dry ether was added to a stirred slurry of 0.595 g (0.016 mol) of lithium aluminum hydride in 5.0 ml of dry ether. Work-up was as previously described[6] except that chloroform was used in the extraction, which made a continuous extraction unnecessary, and yielded 1.83 g (96%) of 3,4-dimethylphenol as a pale yellow solid. Recrystallization of the product thrice from hexane gave colorless needles, mp 63.5–64.5° (lit.[21] mp 62–65°); ir (KBr) 3180 cm^{-1} (br, OH); nmr ($CDCl_3$) δ 6.75 (br m, 3, Ar*H*), 5.35 [br s (exchanged with D_2O), 1, O*H*], and 2.16 ppm (s, 6, ArCH_3).

Methylation of 3,4-Dimethylphenol. 3,4-Dimethylanisole. 3,4-Dimethylphenol, 1.69 g (0.014 mol), and dimethyl sulfate, 2.65 ml (3.53 g, 0.028 mol), yielded 1.73 g (92%) of crude 3,4-dimethylanisole by the reported procedure.[6] The product was distilled to give a colorless liquid, bp 43–45° (1 mm) [lit.[6] bp 68.5–69° (5 mm)], which was found to be >99.9% pure by vpc analysis: nmr ($CDCl_3$) δ 6.85 (br m, 3, Ar*H*), 3.73 (s, 3, OCH_3), 2.21 (s, 3, ArCH_3), and 2.17 ppm (s, 3, ArCH_3).

Oxidation of 3,4-Dimethylanisole. 4-Methoxybenzene-1,2-dicarboxylic Acid. A 1.48-g (0.011 mol) sample of 3,4-dimethylanisole was oxidized as reported previously except that the addition period of the potassium permanganate solution was shortened to 40 min due to the smaller quantities used. Work-up as described yielded 31 mg (2%) of 2-methyl-4-methoxybenzoic acid: ir (KBr) 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity, fragment ion) 166 (100, M^+), 149 (86, $M^+ - OH$), 148 (73, $M^+ - H_2O$), 121 (38, $M^+ - CO_2H$), 120 (31, 121 − H), 91 (35, $C_6H_3O^+$), 77 (38).

The aqueous filtrate from above was evaporated to near dryness, water was added, and the mixture was heated until the solids had completely dissolved. The desired diacid was allowed to crystallize slowly to yield 1.45 g of a white solid. The filtrate was recycled using the procedure described above to yield an additional 0.15 g of product; the combined weights of the two crystallizations represent a yield of 75% of crude 4-methoxybenzene-1,2-dicarboxylic acid. The diacid was recrystallized once from water, twice from 4:1 benzene–acetone, and vacuum-dried; no melting point was determined since the acid readily forms the anhydride on heating:[6] ir (KBr) 1730 (C_2=O) and 1680 cm^{-1} (C_1=O); nmr [$(CD_3)_2CO$] δ 7.51 (br m, 3, Ar*H*), 7.84 [s (exchanged with D_2O), 2, CO_2H], and 3.91 ppm (s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity, fragment ion) 196 (22, M^+), 179 (15, $M^+ - OH$), 178 (52, $M^+ - H_2O$), 152 (37, $M^+ - CO_2$), 135 (41, 179 − CO_2), 134 (100, 178 − CO_2), 106 (69, $M^+ - 2CO_2H$).

Brominative Decarboxylation of 4-Methoxybenzene-1,2-dicarboxylic Acid. 2,4-Dibromo-5-methoxybenzoic Acid. A 0.86-g (0.0044 mol) sample of 4-methoxybenzene-1,2-dicarboxylic acid in 10.5 ml of 10% aqueous sodium hydroxide and 17.5 ml of water was treated with 1.41 g (0.0088 mol) of bromine using the prescribed procedure.[6] The desired 2,4-dibromo-5-methoxybenzoic acid, 0.414 g (30%), was obtained as a cream-colored solid which, on recrystallization once from 50% aqueous ethanol and twice from benzene, yielded white needles: mp 202.5–203.5° (lit.[22] mp 203°); ir (KBr) 1700 cm^{-1} (C=O); nmr [$(CD_3)_2CO$] δ 7.82 (s, 1, Ar*H*), 7.48 (s, 1, Ar*H*), 5.34 [br s (exchanged with D_2O), 1, CO_2H], and 3.94 ppm (s, 3, OCH_3).

The original filtrate from above was cooled to room temperature and refrigerated to precipitate 4-bromo-5-methoxybenzene-1,2-dicarboxylic acid, 0.288 g (24%), which was obtained as a pale yellow solid. The product was purified by recrystallization from water and ethyl acetate to give a white solid; no melting point was determined because the acid forms the anhydride on heating:[6] ir (KBr) 1730 (C_1=O) and 1700 cm^{-1} (C_2=O).

Liquid Scintillation Counting. Radioactive samples (0.47–7.23 mmol) from the degradation of 3,4-dimethylacetophenone formed from camphor-8-^{14}C and camphor-9-^{14}C were dissolved in 10 ml of scintillation grade toluene[23] containing 4.00 g/l. of 2,5-diphenyloxazole (PPO)[24] and 50 mg/l. of *p*-bis-2-(5-phenyloxazoyl)benzene (POPOP)[24] in a counting vial and counted for 20 min with a Nuclear Chicago Counter Model 723. In the case of 4-methoxybenzene-1,2-dicarboxylic acid it was necessary to first dissolve the sample in 200 μl of reagent grade acetone before adding the scintillation cocktail to effect complete solution of the diacid. The counting efficiencies of all samples were determined from quenching curves obtained by diluting samples of known radioactivities (disintegrations per minute) with increasing amounts of chloroform and of acetone.[25]

(21) Reference 19, Vol. 2, p 1209.

(22) H. Davies and W. Davies, *J. Chem. Soc., London*, 602 (1928).
(23) Mallinckrodt/Nuclear, St. Louis, Mo. 63145.
(24) Pilot Chemicals, Inc., Watertown, Mass.
(25) We wish to thank Dr. Clive Bradbeer, Department of Biochemistry, University of Virginia, for making these data available to us.

Proton Magnetic Resonance Studies of the Conformations and Conformational Equilibrations of *cis*- and *trans*-1,5-Diacetoxycyclooctane

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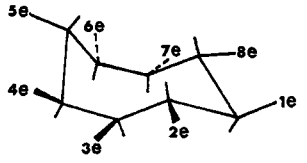
Contribution from the Department of Chemistry, University of Montreal, Montreal, Canada. *Received December 21, 1971*

Abstract: The pmr spectra of partially deuterated *cis*- and *trans*-1,5-diacetoxycyclooctane were studied at variable temperature. Both molecules showed a spectral change at different temperatures such that the low-temperature spectra defined the stable conformations to be boat–chair forms (**3** and **4**) containing the substituents at different positions for each isomer. The spectral change for the cis isomer was interpreted in terms of a pseudorotation while that of the trans isomer was explained in terms of an inversion process.

While the conformational analysis of cyclohexane and its derivatives is rather well understood, the conformational possibilities for derivatives of cyclooctane are not as easily envisaged because of the greater complexity of the ring system and the relative paucity of experimental results. Several publications have recently been concerned with experimental[1–3] and theoretical[4] studies on cyclooctane. From this work it has emerged that cyclooctane exists in the boat–chair

(1) (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, 2586 (1966); (c) M. St-Jacques, Ph.D. Thesis, University of California at Los Angeles, 1967.
(2) J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 1386 (1969).
(3) (a) M. Dobler, J. D. Dunitz, and A. Mugnoli, *Helv. Chim. Acta*, **49**, 2492 (1966); (b) H. B. Burgi and J. D. Dunitz, *ibid.*, **51**, 1514 (1968); (c) P. Groth, *Acta Chem. Scand.*, **21**, 2695 (1967); (d) J. V. Egmond and C. Romers, *Tetrahedron*, **25**, 2693 (1969); (e) G. Ferguson, D. D. MacNicol, W. Oberhansli, R. A. Raphael, and J. A. Zabkiewicz, *Chem.*

(BC, **1**) conformation, although caution in generalizing to all cyclooctane derivatives is suggested from X-ray crystallographic studies of *trans-syn-trans*-1,2,5,6-tetrabromocyclooctane which revealed a twist-crown conformation.[3e]



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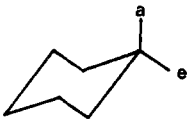
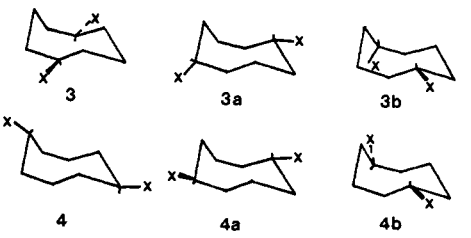


2

The symmetry (C_s) of BC is such that it contains five nonequivalent carbon atoms and consequently five magnetically different equatorial-like positions (labeled e in **1**) and five different axial-like positions in contrast to the cyclohexane chair (**2**) which contains only two types of positions, equatorial and axial. Pmr studies[1,2,5] of substituted cyclooctanes have been largely concerned with monosubstituted and 1,1-disubstituted derivatives and in particular it has been shown[1b] that the bulky *tert*-butyl group is unable to "fix" the BC form of cyclooctane as it does the chair conformation of cyclohexane. As an extension of our interest in the conformational behavior of substituted cyclooctane derivatives we have studied *cis*- and *trans*-1,5-diacetoxycyclooctane (referred as *cis*-DAC and *trans*-DAC in the text). The substitution pattern of these compounds is analogical to that of cis and trans 1,4-disubstituted cyclohexane derivatives whose conformational possibilities and behavior are well known.[6]

Eight-membered rings offer more possibilities than six-membered rings so that based on calculations by Hendrickson[4d] and nmr studies by Roberts,[2] Anet,[5] and coworkers it is suggested that the axial positions at C_4 and C_6 of BC (numbers refer to carbon position on conformation **1**) are of comparable energy to the equatorial positions and therefore constitute more favorable sites to locate a substituent than the other hindered axial positions. Restricting the substituents to favorable locations, it is possible to predict that members of the group of conformations **3**, **3a** and **3b** (sometimes referred to collectively as **3ab** in the text) are possible for *cis*-DAC whereas the group **4**, **4a**, **4b** (**4ab** later in the text) represents possible conformations for *trans*-DAC. Conformations **3** and **4** each contain a plane of symmetry through the C_1 and C_5 atoms of the BC skeleton while the others lack symmetry but are related to each other as mirror images (*e.g.*, **3a** and **3b** constitute an enantiomeric pair).

If, in addition to **3ab** and **4ab**, we also consider BC forms containing an unfavorable axial substituent and other forms arising from other low-energy ring skeleton conformations such as members of the crown family,



it is evident that there could *a priori* be many nonequivalent conformations possible for each DAC isomer. The problem of choosing between these might not be trivial especially since it is known that solid *trans*-1,4-dichlorocyclooctane[3d] contains an axial chlorine atom and that *trans-syn-trans*-1,2,5,6-tetrabromocyclooctane[3e] exists as a twist-crown.

In addition to the question of the stable conformation, the modes of conformational equilibration available to cyclooctane derivatives are more numerous and more complex than the straightforward ring inversion of cyclohexane. Nmr results[1,2,5] have shown that two mechanisms of equilibration are possible for BC. The lower energy process is a pseudorotation which when rapid on the nmr time scale causes each carbon to move through all the positions of the BC conformation so that the carbons on the average are equivalent. Thus there occurs a partial averaging of the magnetic environments of all the proton positions resulting in two averaged environments. One consists of the set of bonds 1e, 2e, 3e, 4a, 5a, 6a, 7e, and 8e (see structure **1** for number system) and the other contains the set of bonds 1a, 2a, 3a, 4e, 5e, 6e, 7a, and 8a. The higher energy process is termed inversion and results in a mixing of both sets of bonds leading to an exchange of environment of the protons of a methylene group and therefore to a complete averaging of chemical shifts for all different protons of cyclooctane.

The aim of this paper is then to define the conformational behavior of *cis*- and *trans*-DAC in terms of its stable conformations and its equilibrating mechanisms as revealed from the pmr spectra at low temperature. The complexity of the pmr spectra often imposes severe limitations on the kind of information which can be obtained directly from this technique. Partial deuteration at selected positions offers a mean of simplifying spectra without modifying the conformational properties of a molecule. This approach has been used in our study for which the deuterated *cis*-DAC-d_8 (**9**) and *trans*-DAC-d_8 (**10**) were prepared by the sequence of reactions outlined in Scheme I.

Results

The deuterium decoupled 100-MHz pmr spectra of a solution of *trans*-DAC-d_8 in chlorodifluoromethane are shown in Figure 1 at several temperatures. The high-temperature spectrum contains a singlet at δ 1.69 associated with equivalent methylene protons and a singlet at δ 2.00 due to the methyl protons of the acetoxy group, while the singlet at δ 4.84 is characteristic of the methine protons at the substituted carbon atoms. As the temperature is lowered the downfield singlet broadens and appears as a doublet below $-112°$, the coalescence temperature (T_c), and remains a doublet down to $-160°$, the lowest temperature at which the spectrum could be recorded without excessive crystallization. The peak separation at $-140°$ is 18.5 Hz ($\Delta\nu$). The

Commun., 103 (1968); (f) D. Grandjean and A. Leclaire, *C. R. Acad. Sci., Ser. C*, **265**, 795 (1967); (g) R. Shrinivasan and T. Srikrishnan, *Tetrahedron*, 27, 1009 (1971).

(4) (a) K. B. Wiberg, *J. Amer. Chem. Soc.*, **87**, 1070 (1965); (b) M. Bixon and S. Lifson, *Tetrahedron*, 23, 769 (1967); (c) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7036 (1967); (d) *ibid.*, **89**, 7043 (1967); (e) *ibid.*, **89**, 7047 (1967).

(5) F. A. L. Anet, "Conformational Analysis, Scope and Present Limitations," G. Chiurdoglu, Ed., Academic Press, New York, N. Y., 1971, p 15.

(6) (a) E. L. Eliel, N. L. Allinger, S. L. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 53. (b) M. Hanack, "Conformational Theory," Academic Press, New York, N. Y., 1965, p 104. (c) G. Wood, E. P. Woo, and M. H. Miskow, *Can. J. Chem.*, **47**, 429 (1969).

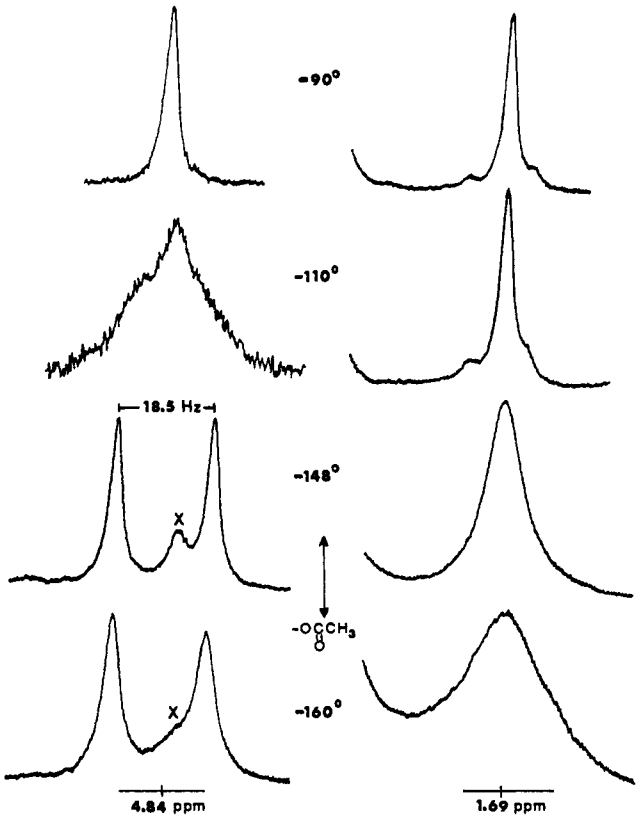
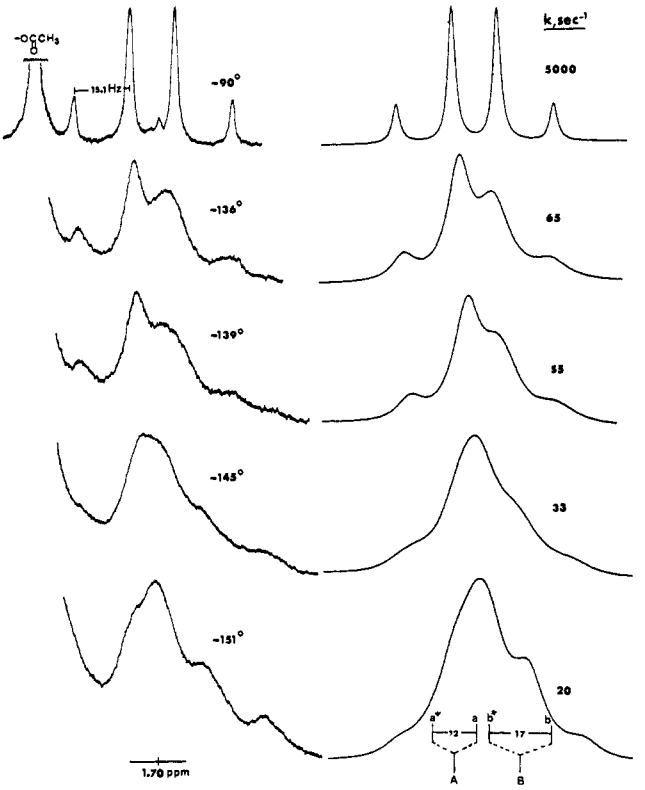
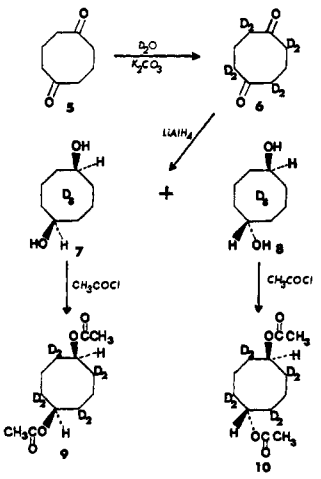


Figure 1. The 100-MHz pmr deuterium decoupled spectra of the methine and methylene protons of *trans*-DAC-d_8 (**10**) at several temperatures. The X in the spectra at -148 and $-160°$ indicates a peak due to a small amount of *cis*-DAC-d_8.



Fiure 2. Comparison of the experimental 100-MHz deuterium decoupled (left) and theoretical pmr spectra of the methylene protons of *cis*-DAC-d_8 (**9**). Under the calculated spectrum corresponding to $k = 20$ sec^{-1} is shown the chemical shift averaging pattern used to calculated the various spectra.

Scheme I



acetoxy signal remains a singlet in this temperature range while the methylene peak broadens but cannot be resolved into a recognizable pattern. A solution in a mixture of chlorodifluoromethane and vinyl chloride permitted a lower temperature to be reached without crystallization but did not afford a better resolved spectrum in the methylene region.

cis-DAC-d_8, on the other hand, gave a different spectral behavior as illustrated in Figure 2. The high-temperature deuterium decoupled 100-MHz spectrum of a solution in chlorodifluoromethane shows an AB pattern ($\Delta\nu = 22.4$ Hz and $J = 15.1$ Hz at $-90°$) centered at δ 1.70 and characteristic of two nonequivalent methylene protons, an acetoxy singlet at δ 2.00, and a methine singlet at δ 4.83. As the temperature is lowered both the methine and the acetoxy signals remain singlets down to $-160°$ while the methylene AB quartet broadens below $-125°$ and eventually changes appearance radically into a pattern not readily analyzable. A better resolution was not obtained down to $-170°$ using a mixture of solvents.

Even though a complete analysis of the spectrum at $-160°$ is not straightforward, it has been possible to simulate this spectrum as well as others at higher temperature (Figure 2) by using the DNMR2 program[7] which when supplied with chemical shifts, coupling constants, T_2 values and the pattern of exchange for the averaging process is able to simulate any spectrum as a function of the rate constant (k in sec^{-1}). Analysis of the AB pattern from -70 to $-120°$ showed that the chemical shift difference ($\Delta\nu_{AB}$) for this averaged AB quartet decreased linearly with temperature (from 24.8 to 20.0 Hz). A graphical extrapolation of this change was used to obtain the appropriate $\Delta\nu_{AB}$ for each simulation. The T_2 value used at each temperature was determined from the line width of the methine singlet whose line width at half-height was 2.4 Hz at $-90°$ and 4.8 Hz at $-150°$. In the same temperature range the TMS line width varied from 0.8 to 2.0 Hz. The calculations were made under the assumption that the spectral change consisted of the splitting of an averaged AB quartet (observed above $-120°$) into two AB patterns (referred to as ab and a*b*) each having $J = 15.1$ Hz and chemical shifts adjusted by trial and error until a

(7) G. Binsch, *J. Amer. Chem. Soc.*, **91**, 1304 (1969). A copy of the DNMR program was obtained from QCPE, Bloomington, Ind.

good fit between experimental and calculated spectra was obtained.

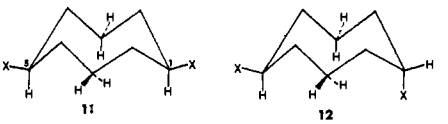
The chemical shifts of the ab and a*b* subspectra and their averaging pattern are shown in Figure 2 under the calculated spectrum for $k = 20$ sec^{-1}. Throughout the calculation it was assumed that the separation between a and a* was kept constant at 12.0 Hz while that between b and b* was fixed at 17.0 Hz, thus implying that only the averaged chemical shift difference ($\Delta\nu_{AB}$) varies with temperature.

It is evident from Figure 2 that the fit is rather good in spite of distortions brought about below $-140°$ by the overlap of the broad acetate peak with the low field components of the methylene protons patterns. Distortion being less above $-140°$, the free energy of activation ($\Delta G^{\mp}$) was calculated at $-139°$ using the value $k = 55$ sec^{-1} and the Eyring equation with a transmission coefficient of 1. The value 6.5 ± 0.3 kcal/mol was obtained. The uncertainty involved in obtaining very accurate pmr parameters from the analysis of the low-temperature spectrum and the approximate values of T_2 used do not justify an attempt to determine other kinetic parameters ($\Delta H^{\mp}$ and $\Delta S^{\mp}$) from the complete line-shape analysis.

The $\Delta G^{\mp}$ value at T_c characteristic of the conformational equilibration responsible for the spectral change of the methine region of *trans*-DAC-d_8 (Figure 1) can be obtained from the rate constant k given by the relationship[8] $k = \pi\Delta\nu/\sqrt{2}$ which corresponds to $\Delta G^{\mp} = 8.0 \pm 0.3$ kcal/mol[9] at $-112°$. A computer simulation of this spectral change with the DNMR program[7] confirmed the value of k at $-112°$ within the accepted error limit. While it is relatively straightforward to reproduce the general appearance of the collapsing doublet, an accurate line-shape comparison with the observed spectrum over a reasonable temperature range necessitates a knowledge of accurate T_2 values. Normally T_2 is estimated from the line of protons in the molecule that are unaffected by the averaging process. Since the spectrum of *trans*-DAC-d_8 contains no such peak and TMS is not an acceptable substitute at such low temperatures, the evaluation of all the kinetic parameters was not attempted for this molecule because even under more ideal conditions the accuracy of $\Delta S^{\mp}$ obtained from such an analysis is doubtful.[10] We therefore restricted our calculation to $\Delta G^{\mp}$ at T_c. This parameter is sufficiently precise to characterize the averaging process and is the one most used for the comparison with other eight-membered compounds.[5]

Discussion

Ground-State Conformation. First, it is expected that the low-temperature pmr spectra of each DAC isomer should permit the determination of its most stable conformation. Barring accidental chemical shift equivalence, the analysis of the spectrum usually provides information about the symmetry of the molecule and thus allows certain conformations to be rejected. For example, *cis*-DAC-d_8 could not exist in the crown conformation (**11**, where the acetoxy groups are represented by X) for which the low-temperature spectrum should contain a methine singlet as observed but only one AB quartet (because the methylene groups are made equivalent by the plane of symmetry through C_1 and C_5) instead of the two AB patterns which were deduced from the computer simulation of the spectra shown in Figure 2. The twist-crown or the chair–chair are also unlikely since they would all interconvert rapidly at $-160°$ to give the average symmetry of the crown.[1,4e]



11 **12**

Although symmetry arguments cannot exclude the crown (**12**) for *trans*-DAC-d_8, the necessity of an axial acetoxy group makes this conformation much less likely than **11** was for *cis*-DAC-d_8 and consequently much less favorable than members of the group **4ab**. This argument implies the reasonable assumption that locating acetoxy groups at favorable positions of BC does not give rise to polar interactions sufficiently strong to overcome the stabilization energy of BC and make another skeleton conformation, which would minimize these interactions, more stable.

The spectrum at $-160°$ of *trans*-DAC-d_8 (Figure 1) is most compatible with conformation **4** which contains two types of methine protons associated with each component of the low field doublet and one type of methylene group in agreement with the broad upfield band which represents an unresolved collapsed AB quartet. On the other hand, the low-temperature spectrum of *cis*-DAC-d_8 (Figure 2) is readily accounted for using conformation **3** which contains only one type of methine proton, in accord with the unchanged low field singlet, and two nonequivalent methylene groups giving rise to two AB quartets which when overlapping and unresolved account for the complex upfield pattern.

While we have shown that conformations **3** and **4** are stable forms of *cis*- and *trans*-DAC, we cannot be certain that they are the only forms populated since the nmr method is unable to distinguish between a single "fixed" conformation or a mixture of conformations in rapid equilibrium resulting in an averaged symmetry equivalent to that of the single conformation. For the latter possibility, a much lower temperature (not accessible experimentally) would be required to slow down the residual process on the nmr time scale. Knowing that the pseudorotation (abbreviated by Ψ) of cyclooctane has a very low $\Delta G^{\mp}$, less than 5 kcal/mol,[1,5] suggests that rapid partial pseudorotation (abbreviated by PΨ) between the members of **3ab** and **4ab** (*i.e.*, **3a** $\rightleftharpoons$ **3** $\rightleftharpoons$ **3b** and **4a** $\rightleftharpoons$ **4** $\rightleftharpoons$ **4b**), which results in the correct averaged symmetry, could still be rapid at $-160°$. This suggestion is supported by the observation that all members of each mixture are expected to be of comparable stability on steric grounds.

It therefore follows that if these partial pseudorotations could be slowed down on the nmr time scale, the methine singlet of *cis*-DAC-d_8 would change and consist of the sum of signals corresponding to the different nonequivalent positions on populated conformations with intensities proportional to their population. Similarly *trans*-DAC-d_8 would show a methine region more complex than a doublet depending on the number and population of the conformations in the mixture.

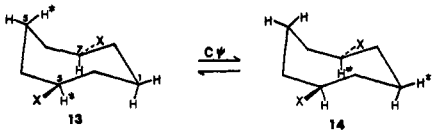
(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 223.

(9) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).

(10) S. Van der Werf and J. B. F. N. Engberts, *Recl. Trav. Chim. Pays-Bas*, **90**, 663 (1971).

In conclusion we can state that the pmr spectra of *cis*- and *trans*-DAC-d_8 at $-160°$ are consistent with the fixed conformations **3** and **4** but most likely are characteristic of the rapidly equilibrating mixtures **3ab** and **4ab** whose averaged symmetry is equivalent to that of **3** and **4**.

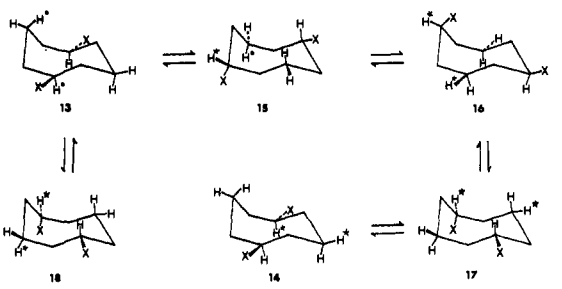
Mechanisms of Equilibration. Our next objective is to define the mechanisms of conformational equilibration responsible for the spectral changes illustrated in Figures 1 and 2. Since the BC conformation of cyclooctane is capable of two modes of equilibration, namely a pseudorotation and an inversion (see introductory paragraphs), we shall be interested in determining the manner in which these processes are affected by the presence of two acetoxy groups.



As seen in Figure 2, the averaging process of *cis*-DAC-d_8 gives rise to a spectral change only in the methylene region of the spectrum. Conformation **3** is best suited to rationalize this observation through the use of the equivalent structures **13** and **14** which are forms of **3** differing only in the position of the asterisk label (*). The transformation of **13** to **14** shows that there is an exchange of magnetic environments of C_1 with C_5 and C_3 with C_7 as shown by the change of positions of the labels. Thus an axial proton on C_5 becomes equatorial on C_1 and an axial proton on C_3 remains in an identical axial position on C_7. Consequently when the process **13** $\rightleftharpoons$ **14** is rapid on the nmr time scale, there occurs an interconversion of BC into itself (*i.e.*, only the asterisks change positions) accompanied by the passage of the C_1 and C_5 carbon atoms through all different positions of BC, thus making them equivalent. As a result, the two methylene groups on C_1 and C_5 become magnetically equivalent so that their pmr spectrum is expected to give an averaged AB quartet as observed above $-130°$ in Figure 2. On the other hand, the methine protons merely exchange their identical environments in accord with the temperature independent pmr singlet.

Two mechanisms can be imagined for the above interconversion. First, one can envisage the flip of C_5 in **13** to give a conformation of the crown family[1c,4d] which when followed by a flip of C_1 gives **14** after a rotation in the plane of the paper. (A similar double flip *via* the boat–boat form gives an identical result.) Hendrickson[4d] has calculated that such ring flips are of relatively high energy for cyclooctane and nmr results[1,2,5] have shown that they are not involved in the low-energy averaging process of cyclooctane but that instead a pseudorotation is actually involved. It is most likely that the interconversion **13** $\rightleftharpoons$ **14** also proceeds by a pseudorotation itineary analogical to that of cyclooctane and which in this case is termed complete pseudorotation (abbreviated CΨ) in contrast to partial pseudorotation (PΨ) described previously.

A detailed mechanism for complete pseudorotation involves the BC intermediates **15**, **16**, and **17**.[1c,2] The examination of molecular models shows that there are two equivalent paths for the transformation of **13** into **14**, each proceeding *via* intermediates related as mirror images. One such itinerary is detailed above where



the first intermediate (**18**) for the alternate path is also shown. It is clear that **15** and **18** are mirror images.

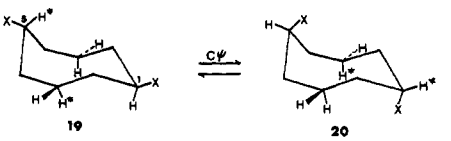
Partial pseudorotation, the mechanism of equilibration of the group of conformations **3ab**, is illustrated by the labeled forms **18** $\rightleftharpoons$ **13** $\rightleftharpoons$ **15** and obviously involves a similar deformation of the BC skeleton as CΨ. The difference between these processes is the extent of averaging produced when they become rapid on the nmr time scale. PΨ equilibrates only a few BC forms, each potentially constituting an intermediate on the itinerary for CΨ which involves a larger number of BC intermediates including **16** with its energetic axial substituent. It therefore seems reasonable to predict that PΨ should have a smaller $\Delta G^{\ddagger}$ than CΨ. Consequently, when rapid on the nmr time scale, PΨ leads to a partial averaging of the C_1 and C_5 methylene groups whereas CΨ exchanges their magnetic environment and thereby makes them equivalent on the average.

Studies on gem-disubstituted cyclooctanes[5] have shown that $\Delta G^{\ddagger}$ for pseudorotation increases with the size of the substituent most likely because of the presence on the itinerary of a sterically hindered conformation (possibility an axial substituent on BC). Analogically, the itinerary for CΨ of *cis*-DAC-d_8 contains the high-energy form **16** with an acetoxy group at a hindered axial position and is therefore able to rationalize the comparatively high $\Delta G^{\ddagger}$ as summarized later in Table I.

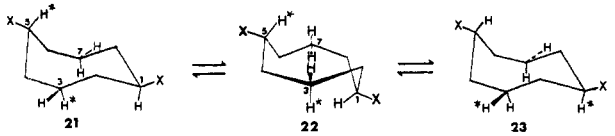
Table I. Free-Energy Barriers for *cis*- and *trans*-DAC, Cyclooctane, and Some of its Derivatives

Compound	$\Delta G^{\ddagger}$, kcal/mol Inversion	Pseudorotation	Ref
trans-DAC	8.0	*a*	This work
cis-DAC	*b*	6.5[c]	This work
Cyclooctane	8.1	<5	*d*, *e*
1,1-Difluorocyclooctane	7.5	4.9	*f*
1,1-Ethylenedithioxycyclooctane	8.5	6.6	*e*

[a] Although CΨ is possible, it does not lead to an observable spectral change because it results in a high-energy conformation and consequently its $\Delta G^{\ddagger}$ cannot be obtained by nmr. The process PΨ also does not give rise to a spectral change because it probably has a barrier less than 5 kcal/mol. [b] Inversion, although possible, does not give rise to an observable spectral change for this compound so that nmr cannot provide an estimate for its $\Delta G^{\ddagger}$. [c] This value is for CΨ and should be contrasted to that of PΨ which cannot be obtained by nmr and is therefore probably lower than 5 kcal/mol. [d] Reference 1. [e] Reference 5. [f] Reference 2.



It is interesting to note that, for *trans*-DAC-d_8, CΨ of conformation **4** (illustrated with the labeled forms **19** and **20**) does not lead to an equivalent BC conformation when the substituted carbon atoms exchange positions on the BC skeleton. Instead, the energetic form **20** with two axial substituents results. If an appreciable amount of **20** were present at equilibrium at $-160°$, then the methine region should consist of more than two lines and the rapid equilibration **19** $\rightleftharpoons$ **20** can never explain the coalescing of the methine doublet at $-112°$. Therefore CΨ cannot be the process responsible for the spectral change of the methine protons shown in Figure 1.

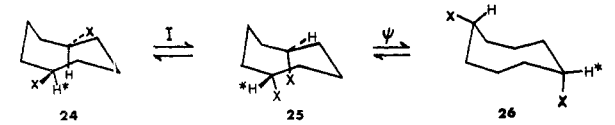


21 **22** **23**

The other more energetic mode of equilibration (inversion, abbreviated I) possible for BC is best able to explain the spectral change of *trans*-DAC-d_8. Thus conformation **21** can be transformed into the equivalent conformation **23** by inversion. Each of these forms contains two types of methine protons and one type of methylene group (*i.e.*, two types of methylene protons, axial and equatorial). The labels indicate that the transformation of **21** into **23** exchanges the environments of the two methine protons as well as the environments of each type of methylene proton within each methylene group.

Two possible mechanisms for inversion in cyclooctane and gem-disubstituted derivatives have been discussed previously[1,2,5] and are applicable to *trans*-DAC-d_8. Each of these involve different model manipulations to reach closely related high-energy intermediate (or transition states), namely the chair or twist-chair conformations. Since both pathways lead to identical results, it is from a practical point of view more convenient to describe in details the itinerary requiring fewer model manipulations. This mechanism of inversion involves moving C_3 and C_7 apart in **21** to give the high-energy twist-chair conformation (**22**). This form possesses a plane of symmetry though the C_1 and C_5 atoms and a twofold axis of symmetry through C_3 and C_7 such that all methylene protons are equivalent. Conformation **22** can be converted back to **21** by a downward movement of C_3 and C_7 whereas an upward movement gives **23**, an equivalent BC form in which the labels have exchanged positions.

Thus, inversion is able to rationalize the spectral change of the methine protons from a doublet to a singlet and that of the methylene protons from a collapsed unresolved AB pattern to a singlet as the temperature is increased.



24 **25** **26**

It is interesting to point out that a similar inversion of conformation **24** for *cis*-DAC-d_8 leads to an energetic conformation (**25** with two axial substituents). These forms are incompatible with the requirements of the low-temperature spectrum which would require **24** and **25** to have methine protons with identical chemical shifts in order to give a temperature independent singlet. The combination of inversion and pseudorotation to give other conformations such as **26** still cannot explain the singlet methine peak at $-160°$. Thus, a mechanism involving an inversion step does not interconvert equivalent conformations and consequently cannot rationalize the spectral behavior of *cis*-DAC-d_8. Moreover, even if inversion could offer an adequate explanation it is unlikely that it could be responsible for the spectral change since the lower energy pseudorotation is capable of interconverting the conformation of *cis*-DAC-d_8 at a much faster rate than a mechanism involving the more energetic inversion step.

The $\Delta G^{\ddagger}$ value for inversion of *trans*-DAC-d_8 determined from its spectral change is significantly larger than that characteristic of the complete pseudorotation of *cis*-DAC-d_8. The difference in activation energy for these isomers is comparable to that of analogical processes in cyclooctane and its gem-disubstituted derivatives for which $\Delta G^{\ddagger}$ of inversion is also larger than $\Delta G^{\ddagger}$ of pseudorotation as summarized in Table I.

Conclusion

We have thus demonstrated that the conformational analysis of *cis*- and *trans*-DAC is much more complex than that of the analogous cyclohexane derivatives and is completely rationalized in terms of BC conformations. The positions of the substituents of the BC form govern the nature of the process responsible for spectral averaging at higher temperatures such that for *cis*-DAC it is a pseudorotation and for *trans*-DAC it is an inversion.

Our study also indicates that information on the stable conformation of eight-membered ring compounds is more difficult to obtain by nmr than for six-membered ring compounds because a larger number of low-energy conformations and a larger number of low $\Delta G^{\ddagger}$ processes are available such that there often exists the possibility of residual averaging from a rapid equilibrium at the lowest temperature experimentally accessible. Another difficulty arises because not all processes available to the skeleton conformation give rise to spectral changes since for certain substitution patterns a given process leads to a high-energy conformation and therefore does not influence the spectrum. For example, both *cis*- and *trans*-DAC-d_8 show only one spectral change while geminal-disubstituted derivatives[5] usually show two spectral changes characteristic of inversion and complete pseudorotation processes.

Cautious examination and search for all these subtle effects are therefore imperative before attempting to apply to eight-membered rings the straightforward rules of conformational analysis deduced from studies on cyclohexane and its derivatives.

Experimental Section

The vpc analyses and separations were carried out on a Varian-Aerograph A90-P3 instrument using 0.25-in. columns and helium as carrier gas. Melting points are uncorrected.

Routine analytical pmr spectra were recorded on a JEOL C-60H spectrometer operating at 60 MHz in external lock mode. The variable-temperature pmr spectra were recorded on a JEOL JNM-4H-100 spectrometer operating at 100 MHz using solutions in chlorodifluoromethane (mp $-160°$). A small quantity of tetramethylsilane was added and the sample was degassed and sealed. Temperatures were monitored by means of a JEOL temperature control

unit model JES-VT-3 and read off a calibration chart obtained with a thermocouple inside a solvent-containing dummy nmr tube. Checks on the accuracy of the calibration curve were made repeatedly and are believed accurate to within ±2°. Deuterium decoupling was effected by means of the JEOL hetero spin decoupler Model JNM-SD-HC.

Mass spectra were performed on a Hitachi-Perkin-Elmer mass spectrometer Model RMU-6-D operating at 70 and 12.5 eV.

The theoretical spectra were generated by a CDC 6600 computer coupled to a Calcomp plotter.

2,2,4,4,6,6,8,8-Octadeuterio-1,5-cyclooctanedione (6). 1,5-Cyclooctanedione[11] (**5**, 5.0 g) was stirred for 12 hr at room temperature with 0.075 g of potassium carbonate dissolved in 42 ml of deuterium oxide. Fifteen extractions with 15-ml portions of chloroform were combined, dried with magnesium sulfate, and stripped of their solvent. After two additional similar exchanges using 20 ml of fresh deuterium oxide each time, the solid product isolated showed essentially complete deuteration as revealed from its greatly simplified pmr spectrum in $CDCl_3$ which consists of a singlet at δ 2.10 in accord with that expected for 1,5-cyclooctanedione-d_8 (**6**).

***cis*- and *trans*-1,5-Cyclooctanediol-d_8 (7 and 8).** 1,5-Cyclooctanedione-d_8 (11.0 g) was reduced with lithium aluminum hydride following the procedure described by Allinger and Maul[11] to give 9.0 g of a viscous oil after vaporation of the ether. Chromatography on 300 g of activity II alumina using ether and then 1% methanol–ether as eluent gave some fractions which crystallized on standing. These crystals were collected and recrystallized from ether–pentane to give about 1.0 g of *cis*-1,5-cyclooctanediol-d_8 (**7**), mp 68–70° (lit.[12] *cis*-1,5-cyclooctanediol, mp 73.8–74.8°). The pmr spectrum of **7** in $CDCl_3$ confirmed its identity: singlet (two protons) at δ 1.90 which disappeared on adding D_2O and an AB quartet (four protons) centered at δ 1.65, and a singlet (two protons) at δ 3.80.

Fractions eluted with 20% methanol–ether afforded a viscous oil which did not crystallize on standing. Two successive chromatographies of this residue on activity II alumina using methanol–ether as eluent with increasing proportion of methanol gave more *cis*-diol-d_8 and fractions (~0.5 g) of an oil identified as *trans*-1,5-cyclooctanediol-d_8 (**8**)[12] by its pmr spectrum: singlet (four protons) at δ 1.62, singlet (two protons) at δ 3.80, and a singlet (two protons) at δ 2.20 which disappeared on adding D_2O. Additional proof of this structure is provided later from its diacetate (**10**). (Note: attempts were not made to maximize the yields of each diol since only a small quantity was required for the next reaction.)

***cis*-1,5-Diacetoxycyclooctane-d_8 (9).** *cis*-1,5-Cyclooctanediol-d_8 (**7**) (0.20 g) and 10 ml of acetyl chloride were placed in a dry flask protected with a calcium chloride tube. The mixture was stirred overnight at room temperature. Ether (100 ml) was then added followed by 50 ml of water. The aqueous phase was extracted three times with 50 ml of ether. The combined ether solutions were washed successively with a solution of sodium bicarbonate and water until neutral and the ether was evaporated. The liquid residue was purified by preparative vpc using a SF-96 column at 200°. A 6% solution in chlorodifluoromethane was then prepared, degassed, and sealed. The pmr spectrum described in the text (Figure 2) is in accord with structure **9**. Mass spectral analysis at low ionization potential gave the following isotopic distribution: d_8 = 21%, d_7 = 68%, d_6 = 11%.

***trans*-1,5-Diacetoxycyclooctane-d_8 (10).** *trans*-1,5-Cyclooctanediol-d_8 (**8**) (0.20 g) was treated with acetyl chloride as described above to give a product which was purified by preparative vpc. A 6% solution in chlorodifluoromethane gave the pmr spectrum shown in Figure 1 which together with the mass spectral analysis supports structure **10**. The following isotopic composition was calculated from the mass spectrum at low ionization potential: d_8 = 21%, d_7 = 68%, d_6 = 11%.

Although this product is pure diacetate, it is not all trans as revealed from its pmr spectrum at −135° (Figure 1) where the labeled peak indicates that a small percentage of *cis*-DAC-d_8 is also present in solution. This therefore indicates that the chromatographic separation provided the starting *trans*-diol-d_8 at a purity above 90%.

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Effects of Halogen Substitution on Alkyl Radicals. Conformational Studies by Electron Spin Resonance

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Abstract: The esr spectra of a variety of alkyl and allyl radicals with halogen substituents are examined in solution. The hyperfine splitting due to the β protons and their temperature dependence, as well as selective line broadening effects in the esr spectra, are used to deduce the conformational changes in alkyl radicals as they are affected by halogen substitution. Chlorine and bromine exert a particularly noticeable influence when located in the β and γ positions. The conformational effects of substitution further along the alkyl chain are not observed. The esr spectra of the γ-chloro and γ-bromopropyl radicals show an unusual alternation of line widths in which the hyperfine splittings of the β protons undergo in-phase modulation. The β-bromoallyl radical is tentatively identified (with the bromine splitting), but the esr spectra of β-bromoalkyl and iodoalkyl radicals have not been observed. Product studies of reactions carried out in the spectrometer show that the β-bromoethyl radical is particularly unstable.

Halogen substituents are particularly noteworthy in their influence on the stereochemistry and kinetics of various homolytic reactions. The presence of bromine in the β position is especially conspicuous and the effect has also been noted for iodine in the γ position.[1] Generally, the influence of the halogen

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