Application of Strain Energy Minimization to the Dynamics of Conformational Changes[1a]

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Abstract: A method is described for calculating the course of conformational changes using a strain energy minimization technique. It is applied to the cyclohexane chair–boat conversion using two different models for the activated complex and two different sets of potential functions. The calculated enthalpy and entropy of activation agree well with the values determined by low-temperature nmr studies. The procedure is also applied to the ring inversion of bicyclo[3.1.1]heptane and gives a barrier height of 0.7 kcal/mol.

The strain energy minimization technique developed by Westheimer and Mayer[2] has been applied to a variety of conformation problems with considerable success.[3] However, a problem of major interest, the potential energy surface for the interconversion of conformers, has not received much attention.[4] The standard energy minimization technique cannot directly be applied to this problem since the species along the reaction coordinate are not minimum energy species. However, the reaction coordinate is a minimum energy path in the sense that for variations in molecular geometry corresponding to motions orthogonal to the reaction coordinate the energy is at a minimum. If the transition from reactant to product involves continuous changes in one of the internal coordinates (*e.g.*, a torsional angle) and this internal coordinate is single valued over the transitional path, then the reaction coordinate and its associated energies can be determined by minimizing the energy with this internal coordinate constrained at various fixed values. Computationally these minimizations that determine the reaction path can be conveniently effected using conventional energy minimization algorithms if the true torsional potential of the internal coordinate to be constrained

$$V = (^1/_2)V_0(1 + \cos 3\phi) \qquad (1)$$

is replaced by the function

$$V = (c_1/2)V_0(1 + \cos 3(\phi + c_2)) \qquad (2)$$

in the energy minimization algorithm. c_2 represents an angular offset which makes the apparent minimum energy of the "driving" bond come to angles other than 60, 180, and 240°. c_1 is introduced in order to make this interaction appear to be stiffer than normal.[7]

We have applied this idea to the inversion of cyclohexane. The energy minimization was carried out using the scheme we have used previously in which the coordinates of all atoms are allowed to vary.[8,9] In the calculations, the strain energy was calculated using eq 1 for all torsional interactions including those which represent the reaction coordinate. The modified potential (eq 2) was used in the calculation of the first and second derivatives of the driving bond which are needed in the energy minimization algorithm.

To investigate the possibility that the reaction coordinate might involve motion more complicated than a single valued function of the driving bond, the reaction coordinate for the conversion of the chair conformation of cyclohexane to the boat was described in two different ways. The first uses two adjacent torsional angles. In the chair form, these will have 55.7° angles in the calculated minimum energy conformation. The energy will increase as the angles go to 0° and then will decrease to that of the twist boat form as the angles continue to change to those characteristic of this conformation. In this simple case, the resulting activated complex is readily visualized, and will have five carbons lying in a plane.[5]

The calculations were carried out using two different sets of bond angle stretching and bending force constants (Table I). Set 1[9b,c] was derived by adjusting the transferrable force constants of Snyder and Schactschneider[10] so as to give a good fit to the heats of formation and entropies of a series of hydrocarbons and to compensate for the superposition of the nonbonded interactions. Set 2 was derived by fitting the vibrational spectrum of cyclohexane using only the on-diagonal force constants[11] and then adjusting the HCH bending constant from 0.523 to 0.473 to compensate for the nonbonded interactions, which are present in the strain energy minimization but which are not included in the normal coordinate treatment.

The results of the calculations are shown in Table II. The vibrational frequencies for each species also were

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[1] (a) This investigation was supported by grants from the U. S. Army Research Office; (b) Yale University; (c) University of Utah.

[2] F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.*, **14**, 733 (1946); F. H. Westheimer, *ibid.*, **15**, 252 (1947).

[3] The subject has been reviewed by J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968).

[4] The barrier to cyclohexane inversion has been calculated by Hendrickson[5] and by Pickett and Straus.[6] In both treatments the geometrical changes on going to the activated complex were handled analytically, and neither treatment allowed the hydrogens full freedom of motion.

[5] J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961), discusses both models for the activated complex for cyclohexane.

[6] H. M. Pickett and H. L. Strauss, *ibid.*, **92**, 7281 (1970).

[7] This treatment has recently been used by R. H. Boyd and S M.. Breitling, *Macromolecules*, **5**, 1 (1972), in a study of the conformational properties of polyisobutylene.

[8] K. B. Wiberg, *J. Amer. Chem. Soc.*, **87**, 1070 (1965).

[9] (a) R. H. Boyd, *J. Chem. Phys.*, **49**, 2574 (1968); (b) C. F. Shieh, D. McNally, and R. H. Boyd, *Tetrahedron*, **25**, 3653 (1969); (c) S. J. Chang, D. McNally, S. Shary-Tehrany, J. J. Hickey, and R. H. Boyd, *J. Amer. Chem. Soc.*, **92**, 3109 (1970).

[10] R. G. Snyder and J. H. Schachtschneider, *Spectrochim. Acta*, **21**, 169 (1965).

[11] A. S. Shrake, Ph.D. Thesis, Yale University, 1969; K. B. Wiberg and A. S. Shrake, *Spectrochim. Acta*, in press.

Table I. Bond Stretching and Bending Force Constants

Internal[a] coordinate	Force constants, mdyn/Å[b] A	1	B	C	2
C–H str	4.55	4.55	4.56	4.56	4.56
C–C str	4.39	4.40	4.28	3.57	3.57
HCH bend	0.550	0.508	0.579	0.523	0.473
HCC bend	0.656	0.608	0.687	0.677	0.677
CCC bend	1.130	0.800	1.082	1.336	1.336
Rms error,[c] cm^{-1}	69	65	76[d]	59	56

[a] $r_{\text{CH}} = 1.09$, $r_{\text{CC}} = 1.54$ Å; $\theta_{\text{HCH}} = 107.9°$, $\theta_{\text{HCC}} = 109.5°$, $\theta_{\text{CCC}} = 111.0°$. [b] The sets of force constants are (A) Snyder and Schachtschneider;[10] (1) Boyd, modification of set A;[9b,c] (B) Wiberg and Shrake, fit of cyclohexane using a general force field;[11] (C) Wiberg and Shrake, fit of cyclohexane using only on-diagonal force constants;[11] (2) Wiberg, modification of set C. [c] Rms error in fitting the vibrational spectrum of cyclohexane and cyclohexane-d_{12} using the given force constants along with the torsional barrier and nonbonded interactions used in the strain energy minimization calculations. [d] When a full set of interaction constants was used with this set in a usual normal coordinate treatment, the rms error decreased to 15 cm^{-1}.

Table II. Comparison of Energy Terms Using Two Sets of Potential Functions (25°)

		Set 1[a]			Set 2[a]			Observed	
Conformation	σ	E_s	ΔH_f	$S°$	E_s	ΔH_f	$S°$	ΔH_f	$S°$
Chair	6	3.7	−29.7	71.6	3.7	−28.7	70.4	−29.4	71.3
Twist (D_2 sym, *d,l* pair)	2	9.4	−24.1	75.7	9.4	−23.0	74.7		
Boat[b]	2	10.0	−24.0	72.1	10.1	−22.9	71.0		
One torsional angle activated complex	2	13.2	−20.7	73.6	14.6	−18.1	72.6		
Two torsional angle activated state	1	13.7	−20.3	75.8	15.4	−17.6	75.0		
		ΔE_s	ΔH_r	ΔS_r	ΔE_s	ΔH_r	ΔS_r	ΔH_r	
Chair ⇄ twist		5.7	5.6	4	5.7	5.7	4	5.7	
Chair ⇄ boat		6.3	5.7	0	6.4	5.8	1		
		ΔE_s	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	ΔE_s	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Inversion, one angle activated complex		9.5	9.0	2	10.9	10.6	2	10.8	1.5
Inversion, two angle activated complex		10.0	9.4	4	11.5	11.1	5		

[a] The potential functions are given in Table I. [b] Unstable with respect to deformation to the twist conformation.

calculated using the force field employed in the energy minimization. This permitted the calculation of the entropy and enthalpy of both the reactant and the activated complex. In the case of the activated complex, one vibrational frequency was found to be imaginary. This represents the vibrational mode associated with transition over the barrier.

The calculated strain energy of the chair form of cyclohexane is 3.7 kcal/mol and results from the six gauche torsional interactions.[12] The strain energy of the activated complex is calculated to be 13.7 or 15.4 kcal/mol depending on which set of force constants was used. The enthalpy of activation was estimated as 9.4 or 11.1 kcal/mol, and the corresponding entropy of activation was 4–5 eu. The major component of the increase in strain on going to the activated complex is due to the torsional interaction (6.1 kcal/mol for set 2), but bond angle bending is also of major importance (4.2 kcal/mol). The nonbonded interactions increase relatively little on going to the activated complex.

The other and more direct approach to determination of the reaction coordinate is one in which only one torsional angle is driven. Here, the activated complex is reached when four carbons lie in a plane. The results of the calculation are given in Table II and are presented in more detail in Figures 1 and 2. The calculated strain energy of the activated complex is somewhat smaller than that for the one formed using two torsional angles as the reaction coordinate because of a slightly lower torsional strain (5.7 kcal/mol). The angle strain is essentially the same. The difference in enthalpy of activation is essentially the same as the difference in strain energy for the two models of the activated complex. The five coplanar atom state (two torsional angle activated state) is reached by a continuous increase in energy from the four coplanar atom state, and it appears that the latter is a true saddle point and the former lies displaced slightly on the side of the saddle. The six lowest frequency vibrations of the chair form and the activated complex (four coplanar atoms) are compared in Table III. These modes correspond to skeletal deformations by bond torsion and bending and are also the modes most sensitive to the change to the transition state. Being low frequency modes, the entropy of activation will be most sensitive to frequency changes in this group. The most important change in the activated complex over the chair form is the replacement of the doubly degenerate E_u vibration by the imaginary frequency corresponding to translation over the barrier and a vibration of considerably lower frequency than any of those of the chair form. The relatively large entropy of this low frequency mode for-

Table III. Comparison of the Low Frequency Vibrations of Chair Cyclohexane with the Activated Complex (cm^{-1})[a]

Chair	Activated complex	Chair	Activated complex
565 A_{2u}	625	350 A_{1g}	305
429 E_g	448	221 E_u	100
429	440	221	Imaginary

[a] Parameter set 1.

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[12] Although cyclohexane is frequently considered to be strain-free, it is clear that its energy per methylene group must be greater than for a methylene group of an *all-trans-n*-alkane because of its gauche conformation. The similarity in the methylene group equivalent[13] between cyclohexane and the *n*-alkanes results from the low probability for the all-trans form of the alkanes in comparison to the large number of conformations having one or more gauche arrangements; see P. v. R. Schleyer, J. E. Williams, and R. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).

[13] J. L. Franklin, *Ind. Eng. Chem.*, **41**, 1070 (1949).

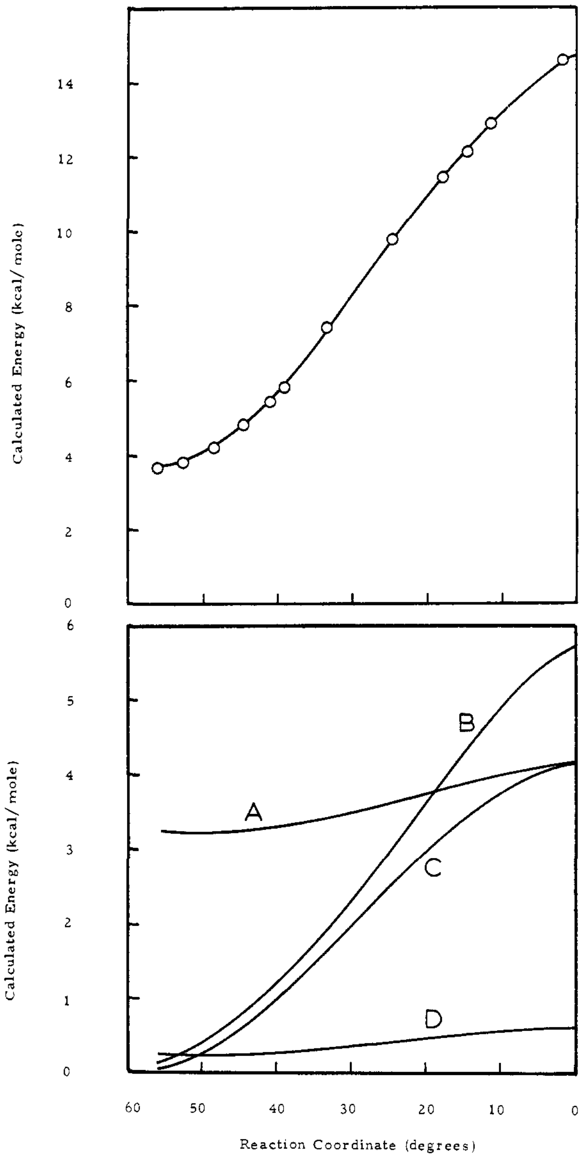

Figure 1. (Top) Change in strain energy using one torsional angle as the reaction coordinate. (Bottom) Components of the strain energy using one torsional angle as the reaction coordinate. The curves are: (A) nonbonded interactions; (B) torsional strain; (C) angle strain; (D) bond stretching.

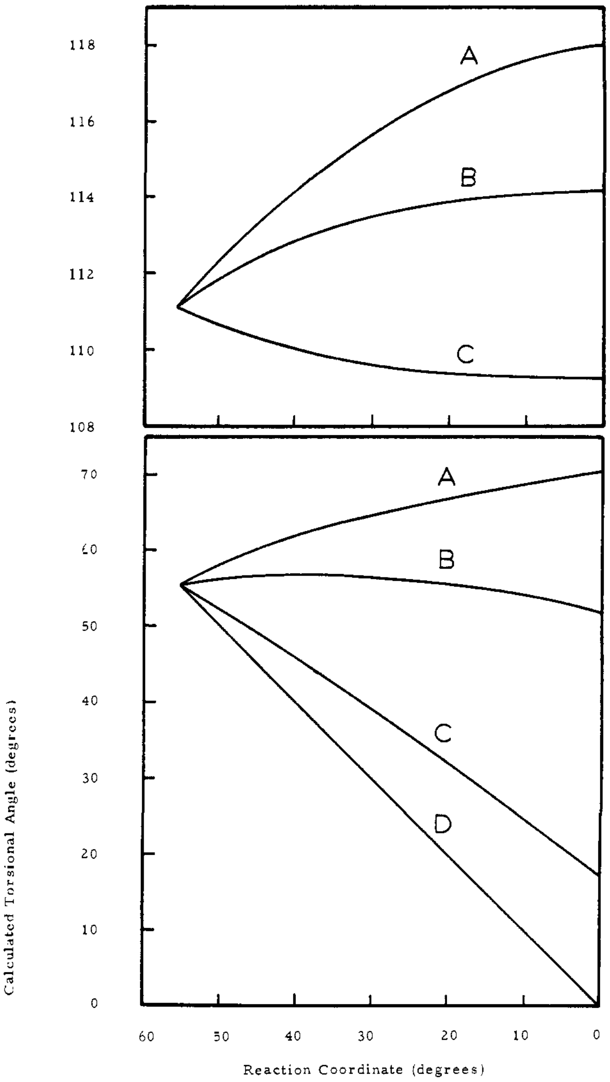

Figure 2. (Top) Changes in bond angles using one torsional angle as the reaction coordinate. The curves are (A) θ_{123}, (B) θ_{234}, (C) θ_{345}. (Bottom) Changes in torsional angles using a single torsional angle as the reaction coordinate. The curves are (A) ϕ_{3456}, (B) ϕ_{2345}, (C) ϕ_{1234}, (D) ϕ_{6123}.

tuitously turns out to largely compensate for the entropy of the "missing" frequency of the activated complex, and there is very little vibrational entropy change contribution to the entropy of activation.

To complete the set of calculations, the strain energies of the boat and twist boat forms were calculated using the same set of potential functions giving 10.1 and 9.4 kcal/mol as the respective strain energies.

The results may be compared with experimental data. The activation barrier for the inversion of cyclohexane has been found by low-temperature nmr studies to be $\Delta H^{\ddagger} = 10.8 \pm 0.1$ kcal/mol.[14] The corresponding $\Delta S^{\ddagger}$ equals 1.5 eu. Both of the calculated barriers for the one torsional angle activated complex are close to this value, and that from set 2 leads to a remarkably good fit. Thus, there is now available a simple method for estimating the barrier to conformational change. Because of the compensation effect mentioned above, the entropy change is large due to the difference in symmetry numbers between the activated complex and the chair conformation of cyclohexane.[15] The difference in energy between the chair and twist boat conformations (5.7 kcal/mol) is also in good accord with the observed values.[16] The boat form was found

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[14] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **89**, 760 (1967). These workers obtained $\Delta S^{\ddagger} = 2.8$ for C_6HD_{11}. We have converted it to an experimental value for C_6D_{12} or C_6H_{12} (1.5 eu) by a symmetry number correction. Comparison of calculated vibration frequencies and resultant entropy changes for several isomers of the ground and transition states of C_6HD_{11} with C_6H_{12} fully justifies this correction.

[15] Picket and Strauss[6] attribute the positive entropy of activation to pseudorotation in the activated complex. However, with our potential function parameters the most flexible motion of the ring (exclusive of and orthogonal to the motion over the barrier) corresponds to a vibrational motion largely along a coordinate connecting the four coplanar and five coplanar atom configurations. The calculated frequency (100 cm^{-1}) of this mode is such that we prefer to regard it as a true vibration rather than a pseudorotation.

[16] Using different methods N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960), and W. S. Johnson, J. L. Margrave, V. J. Bauer, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *ibid.*, **83**, 606 (1961), estimate the twist-boat–chair energy difference as 5.9 ± 0.6

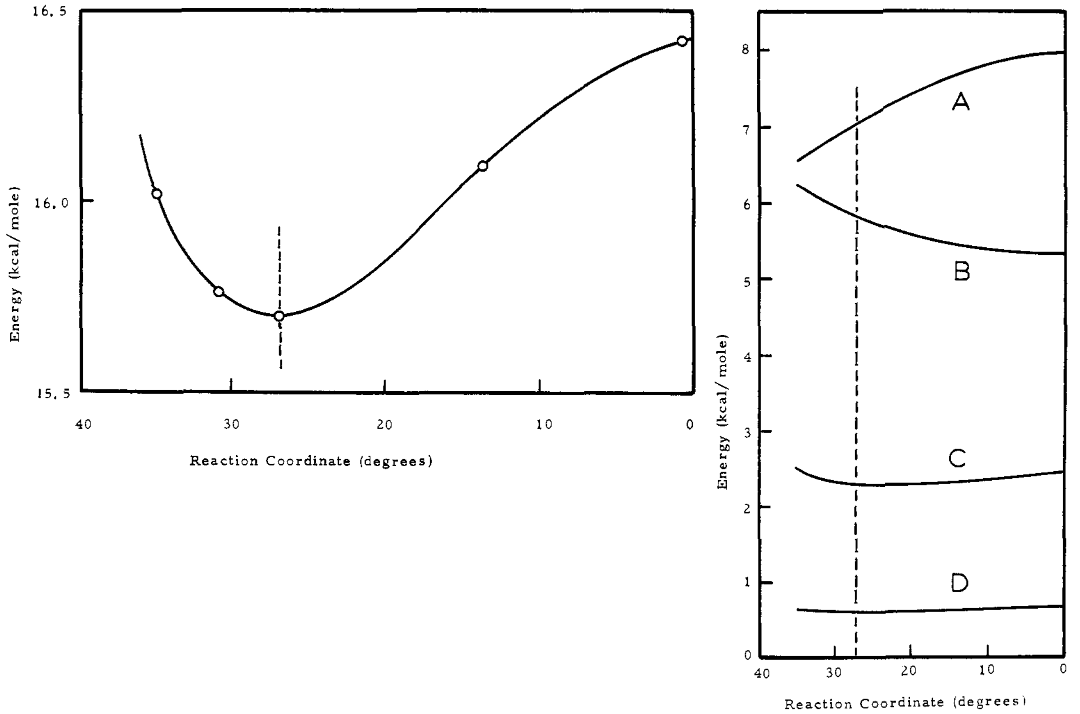

Figure 3. (Left) Change in strain energy for the inversion of bicyclo[3.1.1]heptane. The values of the strain energy do not include the angle strain present in cyclobutane itself. The dotted line indicates the equilibrium geometry. (Right) Components of the strain energy for the inversion of bicyclo[3.1.1]heptane. The curves are: (A) torsional strain; (B) nonbonded interactions; (C) angle strain (not including that present in cyclobutane itself); (D) bond stretching.

to have an imaginary vibrational frequency, indicating it to be a saddle point for the interconversion of twist-boat forms.

We have previously found that bicyclo[3.1.1]heptane undergoes ring inversion at a rate too high to be determined by low-temperature nmr spectroscopy.[17] It was therefore of interest to estimate the magnitude of the barrier to inversion using the procedure described above. The results of the calculations are shown in Figures 3 and 4. The energy barrier was calculated to be only 0.7 kcal/mol. In this case the energy terms resulting from bond angle deformation cancel leading to essentially no change along the reaction coordinate. Crossring nonbonded interactions are calculated to be significant in the equilibrium conformation, and these decrease somewhat along the reaction coordinate. The increase in torsional strain is partially compensated by the decrease in nonbonded interaction and leads to only a small energy barrier.

In the cases discussed above, the possible activated complexes are easily visualized, and the barrier could be obtained by just calculating the energies of the equilibrium form and of models for the activated complexes. However, this is not always the case. The present method does not require *a priori* knowledge of the geometry of the activated complex and will determine that geometry during the course of the calculations. In addition, it provides information on the nature of the changes in energy and geometry during the course of the process.

This method should prove valuable in studying the more complex conformational changes which are found with the larger ring cycloalkanes. Calculations on some of these systems will be presented subsequently.

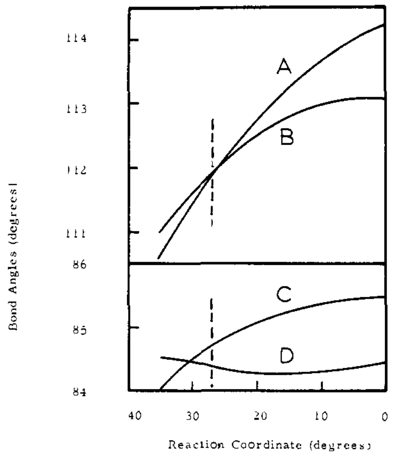

Figure 4. Changes in bond angles for the inversion of bicyclo-[3.1.1]heptane. The curves are: (A) θ_{234}; (B) θ_{123}; (C) θ_{617}; (D) θ_{165}.

Calculations

The calculations were carried out using a modification of the computer program of Boyd.[9b,c] The value of c_2 was varied from 0 to 60°. In order to come within 0.5–1° of the final torsional angles, the value of c_1 had to be raised to a value on the order of 200. The initial calculations were carried out with $c_1 = 10$ and c_2 increased in 5–10° steps. The geometry found in a given calculation was used as the input datum for the following calculation. When c_2 had reached 60°, c_1 was increased stepwise in the same fashion. When large values of c_1 and c_2 were used, it was sometimes necessary to limit the

and 5.5 ± 0.3, respectively. The difference in energy between the boat and twist-boat conformations is not available from experimental data although clearly the boat form has the higher energy.

(17) B. A. Hess, Jr., Ph.D. Thesis, Yale University, 1966.

magnitude of the geometrical changes which were permitted in any one iteration.

The bending and stretching force constants for cyclohexane are given in Table I. It is not possible to obtain a unique set of constants in this case because the six bond angles about a carbon are not independent. Further, the C–C stretching modes are coupled with angle bending. As a result, the two quite different sets of force constants, 1 and 2, both lead to a reasonably small rms deviation between calculated and observed vibrational frequencies. The calculations for bicyclo[3.1.1]heptane were carried out using the methylene force constants given in set 2, along with the cyclobutane force constants summarized in Table IV.

Table IV. Force Constants for Bicyclo[3.1.1]heptane

Internal coordinate[a]	k, mdyn/Å[b]	Internal coordinate[a]	k, mdyn/Å[b]
C′–C	3.57[c]	H–C–C′	0.677
C′–H	4.69	H–C′–C	0.65[c]
C′–C′	2.85	H–C′–C′	0.636
C–C–C′	1.336	H–C′–H	0.393
C–C′–C′	0.8[c]		
C′–C′–C′	0.762		

[a] C refers to a carbon in a cyclohexane ring and C′ refers to a carbon in a cyclobutane ring. [b] The force constants for the cyclobutane ring were derived from a vibrational analysis for C_4H_8 and C_4D_8 using only the diagonal force constants (ref 11). [c] Estimated value.

The equilibrium geometry for cyclohexane[18] was taken as θ(CCC) = 111°, θ(HCC) = 109.5°, and θ(HCH) = 107.9°; that for cyclobutane[19] was taken as θ(CCC) = 90°, θ(HCC) = 113.9°, and θ(HCH) = 110°. The torsional interaction and nonbonded interaction functions suggested by Boyd[9b,c] were used. The former was set to correctly represent the barrier to rotation about the C_2–C_3 bond of ethane and the latter adapted from functions derived by Williams[20] from crystalline hydrocarbon data.

[18] M. I. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963); private communication, M. I. Davis, University of Texas.

[19] L. Wolloe, Ph.D. Thesis, University of Oslo, 1965.

[20] D. E. Williams, *J. Chem. Phys.*, **47**, 4680 (1967).

1-Hydroxy- and 1-Oxo[2.2]metacyclophane. Optical Resolution and Ring Rotation

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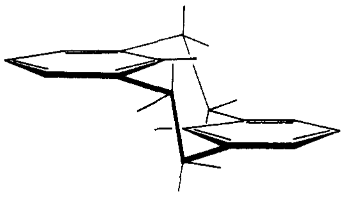
Abstract: The synthesis and optical resolution of 1-oxo[2.2]metacyclophane and the equatorial and axial isomers of 1-hydroxy[2.2]metacyclophane are described. One antipode of the ketone was transformed *via* reduction, thermal equilibration, and oxidation into its mirror image. The kinetic parameters for the ring inversion of 1-hydroxy[2.2]metacyclophane were determined by measuring the rates of their respective thermal equilibration: equatorial isomer, $\Delta H^{\ddagger} = 29.6 \pm 1.7$ kcal/mol, $\Delta S^{\ddagger} = -8.5 \pm 4.0$ eu, $\Delta G^{\ddagger}_{150} = 33.2$ kcal/mol from k_2 values; axial isomer, $\Delta H^{\ddagger} = 31.7 \pm 1.7$ kcal/mol, $\Delta S^{\ddagger} = -2.75 \pm 4.0$ eu, $\Delta G^{\ddagger}_{150} = 32.9$ kcal/mol from k_1 values. At 151.5° the equilibrium constant was found to be $K = 1.49$ for equatorial/axial. The kinetic parameters for the ring inversion of 1-oxo[2.2]metacyclophane, accessible by measuring the rates of racemization, were determined to be: $\Delta H^{\ddagger} = 10.75 \pm 0.19$ kcal/mol, $\Delta S^{\ddagger} = -48.4 \pm 0.6$ eu, and $\Delta G^{\ddagger}_{150} = 25.05$ kcal/mol. A hypothesis for the extremely large negative entropy term and thus the transition state is discussed.

For many years various research groups have been attracted by the chemistry and the spectral properties of the [2.2]metacyclophane skeleton **1**.[1,2] Its conformation, which was elucidated by X-ray measurements,[3] is apparently frozen into a chair-like nonplanar form. This very feature allows the possibility of preparing chiral structures simply by introducing substituents into the aromatic rings in a manner that destroys the plane of symmetry bisecting the unsubstituted [2.2]metacyclophane. Molecules with such inherent asymmetry have in fact been prepared[4] and reports have appeared on the optical resolution of 4,14-dimethyl[2.2]metacyclophane.[5] Another way to produce chiral metacyclophanes is in the introduction of substituents on the ethano bridge; this too has been realized in the syntheses of 1,2-dimethyl[2.2]metacyclophane (CH_3 groups cis)[6] and isomeric mixtures of 1,9(and 1,10)-bismethylsulfido[2.2]metacyclophane.[7] Chiral [2.2]metacyclophanes appear to be ideal sub-



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[7] R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, **92**, 3511 (1970).