Conclusions

We conclude that the present results clearly establish the possibility of using heuristic pattern recognition-based interpretation of ^{13}C nmr data as a structural elucidation tool. Our model study, using a set of spectra obtained under a rather broad range of experimental conditions, certainly suggests that the use of ^{13}C nmr in this way is comparable in speed, reliability, and specificity with the earlier infrared and mass spectral methods using the same approach. Encouraged as we are by the results thus far obtained, studies of the direct interpretation of untransformed digitized impulse response (free induction decay) data, as suggested by Kowalski and Reilly,[16] are under way. Furthermore, we are also examining the use of Hadamard transform[17]

(16) B. R. Kowalski and C. A. Reilly, *J. Phys. Chem.*, **75**, 1402 (1971).
(17) B. R. Kowalski and C. F. Bender, *Anal. Chem.*, **45**, 2234 (1973).

preprocessing of nmr data as an alternate method of preliminary data reduction. Spectral simulation *via* a related approach *bypassing derivation of chemical shift and coupling constant parameters* is also being examined. It is our belief that the promise of the present and related studies is that an integrated ^{13}C pattern recognition–Fourier nmr laboratory computer system is a realistic possibility. Thus, we are proceeding with plans for implementation of such a system which, ultimately, will provide the possibility of placing the experiment itself in the data interpretation feedback loop.

Conformational Analysis of Cycloheptene Oxide by ^{13}C and ^1H Nuclear Magnetic Resonance Spectroscopy

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Abstract: Pmr spectra of cycloheptene-*1,3,3-d₃* oxide in vinyl chloride solution were studied as a function of temperature from $-150°$ to room temperature. Two different conformations in the ratio of 71:29 were observed at low temperatures. The free energy barrier ($\Delta G^{\neq}$) for conversion of the major conformation to the minor conformation is calculated to be 7.9 kcal/mol from a line-shape analysis at intermediate temperatures. Cmr spectra of cycloheptene oxide in a solution of $CHCl_2F/CHClF_2$ were obtained at temperatures in the range of -170 to $-60°$. In this case, two forms in the ratio of 60:40 were detected at low temperatures and a $\Delta G^{\neq}$ of 7.5 kcal/mol was obtained. It is suggested that cycloheptene oxide exists in two chair conformations of slightly different energies. Interconversion paths between these conformations are discussed.

Because the substituent sites in many seven-membered rings rapidly equilibrate by pseudorotation even at very low temperatures, relatively few low-temperature nmr studies of the conformations and barriers to conformational changes have been reported for rings of this size.[4] In the work described here, we have used nmr spectroscopy to study the conformational equilibration of cycloheptene oxide and its deuterated derivative, cycloheptene-*1,3,3-d₃* oxide (**1**). As in cycloheptene, the pseudorotation pathway in the chair form of this epoxide is precluded by the restriction of the C_7–C_1–

1
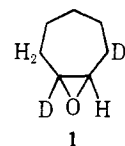
C_2–C_3 dihedral angle to a value near $0°$, thus removing one possible conformational change.

Results

The deuterated epoxide, **1**, was synthesized from cycloheptanone by the route outlined in Scheme I. The compound was purified by preparative vpc[5] and identified by its pmr spectrum and by comparison of its vpc retention time with that of unlabeled cycloheptene oxide prepared from cycloheptene and *m*-chloroperbenzoic acid. This unlabeled cycloheptene oxide was also used for the cmr experiments.
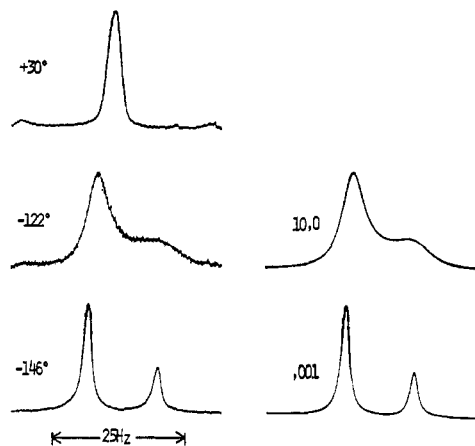
The pmr spectrum at $+30°$ for the proton at C-2 of **1**

(1) Alfred P. Sloan Research Fellow, 1969–1971.
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(4) (a) E. S. Glazer, Ph.D. Thesis, California Institute of Technology, Pasadena, Calif., 1966; (b) J. D. Roberts, *Chem. Brit.*, 529 (1966); (c) R. Knorr, C. Ganter, and J. D. Roberts, *Angew. Chem.*, **79**, 577 (1967); (d) M. St. Jacques and C. Vaziri, *Can. J. Chem.*, **49**, 1256 (1971); (e) K. von Bredow, H. Friebolin, and S. Kabuss, *Org. Magn. Resonance*, 2, 43 (1970), and references therein; (f) K. von Bredow, H. Friebolin, and S. Kabuss in "Organic Chemistry: A Series of Monographs," Vol. 21, G. Chiurdoglu, Ed., Academic Press, New York, N. Y., 1971, p 51; (g) E. A. Noe and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 7261 (1971); (h) E. Grunwald and E. Price, *ibid.*, **87**, 3139 (1965).

(5) A ¹/₈ in. × 6 ft glass column of 10% SE-52 on 60–80 Chromosorb WAW was used; the column temperature was 80°.

Figure 1. Experimental (left) and calculated (right) pmr spectra of the proton at C-2 of cycloheptene-$1,3,3$-d_3 oxide in vinyl chloride. The TMS signal appeared to move upfield as the temperature was lowered; the relative positions of the spectra are approximately those that would be expected in the absence of the apparent temperature dependence of the TMS chemical shift. The rate constant at $-146°$ is an arbitrary value for slow exchange.

Scheme I

1
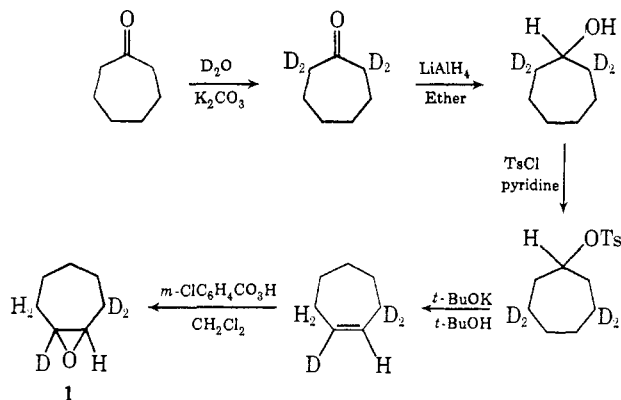
is a singlet[6] with a line width at half-height of 3.0 Hz and centered 292 Hz (2.92 ppm) downfield from internal TMS. At lower temperatures, the line broadens and splits into two lines of unequal intensities (see Figure 1). At $-146°$, the chemical shifts are 304.9 and 292.0 Hz at 100 MHz, and the populations are 0.71$_5$ and 0.28$_5$, respectively; the line widths at this temperature are 1.85 Hz. The rate constant for conversion of the major conformation to the minor conformation was determined to be 10 sec^{-1} at $-122°$,[8] and the free energy of activation was 7.9 kcal/mol.

Carbon-13 nmr spectra were obtained for undeuterated cycloheptene oxide itself. Spectra at $-60°$ in a mixture of CHCl$_2$F and CHClF$_2$ show four resonances in the ratio of 2:1:2:2 (see Figure 2). As the temperature decreases, each of these lines broadens and then ($T_c = -116°$) splits into two lines of unequal intensities. It is interesting to note that the epoxide carbon peak

(6) The signal is broadened by coupling to the adjacent deuterons and possibly also by long-range couplings with some of the remaining protons. Line broadening from long-range proton–proton couplings has been observed for a number of epoxides.[7]

(7) (a) P. J. Nathan and E. Diaz, *Org. Magn. Resonance*, **3**, 193 (1971); (b) L. J. T. Andrews, J. M. Coxon, and M. P. Hartshorn, *J. Org. Chem.*, **34**, 1126 (1969); (c) R. G. Carlson and N. S. Behn, *Chem. Commun.*, 339 (1968); (d) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

(8) The parameters used for calculation of the spectrum at this temperature were $\Delta\nu = 13.4$ Hz, $T_2 = 0.16$ sec, and $p_1 = 0.68$.
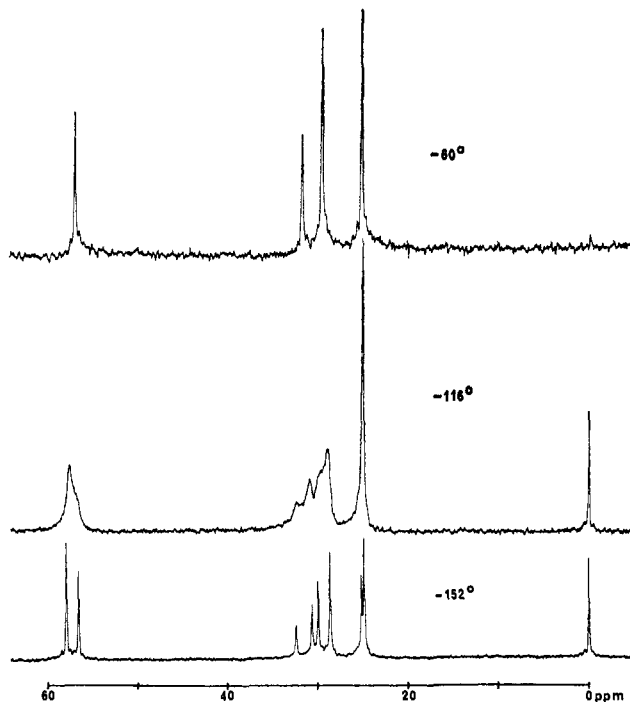
Figure 2. Carbon-13 nmr spectra of cycloheptene oxide in CHCl$_2$F/CHClF$_2$ in the region of rapid exchange, at coalescence, and in the slow exchange region. The chemical shifts are in ppm downfield from internal TMS.

corresponding to the minor conformer is found upfield from that of the major conformer while the minor conformer peaks corresponding to the other carbons are all found downfield from their respective major conformer peaks. At lower temperatures, the ratios of the intensities of these lines is 60:40. Using computer simulated spectra of the epoxide carbon resonances, the free energy of activation for conversion of the major conformer to the minor conformer was calculated to be 7.5 kcal/mol at T_c.

Discussion

The low-temperature cmr spectra of cycloheptene oxide indicate the presence of two different conformations, both of which possess a mirror plane (or a time-averaged mirror plane). The pmr results from cycloheptene-d_3 oxide also show the presence of two epoxide hydrogen sites with different chemical shifts. These results are similar to those obtained from the cmr spectra and may also be explained by the presence of two different conformations, each containing a mirror plane.

Strain-energy calculations have been carried out for cycloheptane[9] and cycloheptene,[10] but not for cycloheptene oxide, nor indeed for any ring system containing an epoxide group. In view of the lack of the required parameters to make strain-energy calculations on cycloheptene oxide, we have resorted to qualitative considerations based on molecular models and on the known behavior of cycloheptane and cycloheptene.

Of the five conformations (**2** to **6**) shown below for cycloheptene oxide, **6** can be immediately excluded because of extremely unfavorable steric interactions.

(9) (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7036 (1967); (b) J. B. Hendrickson, *ibid.*, **89**, 7047 (1967).

(10) N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972).

2 (chair)   3 (chair)   4 (twist-boat)

5 (boat)   6 (boat)
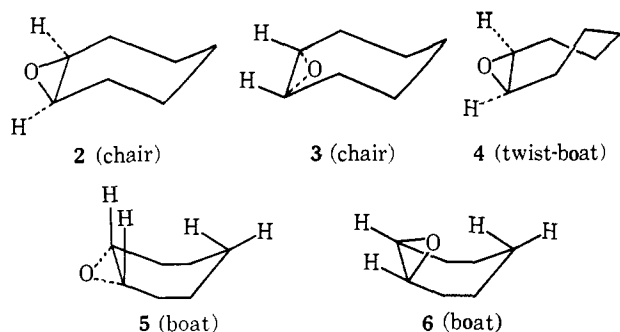
Molecular models of the chair conformations, 2 and 3, appear rigid whereas the boat conformations are fairly flexible and can be interconverted without large bond-angle deformations. The twist-boat conformation (4) occurs roughly half-way between 5 and 6 in the pseudorotation pathway connecting these forms.

The value of the unstrained bond angle, C_1–C_2–C_3, in 1,2 oxides is not well established. Accurate bond angles are available for propane,[11] propene,[12] and propene oxide,[13] as shown below.
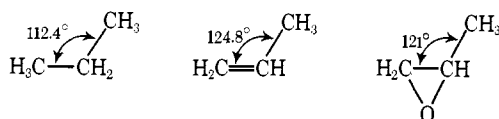
For these three compounds, the bond angle of the epoxide is closer to that of the alkene than the saturated hydrocarbon. The vicinal nonbonded interactions in cycloheptene oxide are more likely to resemble those in cycloheptane. The choice of cycloheptene or cycloheptane as a model for cycloheptene oxide is not entirely clear.

Strain-energy calculations for the conformations of cycloheptene show that the chair conformation is 0.57 kcal/mol more stable than the twist-boat, which is itself 2.8 kcal/mol more stable than the boat.[10] Experimental evidence from nmr studies of 5,5-difluorocycloheptene[4c] and cycloheptene-d_5[4d] rules out the possibility of an axis-symmetrical conformation such as the twist-boat conformation. Both compounds have been suggested to exist in chair forms. Other examples of seven-membered ring compounds which have been assigned the chair conformation include benzocycloheptene, several substituted ε-caprolactones, and γ,γ-difluoro-ε-caprolactam.[4] The twist-boat conformation, 4, of cycloheptene oxide is likely to be substantially higher in energy, relative to the chair form, than is the case for cycloheptene.

A comparison of cycloheptene oxide with calculated conformations of cycloheptane can also be made. The significant conformations of cycloheptane are those that contain one eclipsed C–C bond, namely the chair, boat, and twist forms. These three conformations are analogous to the chair, boat, and twist-boat conformations of cycloheptene or cycloheptene oxide. Calculations show that the chair form of cycloheptane is 1.3 and 5.8 kcal/mol more stable than the boat and the twist forms, respectively.[9]

The comparisons with cycloheptene and cycloheptane made above strongly indicate that the lowest energy conformation of cycloheptene oxide should be of the chair type, i.e., 2 or 3. Of these two conformations, an examination of molecular models suggests that 3 may have greater nonbonded repulsions than does 2, and thus should be slightly less stable than 2. However, in the low-temperature pmr spectrum of 1, Figure 1, the more intense epoxide hydrogen absorption occurs at lower field. Because axial ring protons generally absorb upfield of equatorial ring protons in cycloalkanes, the spectrum suggests that the major conformation has the epoxide hydrogen pseudo-equatorial and the epoxide oxygen pseudo-axial, as in 3. In any case, the energy difference between the two forms appears to be quite small.

Several possible pathways can be drawn for the interconversion of these two lowest energy chair-family conformations. Of the possible pathways, the route which is probably preferred is shown below.

2   5   4

3   6
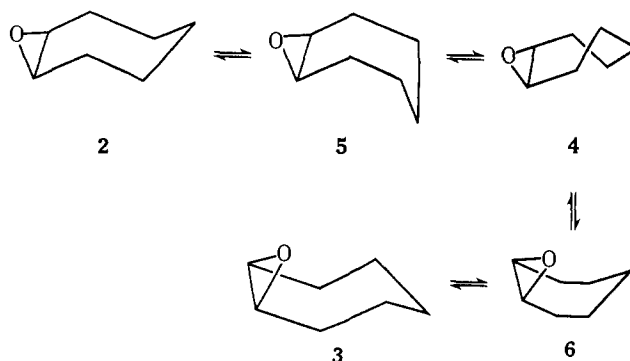
In a second pathway for interconversion, the ring passes through a conformation having six coplanar carbon atoms. The corresponding pathway for interconversion of chair and boat conformations of cycloheptene was calculated to be more favorable by 5.1 kcal/mol than flipping C-5 of the alkene (10.3 vs. 5.2 kcal/mol), because eclipsing of the alkenic hydrogens with the equatorial allylic hydrogens in the chair conformation is relieved in the transition state for the favored pathway. The situation is much different for interconversion of the chair and boat forms of cycloheptane via the form having six coplanar carbon atoms. In the latter case, none of the hydrogens are eclipsed in the chair conformation, but three eclipsed ethane segments appear in the form having six coplanar carbon atoms. In cycloheptane, and probably also in cycloheptene oxide, this interaction should make the latter interconversion pathway less favorable than for cycloheptene. In addition, the smaller bond angles in cycloheptane ($\simeq$118°)[9] and cycloheptene oxide ($\simeq$121°)[13] make this latter process less favorable than for cycloheptene (angle $\simeq$125°).[4g]

The free energies of activation for ring inversion in 5,5-difluorocycloheptene ($\Delta G^{\neq} = 7.4$ kcal/mol)[4c] and cycloheptene-d_5 ($\Delta G^{\neq} = 5.0$ kcal/mol)[4d] are in much better agreement with the calculated barrier for chair cycloheptene (5.2 kcal/mol) than with the calculated barrier for the boat form (0.06 kcal/mol). Recent calculations on cycloheptene by Ermer and Lifson[14] in fact indicate that the cycloheptene boat conformation is an energy maximum rather than a shallow local minimum as

(11) D. R. Lide, Jr., J. Chem. Phys., 33, 1514 (1960).
(12) D. R. Lide, Jr., and D. E. Mann, J. Chem. Phys., 27, 868 (1957).
(13) J. D. Swalen and D. R. Herschbach, J. Chem. Phys., 27, 100 (1957). The $C_1C_2C_3$ bond angle in cyclohexene oxide has been reported to be 118 ± 3°: V. A. Naumov and V. M. Bezzubov, Zh. Strukt. Khim., 8, 530 (1967).

(14) O. Ermer and S. Lifson, J. Amer. Chem. Soc., 95, 4121 (1973).

determined by Allinger and Sprague.[10] Applying these results to the epoxide, we expect that the transition state for the **2** ⇌ **3** interconversion would occur during one of the two chair-to-boat changes (**2** ⇌ **5** and **6** ⇌ **3**). It is difficult to determine *a priori* which of these barriers should be the higher. Although conformation **6** should be of higher energy than conformation **5**, the transition state between **6** and **3** should not have the large non-bonded repulsions which are present in **6**. Thus the **2** ⇌ **5** and **3** ⇌ **6** transition states probably have very similar energies.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer spectrometer, Model 457. The spectra of the deuterated epoxide were recorded using a Varian HA-100 spectrometer, equipped with a variable-temperature accessory, Model No. 4343; temperatures were measured by replacing the sample tube with an nmr tube containing a thermocouple immersed in vinyl chloride. A Varian A-60 spectrometer was used to record the other nmr spectra.

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[15] was used for calculations.

The carbon-13 nmr spectra were taken on a spectrometer equipped with a superconducting solenoid operating at a field strength of 59.1 kG. The low-temperature spectra were measured using a mixture of $CHCl_2F$ and $CHClF_2$ in the ratio of 3:1. A heteronuclear fluorine-19 internal lock was used and the lock signal was the single ^{19}F peak in $CHCl_2F$. Fast Fourier transform techniques were employed on from 500 to 1000 accumulations of 8K data points each for the spectra. All spectra were taken using proton noise decoupling with a power of 10 W. Measurements of temperatures were somewhat affected by the decoupling radiofrequency field but are believed to be accurate to ±3°; small differences in temperatures could be measured to better than ±1°.

Cycloheptanone-2,2,7,7-d_4. The deuterated ketone was prepared as described by Montgomery, *et al.*,[16] using the same amounts of reagents. The yield of product, purified by short-path distillation at reduced pressure, was 34.6 g (71%). A pmr spectrum showed the absence of α protons.

Cycloheptanol-2,2,7,7-d_4. Seventeen grams of LiAlH$_4$ in 280 ml of ether were stirred for 0.75 hr, and the ketone (24.6 g in 280 ml of

(15) (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.

(16) L. K. Montgomery, A. O. Clouse, A. M. Crelier, and L. E. Applegate, *J. Amer. Chem. Soc.*, **89**, 3453 (1967).

ether) was added dropwise over a period of 4 hr. The solution was stirred for 2 hr and let stand overnight. Water (17 ml), 15% NaOH (17 ml), and water (51 ml) were added dropwise in succession. The ether solution was separated by filtration, washed with saturated aqueous NaCl solution, and dried over Drierite. Most of the ether was removed at the rotary evaporator, and the residue was distilled in a micro apparatus at reduced pressure. The yield of clear, colorless alcohol was 32.8 g. An infrared spectrum showed the absence of carbonyl absorption, and a vapor phase chromatogram showed no other detectable peaks.

Tosylate of Cycloheptanol-2,2,7,7-d_4. A mixture of 10 g of cycloheptanol-d_4 and 120 ml of dry pyridine was stirred for 0.5 hr with cooling in an ice bath, and 32.4 g of *p*-toluenesulfonyl chloride was added in one portion. The mixture was kept at 0° for 24.5 hr and then 14 g of ice–water was added. The mixture was stirred for 25 min at 0° and then poured into 600 ml of ice–water. The tosylate was extracted into ether, and the ether solution was washed six times with iced 2 N hydrochloric acid, twice with saturated aqueous NaHCO$_3$ solution, and once with saturated aqueous NaCl solution. The solution was dried over Drierite and concentrated on the rotary evaporator at room temperature. A pmr spectrum showed the absence of tosyl chloride but indicated the presence of a small amount of cycloheptene-1,3,3-d_3.

Cycloheptene-1,3,3-d_3. Potassium *tert*-butoxide (38.0 g) was dissolved in 300 ml of dry *tert*-butyl alcohol, and the tosylate from the previous step was added. The temperature was maintained at 50 ± 4° for 21 hr, then raised to 60° over a period of 3 hr. The reaction mixture was cooled, poured into 1000 ml of ice–water, and extracted with pentane. The pentane solution was washed 15 times with 350-ml portions of water, dried over Drierite, and concentrated by distillation. The olefin was identified by comparison of its vpc retention time with that of a sample of authentic cycloheptene; a substance with a long retention time was also present. A pmr spectrum showed the absence of starting material.

Cycloheptene-1,3,3-d_3 Oxide. Dichloromethane (60 ml) was added to the deuterated alkene, followed by dropwise addition of 15.5 g of *m*-chloroperbenzoic acid in 170 ml of dichloromethane. A temperature of 25° was maintained during the addition. The mixture was allowed to stand for 0.25 hr and then washed with 10% sodium sulfite solution to remove any unreacted peracid. The solution was washed four times with 5% aqueous NaHCO$_3$ solution, once with dilute aqueous NaCl solution, and once with saturated aqueous NaCl solution. Drying over Drierite and concentration by distillation gave 6.3 g of residue, which was distilled in a micro apparatus at reduced pressure. The yield of clear, colorless distillate was 4.94 g. A sample of pure compound for the low-temperature spectra was obtained by vapor phase chromatography.[5] The pmr spectrum shows complex absorption at δ 1–2.1 and a singlet at 2.9.