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Conformational Study of Cyclohexene Oxide by Dynamic NMR Spectroscopy and Ab Initio Molecular Orbital Calculations

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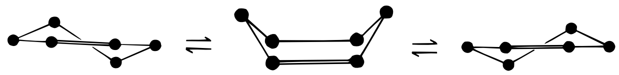
Abstract: The ^{13}C spectra of cyclohexene oxide (**1**) show decoalescence of the peak at lowest frequency, with slow exchange at −187.7 °C and a coalescence temperature slightly above −178.2 °C. The low-temperature NMR results are interpreted in terms of two enantiomeric half-chair conformations, **1a** and **1b**, which could interconvert by way of either the endo-boat (**1c**) or exo-boat (**1d**) conformation. Ab initio calculations indicate that the endo-boat is significantly lower in energy than the exo-boat. Both boat conformations are shallow energy minima, as evidenced by the absence of imaginary frequencies. Relative free energies for the three conformations at −187.7 °C obtained from Allinger's MM3 program are in reasonable agreement with the ab initio results for 25 °C. A possible explanation for the greater stability of the endo-boat in terms of less eclipsing for the CH hydrogens of the three-membered ring with the CH_2 hydrogens on the adjacent carbons is supported by calculated geometries. The experimental rate constant and free-energy barrier for interconversion of **1a** and **1b** were 227 s^{-1} and 4.3 ± 0.2 kcal/mol at −178.2 °C, and the corresponding parameters for the conversion of the half-chair to the endo-boat were 454 s^{-1} and 4.2 kcal/mol at this temperature. Estimates of the free energy at 25 °C of the transition state leading to the ring inversion were obtained at the HF/6-311G* and MP2/6-311G* levels by using the STQN method and were found to be 1.09 and 0.88 kcal/mol, respectively, above the local endo-boat minima. The corresponding calculated half-chair to endo-boat free-energy barriers at 25 °C were 4.87 and 4.96 kcal/mol, in reasonable agreement with the experimental value at −178.2 °C. Chemical shifts for the carbons of **1a** were calculated at the HF/6-311G* and HF/6-311+G(2d,p) levels, using the GIAO method, to assign peaks to specific carbons.

Epoxides are versatile reagents which can undergo a variety of reactions, including opening of the strained three-membered ring with nucleophiles and rearrangement to allylic alcohols or ketones.[1] They have also been widely used in asymmetric synthesis.[2,3] A number of enantioselective reactions of symmetrical epoxides have been described,[3] and cyclohexene oxide (**1**) has frequently been included in these studies.[4] Although the conformations of six-membered rings have been studied extensively by dynamic NMR spectroscopy and other methods,[5] no low-temperature NMR study of **1** has been reported.

The three-membered ring is expected to force the compound to adopt a half-chair conformation as found for cyclohexene (**2**),[6] and evidence for this conformation of **1** has been obtained from electron-diffraction studies[7] and microwave spectroscopy.[8] Half-chair conformations have also been assigned to 3-substituted cyclohexene oxides by X-ray diffraction and by examining the vicinal proton coupling constants.[9] Early studies of **1** with force-field or MINDO/3 calculations indicated that the half-chair conformation was preferred over a boat conformation, but reliable relative energies or barriers to ring inversion could not be obtained.[10]

Ring inversion of cyclohexene occurs by the way of the boat conformation, as shown below. Allinger's molecular mechanics program (MM3) predicts[6a] that the boat is a very shallow local energy minimum, with the transition state only 0.08 kcal/mol above the symmetrical boat. The MM3 free-energy barrier[6a] for ring inversion in **2** was 5.6 kcal/mol at −170 °C, in good agreement with the experimental free-energy barriers of 5.2[6b] and 5.3[6c] kcal/mol. Ab initio calculations at several levels indicated[6a] that the boat is a transition state for ring inversion



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[1] For a review, see: Smith, J. G. *Synthesis* **1984**, 629.

[2] The chemical and biological syntheses of chiral epoxides have been reviewed: Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885.

[3] For a review of enantioselective ring openings for symmetrical epoxides, see: Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.

[4] Examples include: (a) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783. (Enantioselective ring opening.) (b) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721. (c) Su, H.; Walder, L.; Zhang, Z.-da; Scheffold, R. *Helv. Chim. Acta* **1988**, *71*, 1073. References b and c describe the synthesis of optically active allylic alcohols.

[5] *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995.

[6] (a) Anet, F. A. L.; Freedberg, D. I.; Storer, J. W.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10969. (b) Jensen, F. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 5774. This barrier to interconversion of half-chair conformations was calculated by us from the authors' rate constant of 44 s^{-1} at −166.7 °C. They report in Table 6 an axial to equatorial barrier of 5.37 kcal/mol, using a rate constant of 22 s^{-1}. (c) Anet, F. A. L.; Haq, M. Z. *J. Am. Chem. Soc.* **1965**, *87*, 3147.

[7] (a) Traetteberg, M.; Sandnes, T. W.; Bakken, P. *J. Mol. Struct.* **1980**, *67*, 235. (b) Naumov, V. A.; Bezzubov, V. M. *J. Struct. Chem.* **1967**, *8*, 466; translated from *Zh. Strukt. Khim.* **1967**, *8*, 530. (c) Ottar, B. *Acta Chem. Scand.* **1947**, *1*, 283.

[8] Ikeda, T.; Kewley, R.; Curl, R. F. *J. Mol. Spectrosc.* **1972**, *44*, 459.

[9] Zefirov, N. S.; Palyulin, V. A.; Kasyan, L. I.; Bruskin, A. B. *Zh. Org. Khim.* **1980**, *16*, 224.

[10] Todeschini, R.; Pitea, D.; Favini, G. *J. Mol. Struct.* **1981**, *71*, 279.

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of **2**, and the calculated potential energy profiles obtained by varying the ω_{3456} dihedral angle were flat topped. The ab initio barriers were also close to the experimental free-energy barriers.

Cyclohexene oxide has two possible boat conformations, the endo-boat (**1c**) and the exo-boat (**1d**). In this work, we have obtained the relative free energies of the three conformations of **1** from ab initio calculations and have established that the boat conformations are local energy minima, in contrast to **2**. The free energy of the transition state for ring inversion of the half-chair was determined by computational methods and by dynamic NMR spectroscopy for comparison with the barriers for **2** and cyclohexane.

Unlike **2**, which has a 2-fold rotational axis that results in three ^{13}C chemical shifts for the compound regardless of the rate of ring inversion, the epoxide **1** has C_1 symmetry, and six ^{13}C chemical shifts are expected at slow exchange. Rapid ring inversion at room temperature through a boat conformation will average the chemical shifts for carbons 1 and 2, 3 and 6, and 4 and 5, giving rise to three peaks, each of which could decoalesce into two signals of equal intensity at lower temperatures if the chemical shift differences and barrier are sufficiently large.

Experimental and Methods Section

Cyclohexene oxide, listed as 98% pure, was purchased from Aldrich Chemical Co. and used as received. The purity of the compound was established by room-temperature ^{13}C and ^{1}H NMR spectra. A 5% solution of cyclohexene oxide in 5:1:1 $CHClF_2$, $CHCl_2F$, CHF_3 was prepared in a 5 mm thin-walled screw-capped NMR tube. A small amount of tetramethylsilane was added for an internal reference. *Caution*: High pressure. The sample tube was stored and handled below 0 °C most of the time.

Spectra were recorded on a General Electric model GN-300 wide-bore NMR spectrometer operating at 75.58 MHz for ^{13}C. The ^{13}C NMR spectra were obtained from −61.3 to −187.7 °C with a 5 mm dual probe. Spinning was discontinued below about −120 °C. A pulse width of 9 μs was used, corresponding to a tip angle of 83°, and the pulse-repetition period was 8 to 10 s. From 450 to 550 acquisitions were used, with a sweep width of ±12000 Hz, data size of 64K, and 3.0 Hz line broadening to increase the signal-to-noise ratio. Because of the difficulty in ejecting the sample at the lower temperatures, the temperature calibration was performed separately, using a copper−constantan thermocouple immersed in the same solvents contained in a dummy sample tube and under conditions as nearly identical as possible. The emf's were measured with a Leeds and Northrup model 8690-2 millivolt potentiometer. The results of several calibration curves were in close agreement with each other. The uncertainty in the temperatures near coalescence was estimated to be ±2 °C.

The rate constant for **1** at −178.2 °C (slightly below coalescence) was obtained by line shape matching with an Apple computer and a two-site exchange program wrtitten by R. A. Newmark.[11] The relaxation time, T_2, for the calculations was obtained from the line width for the CH carbons at −178.2 °C; the height of the CH peak at −187.7 °C is approximately twice the height of the two peaks at lowest frequency, indicating that the two CH carbons of **1** have nearly the same chemical shifts and that broadening of the peak at δ 53.8 is mainly due to viscosity broadening. Error limits of ±0.2 kcal/mol were estimated for the barriers.

The conformational space of **1** was searched by using Sybyl,[12] a molecular mechanics program built into Spartan.[13] The geometries obtained for the half-chair, endo-boat, and exo-boat conformations were used as starting points for the ab initio calculations, using the Gaussian 92 series of programs.[14] For all three conformers, full geometry optimizations were done at the HF/6-311G*, Becke3LYP/6-311G**, and MP2/6-311G* levels; smaller basis sets were used initially. Energy minimized structures were characterized by calculation of harmonic vibrational frequencies at the same levels. Free energies are more conveniently obtained from Gaussian 94,[15] and this program was used to obtain the free energy at 25 °C for each of the three conformations, using as input the results from Gaussian 92. These calculations were done at each of the three levels listed above. No imaginary frequencies were found, indicating that the boat conformations are shallow energy minima.

The endo-boat conformation is more stable than the exo-boat according to the calculations, indicating that the former conformation is an intermediate in the interconversion of half-chair conformations. The transition state structure for ring inversion in **1** was obtained by the synchronous transit-guided quasi-Newton (STQN) method at the HF/6-311G* and MP2/6-311G* levels. Input included geometries of the half-chair and endo-boat conformations. A single imaginary frequency was found for each calculation, as required (48.6i and 86.4i cm^{-1}, respectively). The Gaussian 94 series of programs[15] was used for the transition state calculations. Allinger's MM3 program[16] was used to calculate free energies for conformations **1a,b**, **1c**, and **1d** and found to predict the same order of stabilities as in the ab initio calculations. An external program, updated on January 1, 1994, and purchased from the Quantum Chemistry Program Exchange at Indiana University was used, as the parameters needed for **1** were not available in the internal MM3 program of Spartan 3.0. Free energies at −187.7 °C were obtained with use of the default parameters.

The gauge-including atomic orbitals (GIAO) method was employed to calculate isotropic absolute shielding constants (σ, in ppm) for TMS and the half-chair conformation of cyclohexene oxide, using Hartree−Fock methods. Subtraction gave the calculated chemical shifts (δ, in ppm) of the half-chair, relative to TMS, which were used to assign ^{13}C chemical shifts to specific carbons. These calculations were done with the Gaussian 94 series of programs.[15]

Results and Discussion

The three ^{13}C peaks of cyclohexene oxide at −61.3 °C appear at 52.7, 24.8, and 20.1 ppm (δ), relative to the carbons of internal TMS (Figure 1). The peak at lowest frequency, from carbons 4 and 5, splits at lower temperatures into two signals of equal intensity, with slow exchange by −187.7 °C and coalescence slightly above −178.2 °C. The central peak broadens but does not split, due to a smaller chemical shift difference for carbons 3 and 6, and the peak for the CH carbons shows little or no exchange broadening. From the chemical shifts calculated at the HF/6-311G* and HF/6-311+G(2d,p) levels, carbon 5 of the half-chair, as drawn and numbered in Chart 1, absorbs at lower frequency than carbon 4, and the experimental shifts assigned to carbons 4 and 5 are δ 21.1 and 18.9, respectively. The calculations correctly predict smaller chemical shift differences for the other two sets of carbons, and the average shifts for C3−C6 and C4−C5 are close to experimental.

Observation of decoalescence for cyclohexene oxide rules out the possibility of a stable plane-symmetrical boat conformation and is consistent with the half-chair conformation. From

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[11] Newmark, R. A. *J. Chem. Educ.* **1983**, *60*, 45.

[12] Clark, M.; Cramer, R. D., III; van Opdensch, N. *J. Comput. Chem.* **1989**, *10*, 982. The Sybyl force-field program is marketed by Tripos, Inc.

[13] Spartan Version 3.0 from Wavefunction, Inc., Irvine, CA.

[14] Gaussian 92: Rev. A.; Frisch M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Replogle, E. S.; Gomperts, R.; Anders, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Defrees, D. J.; Baker, J.; Stewart, J. J.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA 1992.

[15] Gaussian 94: Rev. E. 2; Frisch M. J.; Trucks, G. W.; Gill, P. M. W.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Cheesman, J. R.; Gomperts, R.; Keith, T.; Petersson, G. A.; Montgomary, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, J. V. O.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Fox, D. J.; Head-Gordon, M.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Defrees, D. J.; Baker, J.; Stewart, J. J.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA 1995.

[16] Version MM3(94) was used. The latest version of the MM3 program, which is referred to as MM3(96), is available to academic users from the Quantum Chemistry Program Exchange and to commercial users from Tripos Associates, 1699 South Hanley St., St. Louis, MO 63144.

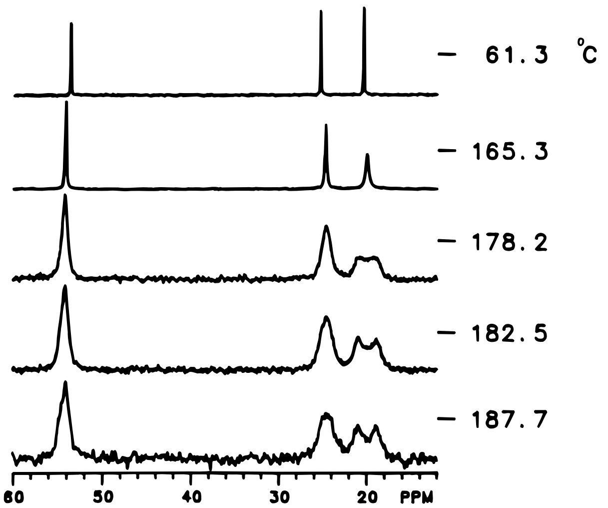
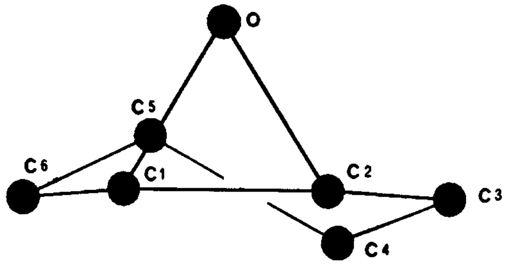


Figure 1. Low-temperature ^{13}C NMR spectra of a 5% solution of cyclohexene oxide in a 5:1:1 mixture of $CHClF_2$, $CHCl_2F$, and CHF_3.

Chart 1



^{13}C Chemical Shifts (δ, in ppm) :

	1		2	Difference
Expt. -61.3 °C (ave.)		52.7		--
Expt. -187.7 °C	53.8		53.8	~0
HF/6-311G*	42.5		41.5	1
HF/6-311+G(2d,p)	44.3		43.7	0.6
	3		6	
Expt. -61.3 °C (ave.)		24.8		--
Expt. -187.7 °C (ave.)		24.5		--
HF/6-311G*	23.8		24.7	0.9
HF/6-311+G(2d,p)	23.3		24.9	1.6
	4		5	
Expt. -61.3 °C (ave.)		20.1		--
Expt. -187.7 °C	21.1		18.9	2.2
HF/6-311G*	21.2		18.4	2.8
HF/6-311+G(2d,p)	21.2		18.3	2.9

line shape matching of the experimental spectrum at −178.2 °C, a rate constant of 227 s^{-1} was obtained, corresponding to a free-energy barrier of 4.3 ± 0.2 kcal/mol for interconversion of **1a** and **1b**.

As noted above, either the endo-boat (**1c**) or the exo-boat (**1d**) could be an intermediate or transition state for ring inversion of the stable conformation. According to Sybyl, **1c** and **1d** are higher in strain energy than the half-chair by 3.94 and 2.42 kcal/mol, respectively, while Allinger's MM3 program calculates the corresponding free energies at −187.7 °C as 3.08 and 5.08 kcal/mol. Ab initio calculations at the MP2/6-311G* level for the three conformations at 25 °C predict that the half-chair is lower in free energy than **1c** and **1d** by 4.08 and 6.40 kcal/mol, respectively (Table 1). No imaginary frequencies were found, and the lowest frequencies at this level were 148.9 (half-chair), 63.5 (endo-boat), and 60.0 cm^{-1} (exo-boat). This finding and the relative free energies of **1c** and **1d** provide evidence that interconversion of **1a** and **1b** occurs through **1c** as an intermediate and not a transition state, as shown below. The transition state was estimated to be 1.09 and 0.88 kcal/mol higher in free energy than **1c** at the HF/6-311G* and MP2/6-311G* levels, respectively, and addition of these values to the endo-boat − half-chair free-energy differences gave the free-energy barriers to ring inversion in Table 1 (4.96 kcal/mol by MP2/6-311G*).

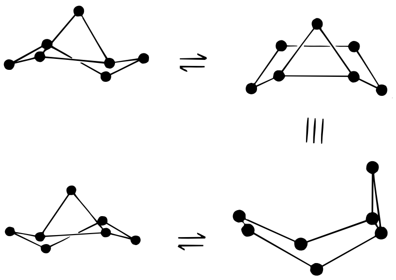
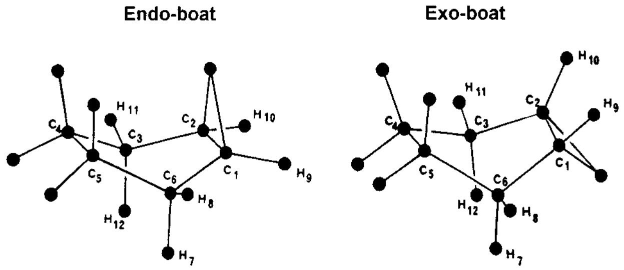


Table 1. Relative Free Energies[a] for Conformations of Cyclohexene Oxide at 25 °C

	ab initio method		
conformer	HF/6-311G*	B3LYP/6-311G**	MP2/6-311G*
half-chair	0.00	0.00	0.00
endo-boat	3.78	3.35	4.08
exo-boat	6.73	6.77	6.40
transition state[b]	4.87		4.96

[a] In kcal/mol. [b] Transition state for conversion of the half-chair to the endo-boat.

Chart 2



Dihedral Angles (MP2/6-311G*)

H11-C3-C2-H10 = -40.5831°
H12-C3-C2-H10 = 75.5132
H8-C6-C1-H9 = 40.6107
H7-C6-C1-H9 = -75.4715

C3-C4-C5-C6 = 0.0799
C3-C2-C1-C6 = 0.0061

H11-C3-C2-H10 = 22.0970°
H12-C3-C2-H10 = 140.0424
H8-C6-C1-H9 = -16.9857
H7-C6-C1-H9 = -132.6414

C3-C4-C5-C6 = 19.6037
C3-C2-C1-C6 = 3.4664

The experimental rate constant for conversion of the half-chair to the endo-boat is 454 s^{-1}, twice the value for interconversion of **1a** and **1b**, because **1c** can convert with equal probability to the original or inverted half-chair. The corresponding $\Delta G^{\ddagger}$ is 4.2 kcal/mol at −178.2 °C, in reasonable agreement with the free energies of the transition state in Table 1. Several factors could cause the calculated and experimental barriers to differ, including possible errors in the barriers, the difference in phase (gas phase vs solution in a moderately viscous solvent), and the different temperatures used (+25 °C vs −178.2 °C). The barrier for **1** is about 1 kcal/mol lower than that for cyclohexene,[6] and substantially smaller than that for cyclohexane (10.2 kcal/mol).[17] Although cyclohexene oxide has a saturated six-membered ring, the compound resembles cyclohexene more closely than cyclohexane with respect to both geometry and conformational mobility.

Schleyer has suggested[18] that greater eclipsing of the CH hydrogens with adjacent CH_2 hydrogens in **1d** than occurs in **1c** is responsible for the increased stability of the latter conformation. HCCH dihedral angles calculated at the MP2/6-311G* level for these hydrogens are shown in Chart 2, and may support this explanation. In addition, the calculations suggest that **1d** has a small deviation from perfect C_s symmetry, while the dihedral angle for carbons 3, 4, 5, and 6 of **1c** is close to zero.

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Supporting Information Available: Details of the geometries obtained from ab initio calculations at the MP2/6-311G* level (3 pages). See any current masthead page for ordering and Internet access instructions.

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(17) Anet, F. A. L.; Bourn, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 760. The authors reported the barrier as 10.3 and 10.22 kcal/mol in the abstract and Table 1 of the paper, respectively, and in ref 6a of our paper, footnote 6, the barrier is given as 10.1 kcal/mol. We use here an average of the three numbers.

(18) Schleyer, P. von R., Department of Chemistry, University of Georgia, Athens, Georgia, private communication.