,3,3*-d_3 Oxide.** The deuterated cyclooctene was dissolved in 20 ml of methylene chloride, and 5.97 g of *m*-chloroperbenzoic acid (~85% pure) in 65 ml of methylene chloride was added dropwise with stirring in the temperature range 20–25°. A white solid appeared. The suspension was stirred at about 25° for 1.75 hr, and then 75 ml of 10% sodium sulfite solution was added with cooling. After shaking in a separatory funnel, the reaction mixture was tested with starch–iodide paper, and the organic phase was separated and washed three times with saturated sodium bicarbonate solution, once with water, and once with saturated sodium chloride solution. Drying over Drierite and removal of most of the solvent at the rotary evaporator afforded a yellow residue, which showed peaks in the nmr spectrum (relative to internal TMS) at δ 2.75 (proton on C-2) and 1.5 ppm, along with two small broad peaks at δ 2.15 and 1.95 ppm. The product, purified by preparative vpc,[7] had mp 54–55° (lit.[8] mp of *cis*-cyclooctene oxide, 56–57°); the vpc retention times were the same as for an authentic sample of *cis*-cyclooctene oxide.

The spectrum of the oxide at $-147°$ indicates that scrambling of the deuterium has not occurred. If formation of the alkene had occurred partially by solvolysis, followed by transannular hydride migration and loss of a proton, then the spectrum of the deuterated oxide under conditions of slow ring inversion would have been expected to be more complex. The pmr spectrum of the protons at C-1 and C-2 of unlabeled *cis*-cyclooctene oxide is complex at about $-150°$ and changes relatively little as the temperature is raised, although extensive changes occur in the spectra of the methylene protons.

Acknowledgment. We are grateful to the Alfred P. Sloan Foundation for financial support.

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[24] (a) G. Binsch, *J. Amer. Chem. Soc.*, 91, 1304 (1969); (b) G Binsch and D. A. Kleier, "Quantum Chemistry Program Exchange," No. 140, DNMR Computer Program, Chemistry Department, Indiana University, Bloomington, Ind.

[25] Much of the base may have been consumed by reaction with *p*-toluenesulfonyl chloride, which could have been present from the previous reaction.