Inflection Points and Chaotic Behavior in Searching the Conformational Space of Cyclononane

Frank A. L. Anet

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received November 27, 1989*

Abstract: We have investigated the nature of two conformations recently discovered by others through extensive searches of the conformational space of cyclononane. Although these conformations are indeed energy minima with the MM2 force field, they have only minute energy barriers separating them from previously known conformations of much lower energy and, therefore, have rather questionable significance. One of the new conformations is not a local energy minimum with some force fields. Explorations of conformational space are shown to benefit from a determination of the lowest energy transition states between all pairs of conformations. Convergence and stability problems in applying the full Newton–Raphson iteration method are investigated, and the key role of inflection points (particularly of the previously unappreciated "positive" type) on the energy hypersurface is presented.

The local energy minima in the conformational space of typical organic molecules can be determined fairly easily by recently developed search methods.[1-4] This has become quite practical because the required computational power is now readily available. The determination of local energy minima is an important problem in the application of molecular mechanics, and it presents a challenge when rings containing many atoms are present. The medium- and large-ring cycloalkanes exemplify these problems well, and they have, therefore, served as test molecules for search programs.[1-3] Indeed, the medium-ring cycloalkanes have historically been in the forefront of conformational developments. In the early days of conformational analysis, only symmetrical conformations of the medium-ring cycloalkanes were thought to be local energy minima or even transition states for conformational interconversion,[5] but this proved not to be the case.[6,7] It is now well appreciated, following the work of Ermer,[8] that energy minima have to be carefully distinguished from conformational transition states (saddle points on the energy hypersurface) as well as from higher order energy extrema, such as hills on the hypersuface. This can best be done by determining (a) that the gradient of the energy with respect to each of the Cartesian coordinates of the atoms in the molecule is zero and (b) that the $3N-6$ (or $3N-5$ for a linear molecule) vibrational frequencies calculated in the harmonic approximation have real values. The latter is equivalent to stating that all the eigenvalues of the mass-weighted Hessian matrix are positive, as the vibrational frequencies are proportional to the square roots of the corresponding eigenvalues. But is this sufficient for an energy minimum to have real significance? We think not.

The early methods of finding energy minima and conformational interconvesion paths of the cycloalkanes made use of mechanical (e.g., Dreiding) models in conjunction with molecular mechanics calculations. The introduction by Wiberg and Boyd[9] of a "driving" procedure was of importance, as it allowed for computer searching and monitoring the energy by changing one or more torsional angles by small increments while keeping other degrees of freedom optimized. Maps of the energy versus two internal coordinates can be obtained by this method, although this requires a large number of calculations, especially if a fine grid is used. In principle, a high-dimensional map of the energy in terms of the N torsional angles of an N-membered cycloalkane can be obtained, but the number of energy calculations for a 10° increment from 0 to 360° for each torsional angle is 36^N, which is greater than 10^{15} for cyclotetradecane and is, therefore, quite impractical. The recently proposed search methods, which are not quite exhaustive for local energy minima, can be done on a VAX-type computer for molecules such as cyclotetradecane, although the time required may extend over days.[10]

Automatic search methods can locate local energy minima that have been missed in previous less extensive studies.[1-3] In contrast, one-dimensional searches have been termed "primitive" and need the subjective judgment of the user.[3] However, the latter methods, with judicious driving of torsional angles and especially in association with the full-matrix Newton–Raphson procedure to converge on energy extrema, can provide much information about the energy surface, including the lowest barriers between all pairs of conformations. Unfortunately, present versions of automatic search programs do not deal with the relationships of the local energy minima on the energy hypersurface, although they may do so in the future; in particular, the (lowest) barriers separating the various conformations have generally been ignored, possibly leading to a poor understanding of the conformational properties of the molecule. The situation is compounded by an almost exclusive use of a single force field (invariably MM2) in automatic searches with molecular mechanics calculations.[1-3] The MM2 force field has the virtue of having parameters for numerous kinds of atoms and structures, so it has been widely used and has proven to be generally useful.[11] For saturated hydrocarbons, several other equally satisfactory but significantly different force fields are available.[8,12,13] Finally, the MM2 program uses a block-diagonal Newton–Raphson procedure, which is efficient for converging on energy minima but is unfortunately not very suitable for locating

---

(1) (a) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150–3152 (b) Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203–208.

(2) (a) Lipton, M; Still, W. C. *J. Comput. Chem.* **1988**, *9*, 343–355. (b) Chang, G; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.

(3) (a) Ferguson, D. M.; Glauser, W. A.; Raber, D. J. *J. Comput. Chem.* **1989**, *10*, 903–910. (b) Ferguson, D. M.; Raber, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4371–4378.

(4) Loncharich, R. J.; Seward, E.; Ferguson, S. B.; Brown, F. K.; Diederich, F.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 3479–3491.

(5) Hendrickson, J. B. *J. Am. Chem. Soc.* **1964**, *86*, 7047–7061.

(6) Anet, F. A. L. *Top. Curr. Chem.* **1974**, *45*, 169–220.

(7) Dale, J. *Top. Stereochem.* **1976**, *9*, 199–270.

(8) (a) Ermer, O. *Tetrahedron* **1975**, *31*, 1849–1854. (b) Ermer, O. *J. Am. Chem. Soc.* **1976**, *98*, 3964–3970. (c) Ermer, O. *Struct. Bonding (Berlin)* **1976**, *27*, 161–211.

(9) Wiberg, K. B.; Boyd, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 8426–8430.

(10) For an extensive study of the conformational space in cycloheptadecane by a variety of methods see: Saunders, M.; Houk, K. N.; Wu, Y-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419–1427.

(11) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. The newly reported MM3 force field for saturated hydrocarbons is significantly better than MM2: Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8566. Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566–8575, 8575–8582.

(12) (a) The conformational properties of *cis,syn,cis*-perhydrophenanthrene have been examined with nine different force fields: Anet, F. A. L.; Anet, R. *Tetrahedron Lett.* **1985**, *26*, 5355–5358. (b) Three different force fields have been used to examine the conformations of medium rings fused to semibullvalene: Anet, F. A. L.; Anet, R.; Trova, M. P.; Paquette, L. A. *Tetrahedron Lett.* **1989**, *30*, 6469–6472.

(13) Ermer, O.; Ivanov, P. M.; Ōsawa, E. *J. Comput. Chem.* **1985**, *6*, 401–428.

0002-7863/90/1512-7172$02.50/0

transition states.[11] In the full Newton–Raphson method, the complete $3N \times 3N$ matrix of the second derivatives of the energy with respect to the Cartesian coordinates of the N atoms in a molecule is calculated, and convergence to local energy minima, transition states, and higher order extrema all take place equally well, provided that a suitable starting point is chosen.

If a barrier of less than a few tenths of a kilocalorie per mole separates one local energy minimum (A) from another one (B), then A and B cannot be treated as separate conformations from either a thermodynamic or quantum point of view.[14] The energy hypersurface in the vicinity of both A and B needs to be considered rather than just the vibrational frequencies in the harmonic approximation. This kind of situation has been extensively investigated when A and B have the same energy or at least similar energies, as in ring inversion in four-membered rings or pseudorotation in five-membered rings. If A is higher in energy than B by more than 1 or 2 kcal/mol with the barrier for the A to B transformation being very small as described above, then B is a "normal" local energy minimum, while A has very little, if any, independent thermodynamic significance; the presence of the A minimum merely affects the relative spacing of the low-energy vibrational levels of B. This is especially true if the calculated zero-point energy (ZPE) level of A lies above the energy of the transition state that separates A from B. Even when the ZPE level of A is below the barrier, tunneling can be important if the energy difference between the ZPE level and the barrier is small. Again, in such a case the energy minimum hardly has an independent existence. Although calculations of ZPE's based on the harmonic approximation are not strictly correct, especially when the apparent ZPE level is higher or comparable to the barier, it is apparent that A is not distinguishable from a vibrationally excited B conformation. The population of the nth vibrational state is dependent on the Boltzmann factor, $e^{-(n+1/2)E/RT}$, where $E = Nh\nu$ and N is Avogadro's number. At room temperature, $RT \approx 600$ cal/mol, while, in matrix isolation work at 50 K, $RT = 100$ cal/mol, so that the B conformation can have appreciably populated vibrational levels that are comparable to the energy of A. Under these conditions, A and B cannot be treated independently and A does not have any real significance.[14]

We have used several force fields to reexamine the cyclononane energy hypersurface in the vicinity of the new conformations to determine whether the claims[2,3] that previous workers[7,15,16] did not find all the local energy minima are really meaningful in the sense described above. In doing so, we have encountered severe convergence and stability problems when using the (full) Newton–Raphson procedure. Such difficulties are rather well-known, and they have been blamed on such things as numerical errors or a bad starting geometry where the hypersurface in any direction has (accidentally) a very small quadratic component.[17] Because we use a program where the derivatives are calculated analytically and all noninteger variables have about 15 digits of accuracy,[12,18] the former cannot be the problem and the latter does not explain oscillating behavior or a sudden instability during the iteration procedure. The results presented below show the origins of these problems and how to deal with them.

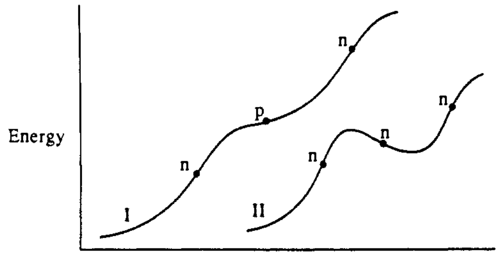


Figure 1. Examples of negative (n) and positive (p) inflection points. Curve II has a local energy minimum that is not present in curve I.

Inflection Points on the Energy Hypersurface. An inflection point corresponds to an extremum (maximum or minimum) in the tangent (or slope) of the function rather than in the function itself.[19] For example, with the one-dimensional function

$$y = x^3 + bx \qquad (1)$$

an inflection point occurs at $x = 0$ because d^2y/dx^2 is 0 and d^3y/dx^3 is finite. The relative signs of d^3y/dx^3 and dy/dx depend on the sign of b, but a distinction between different types of inflection points based on these relative signs has not generally been made in the mathematical literature,[19] but it is important for our purpose. For convenience, the case of the first and third derivatives having like signs is defined as a positive inflection point, and similarly a negative inflection point has opposite signs for these derivatives (Figure 1). A "zero" inflection point can also be defined as that having a zero first derivative; this is sometimes called a horizontal inflection point.[17b]

The Newton–Raphson iteration for finding an extremum in a one-dimensional function is a search for a zero first derivative. In this procedure, the first and the second derivatives (slope and curvature, respectively) at an arbitrary starting point are calculated and the correction to the variable x, which is given by minus the ratio of the slope to the curvature, is used to calculate a new value of x. The second derivative is generally finite at an extremum, and the slope and correction become zero; in the above system this occurs for a *negative b* at $x = \pm[(-b/3)^{1/2}]$.

At an inflection point, by contrast, the first derivative is generally nonzero but the second derivative is zero. Thus, the correction at that point becomes $\pm\infty$, and the Newton–Raphson procedure diverges. Near (but not at) this (negative) inflection point, which occurs at $x = 0$ in the present instance, convergence to a local minimum or maximum occurs for positive or negative x, respectively, as long as b is negative.

If b is positive in eq 1, iteration results in a chaotic behavior for a *general* starting point. Indeed, the Newton–Raphson procedure for finding the roots of a polynomial, especially in the complex plane, is known to lead to chaotic or nonchaotic behavior, depending on the situation, and the behavior of cubic equations in the complex plane has been investigated.[19] However, our interest is not in the roots but in the extrema exhibited by eq 1. For

---

(14) The question of whether the term "conformation" should be restricted to a local energy minimum or should also include transition states and other energy extrema or even geometries that are not any of these has not been resolved.[7] Somewhat similar problems occur in defining the term "isomer": Eliel, E. L. *Isr. J. Chem.* **1976**, *15*, 7–11. See also: Mislow, K.; Bickart, P. *Isr. J. Chem.* **1976**, *15*, 1–6. Wooley, R. G. *Isr. J. Chem.* **1980**, *19*, 30–46. Dugundji, J.; Showell, J.; Kopp, R.; Marquarding, D.; Ugi, I. *Isr. J. Chem.* **1980**, *20*, 20–35. Mezey, P. G. In *Structure and Dynamics of Molecular Systems*; Daudel, R., Korb, J.-P., Lemaistre, J.-P., Maruani, J., Eds.; Reidel: Boston, 1985; pp 41–56. Symmetrical geometries of molecules are always attractive to consider, and for any given symmetry the geometry can always be refined to an energy extremum. But, this is often not a local energy minimum or even a transition state, yet it is often convenient to talk about these as "conformations". Dale[7] has suggested that the term "conformer" be restricted to a definite local energy minimum and that the term "conformation" have a wider meaning, but this suggestion has unfortunately not been widely adopted. In any case, a phrase such as "this hydrocarbon exists in three conformations" clearly implies three local energy minima. For a strictly correct quantum mechanical treatment of flexible molecules, which requires the use of permutations of identical nuclei, see: Bunker, P. R. *Molecular Symmetry and Spectroscopy*; Academic Press: New York, 1979.

(15) Anet, F. A. L.; Krane, J. *Isr. J. Chem.* **1980**, *20*, 72–83.

(16) Rustad, S.; Seip, H. M. *Acta Chem. Scand. Ser. A* **1975**, *29*, 378–380.

(17) (a) Dennis, J. E., Jr.; Schnabel, R. B. *Numerical Methods for Unconstrained Optimization and Nonlinear Equations*; Prentice-Hall: Englewood Cliffs, NJ, 1983. (b) Peressini, A. L.; Sullivan, F. E.; Uhl, J. J., Jr. *The Mathematics of Nonlinear Programming*: Springer-Verlag: Berlin, 1988.

(18) (a) Baas, J. M. A.; van de Graaf, B.; van Veen, A.; Wepster, B. M. *Tetrahedron Lett.* **1978**, 819–820. (b) van de Graaf, B.; Baas, J. M. A.; van Veen, A. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 175–178. (c) van de Graaf, B.; Baas, J. M. A. *J. Comput. Chem.* **1984**, *5*, 314–321. (d) MOL,[12a] an input and database management program interfaced to a modified version of DELPHI, was used for these calculations: Anet, F. A. L.; Anet, R., Unpublished work. The DELPHI program was modified to provide displacements in term of internal coordinates for the normal modes.[8a]

(19) An inflection point corresponds to an extremum (maximum or minimum) in the tangent (or slope) of the function rather than in the function itself: *The VNR Concise Encyclopedia of Mathematics*; Gellert, W., Küstner, H., Hellwich, M., Kästner, H., Eds.; Van Nostrand Reinhold: New York, 1977, pp 424–431.

simplicity, the function with $b = 1$ will be discussed, i.e.

$$y = x^3 + x \qquad (2)$$

With the subscript to x indicating the iteration number, the Newton–Raphson method for searching for an extremum in y gives a correction of $-(3x^2 + 1)/6x$ and thus

$$x_{n+1} = (3x_n^2 - 1)/6x_n \qquad (3)$$

For $x_n = \pm{}^1/_3$, $x_{n+1} = -x_n$, so that continued iteration of eq 3 gives rise to stable oscillations. Mathematically,[20c] $+{}^1/_3$ and $-{}^1/_3$ constitute *periodic points* of order 2, and other values of x, such as ±1, $\pm(1 \pm 2/\sqrt{3})$, etc., are *eventually periodic points* because they lead to periodic points. Equation 1 diverges to infinity for $x_n = 0$ or for any value of x that leads to this value, e.g., $\pm1/\sqrt{3}$, $\pm(1 \pm \sqrt{2})/\sqrt{3}$, etc., which may be considered as the x_{n-1}, x_{n-2}, etc., terms. These special properties of eq 1 upon iteration are valid only for exact arithmetic but not in general for computer arithmetic with finite numerical accuracy. Even a small deviation from the above values ultimately leads to a chaotic behavior; e.g., if x differs from ${}^1/_3$ by 1 ppm, chaos sets in after about 25 iterations (Figure 2). For a starting value of $1.0 + 10^{-20}$, chaos occurs after about 70 iterations, whereas, for a starting value of 1.0, x has changed from the regular $\pm{}^1/_3$ oscillations by less than 1 part in 10^4 after 100 iterations and the entire change is the result of finite numerical accuracy. These calculations were done using FORTRAN REAL*16 variables, i.e., with about 33 digits of accuracy.

If $|x|$ is large ($>1/\sqrt{3}$), continued iteration of eq 3 reduces $|x|$ by about a factor of 2 per iteration while the sign of x is maintained. When $|x|$ becomes less than $1/\sqrt{3}$, which ultimately must happen, a sign inversion takes place and x_{n+1} and x_n then have opposite signs. This sign alteration continues as long as x remains between $-1/\sqrt{3}$ and $+1/\sqrt{3}$, and the number of consecutive sign alternations is larger the closer x is initially to $\pm1/3$. Ultimately, the value of $|x|$ becomes less than $(\sqrt{2} - 1)/\sqrt{3}$, i.e., 0.239, whereupon $|x|$ jumps beyond $1/\sqrt{3}$ and the whole process repeats. There is no regularity, however, so that the iterations lead to a chaotic behavior with an extreme sensitivity to the initial value, as shown in Figure 2 for two closely similar values of x. In the chaotic regime, $|x|$ typically reaches a maximum value of between 5 and 500 during 100 iterations. In principle, arbitrarily large excursions of x can occur, but in practice they are so rare that they are not observed. The *average* value of x converges to the (positive) inflection point ($x = 0$), but the convergence is slow unless the large excursions are omitted from the average or limits are set to the correction to be made to x at each iteration.

The behavior of eq 1 with $b = 1$ also occurs for any other positive value of b, and the presence of a small x^2 term does not change the general features of the system. In molecular mechanics calculations, the energy hypersurface is multidimensional and arises not only from simple quadratic terms (e.g., bond stretching, which is generally quadratic in both internal and Cartesian coordinates) but also from terms (e.g., bond angle bending) that are not quadratic in Cartesian coordinates, even though they may be quadratic in the internal coordinates, as well as terms (e.g., nonbonded and torsional strains) that are not quadratic in either internal or Cartesian coordinates. The full-matrix Newton–Raphson iteration in molecular mechanics is almost always done on the Cartesian coordinates because these form a nonredundant set, whereas the choice of a nonredundant set of internal coordinates is arbitrary. The energy (as a function of the Cartesian coordinates) at any point on the energy hypersurface can be expanded in a power series about that point where the most important terms involve the zero, first, second, and third powers. The analysis given above for a simple one-dimensional case can be extended to a multidimensional surface. Term higher than the third power give important contributions to the corrections if large excursions (changes in the coordinates) are made from the starting point, and in such a system a positive inflection point will ultimately give such a large correction that a return to that inflection point no longer occurs, in contrast to the situation with eq 2. In the absence of a cubic term, the presence of a fourth-order term (as in $x^4 + bx$) does not prevent convergence irrespective of whether a quadratic term is present or not, but the rate of convergence is quite low if the quadratic term is close to zero.

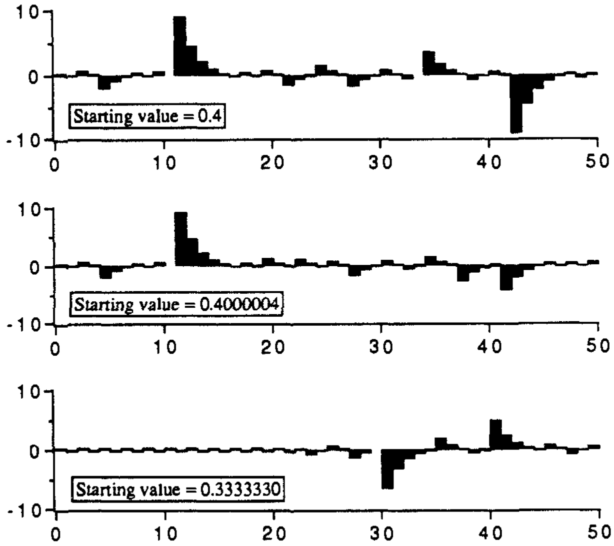


Figure 2. Deterministic chaotic behavior during the first 50 iterations of the Newton–Raphson method for search for an extremum in $y = x^3 + x$ for starting values of $x = 0.4$, 1 ppm more than 0.4, and for 1 ppm less than ${}^1/_3$ (a *stable* oscillatory behavior is observed for precisely ${}^1/_3$). The horizontal axis is the iteration number, and the vertical axis shows the change in x during the iteration.

The Newton–Raphson method is of course well-known to converge on an energy extremum of any order, as long as the starting point is sufficiently close to the extremum.[8,17,18] In particular, convergence can occur to a local (or global) energy minimum or to a conformational transition state (saddle point) on an energy hyersurface. The common type of inflection point is one that separates a local energy minimum from a transition state (saddle point), and the curvature changes from positive to negative as the energy *increases monotonically*, as shown by the points n in Figure 1 for one-dimensional surfaces. This corresponds to a *negative inflection point*, in our terminology, and at such a point the curvature (second derivative) is zero while the first and third derivatives are finite and have *opposite* signs. The Newton–Raphson method becomes unstable at or near a negative inflection point, and extremely large positive or negative corrections to the coordinates are calculated. This instability can be overcome by scaling so that the largest correction is less than some given value, e.g., 0.1 Å. The corrections always result in a change that is away from the inflection point, i.e., the inflection point is never crossed, and the stability tends to increase rather than decrease as the calculations proceed.

However, if the inflection point results from a negative to positive change in curvature as the energy increases montonically, as in point p in curve I in Figure 1, the Newton–Raphson method in general gives an oscillating behavior that is chaotic and is punctuated occasionally by large excursions away from the inflection point, as was described above for a simple cubic curve. If the oscillations are increasingly dampened by the limiting procedure just mentioned, then a near convergence to a *positive inflection point* is achieved and in this case the calculated corrections are always *toward rather than away* from the inflection point. The only smooth way of getting out of this impasse is to constrain the geometry so that convergence to a true energy extremum ultimately follows removal of the constraint. A positive inflection point, unlike a negative one, suggests the presence of

---

(20) (a) Schuster, H. G. *Deterministic Chaos*; Physik-Verlag: Weinheim, 1984; p 132. (b) Barnsley, M. F.; Devaney, R. L.; Mandelbrot, B. B.; Peitgen, H.-O.; Saupe, D.; Voss, R. F. *The Science of Fractal Images*; Springer-Verlag; New York, 1988. (c) Devaney, R. L. *an Introduction to Chaotic Dynamical Systems*, 2nd ed: Addison-Wesley: New York, 1989. An exhaustive search of the mathematical literature for the exact situation described in the present work has not been made, but it likely has been investigated previously.

Table I. Molecular Mechanics Steric Energies (kcal/mol)[a] and Lowest Vibrational Frequencies (cm^{-1}) of Some Cyclononane Conformations and Transition States

	MM2		Boyd-1[b]		Boyd-9[c]		Ermer–Lifson[d]	
conformation	*E*	ν	*E*	ν	*E*	ν	*E*	ν
[333] (TBC)	0.00	177	0.00	173	0.00	168	0.00	193
TCC ([9] or [144])	0.77	131	1.25	129	0.36	126	0.56	140
TCTC	2.22	93	2.97	97	2.119	42	2.48	68
(TCTC–TCC)‡[e]	2.40	69*i*	3.17	77*i*	2.122	39*i*	2.51	56*i*
SCC	5.67	80	5.53	57	*f*, *g*		*f*	
(SCC–TCC)‡[e]	5.75	76*i*	5.60	54*i*				

[a] Energy from molecular mechanics calculations relative to the [333] conformation. The actual force field energies for the [333] conformation are as follows: 23.39 (MM2); 16.16 (Boyd-1); 16.43 (Boyd-9); 23.55 (Ermer-Lifson). These numbers cannot be compared with one another. [b] One torsional parameter per C–C bond. [c] Nine torsional parameters per C–C bond. [d] Modified as described in footnote 22. [e] Transition state. The *i* in the ν column indicates an imaginary frequency. [f] Not a local energy minimum. [g] See Figure 4 for a part of the energy hypersurface; the torsional angles at the inflection point, where the energy is 21.428 kcal/mol, are given in Figure 5.

an incipient local energy minimum, and changes in force-field parameters can conceivably convert such a positive inflection point into a true local energy minimum, as in going from curve I to curve II in Figure 1; in general, the barrier separating this minimum from a lower energy minimum will be small. As described below, this effect is found in the SCC form of cyclononane. In a gradual change from curve I to curve II behavior, the positive inflection point disappears and is replaced by a negative inflection point and a local minimum, with the dividing situation between the domains of curve I and curve II exhibiting a zero inflection point.[21]

Cyclononane Energy Hypersurface Near the TCTC and SCC Forms. We have repeated the molecular mechanics calculations on the two new cyclononane conformations described by Still[2] and Raber[3] (TCTC and SCC in Raber's nomenclature) using a modified DELPHI program.[12,18] Although both of these conformations are indeed local energy minima when the MM2 force field is used, they are separated from the previously known TCC conformation by extremely small barriers. The sequence of ring torsional signs is the same in both the TCTC and TCC forms, with the largest difference in the torsional angles being only 33.4° (Figure 3). In fact, the TCTC is an unsymmetrical variant of the TCC conformation where some torsional angles have slightly increased and others have slightly decreased and where the energy has increased by 1.45 kcal/mol. Futhermore, in proceeding from the TCTC to the TCC form none of the torsional angles cross an eclipsed (120°) situation by more than 2°, so the barrier separating these two forms is expected to be very small. Indeed, the transition state for the TCTC to TCC interconversion is very close to the TCTC conformation (Figure 3), the largest difference in torsional angle being only 10.4°, with only a difference of 0.18 kcal/mol in energy (Table I).

The second cyclononane form found by Still and Raber has C_2 point group symmetry like the TCC conformation, and the signs of the ring torsional angles show the same sequence in both cases, the largest difference being 56.7°. The energy of the SCC is higher than that of the TCC conformation by 4.9 kcal/mol. Only two symmetry-related torsional angles cross the 120° value, but by less than 10°. The SCC is essentially a TCC form that is less open and is elongated along the C_2 axis, as shown in a diagrammatic way in Figure 3. The SCC and TCC forms are separated by a barrier of only 0.08 kcal/mol with the MM2 force field (Table I), and the transition state is close in both geometry and energy to the SCC form.

For comparison with the MM2 force field, we have also used three other force fields, namely, a modified Ermer–Lifson[22] and two versions (Boyd-1 and Boyd-9) of the Boyd force field[23] (Table I). The original Boyd force field for saturated hydrocarbons employed only one torsional parameter per C–C bond. Although this is unambiguous for unbranched cyclic and acyclic hydrocarbons, an arbitrary choice has to be made if there is branching, as in a fused-ring system, and the geometry and energy obtained will then depend on this arbitrary choice.[24] To avoid such problems, we have used nine equal torsional parameters (with the force constant reduced to one-ninth) to do calculations on a perhydrophenanthrene.[12a] However, the energy and optimized geometry obtained with one and nine torsional parameters are not precisely the same with these two methods, especially when there are torsional angels that are far from a staggered arrangement, as indeed occurs in the cyclononane conformations, and we, therefore, report data using both one (Boyd-1) and nine (Boyd-9) torsional parameters per bond.

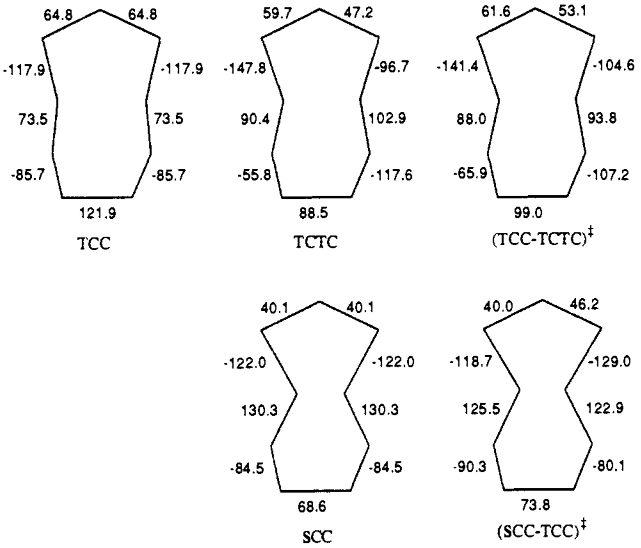


Figure 3. Torsional angles in degrees in the TCC, TCTC, and SCC conformations and in the conformational transition states, (TCC–TCTC)‡ and (SCC–TCC)‡, for the interconversion of these forms, as given by the MM2 force field.

The TCTC conformation is a local energy minimum with all three of the above force fields, but always with very small barriers preventing a downhill slide on the energy hypersurface to the TCC conformation. With the Boyd-9 force field, the barrier separating the TCTC from the TCC conformation is only 0.003 kcal/mol! This value is much lower than the energy difference (0.060 kcal/mol) between the ZPE level and the potential energy minimum for the TCTC form in the harmonic approximation for the lowest energy normal mode, which corresponds to a vibrational frequency of 42 cm^{-1}.

An SCC local energy minimum does not exist with the Boyd-9 and modified Ermer–Lifson force fields, as can be shown by constraining (driving) the two torsional angles (those with a value of 130.3° in the SCC form shown in Figure 3) between 60 and 140° at 5° intervals so as to maintain C_2 symmetry. The only minimum occurs near an angle of 74°, which corresponds to the

---

(21) A zero (horizontal) inflection point can only occur accidentally, and therefore only approximately, on the energy hypersurface of a real molecule.

(22) The modification[12a] of the Ermer–Lifson force field used here neglects (small) cross-interaction terms: Ermer, O.; Lifson, S. *J. Am. Chem. Soc.* **1973**, *95*, 4121–4132.

(23) Boyd, R. H. *J. Chem. Phys.* **1968**, *49*, 2574–2583.

(24) The use of nine torsional parameters is clearly mandatory in calculations on "anti-Newman" rotamers: Hounshell, W. D.; Dougherty, D. A.; Mislow, K. *J. Am. Chem. Soc.* **1978**, *100*, 3149–3156.

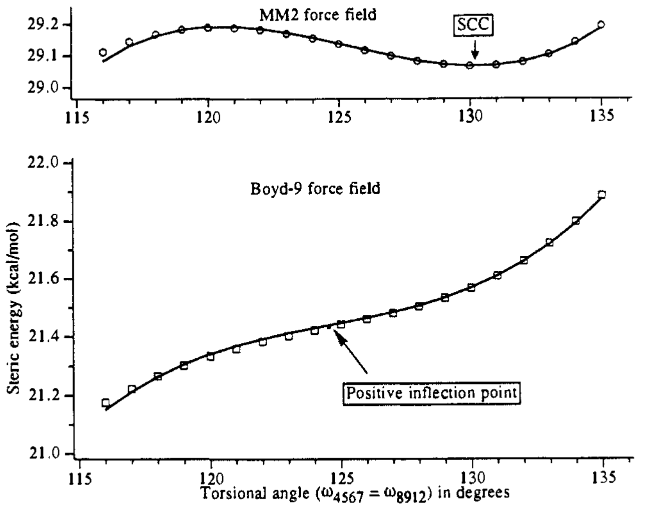
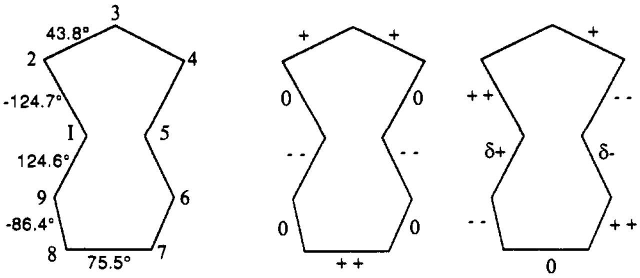


Figure 4. Molecular mechanics steric energies given by the MM2 (circles) and the Boyd-9 (squares) force fields in the vicinity of the SCC form of cyclononane under the constraint of equal ω_{4567} and ω_{8912} torsional angles, i.e., C_2 symmetry. The curves are best fits to the data points between 118 and 135° to cubic equations as described in the text.



I (C_2)
Positive inflection point

II
Symmetric ring distortion

III
Antisymmetric ring distortion

Figure 5. (I) Near-SCC geometry of cyclononane that shows a positive inflection point with the Boyd-9 force field, showing ring torsional angles. Displacements of torsional angles in I for the symmetric (II) and antisymmetric (III) low-energy ring distortion modes (displacements increase in the order δ+, +, and ++).

TCC conformation, and beyond this value the energy increases monotonically. When these angles are near 130°, the other ring torsional angles are within 1 or 2° of those shown for the SCC form in Figure 3. Figure 4 shows calculations of the energy with the Boyd-9 force field at 1° intervals between 116 and 135° for these torsional angles. The driving procedure in the DELPHI program makes use of added torsional constraints that are introduced into the solutions of the coordinate corrections by the Lagrangian method.[17,18] The desired values of the constrained angles are obtained precisely, provided that convergence can be achieved, and this was nearly always the case without having to limit the corrections. A positive inflection point, as will be shown below, occurs in the dependence of the energy with respect to the two torsional angles (ω_{4567} and ω_{8912}) when these reach 124.55°; the other ring torsional angles and the numbering system are shown in Figure 5. For convenience, we discuss torsional angles in terms of only one of the two possible enantiomeric families of TCC–SUC geometries.

The curve passing through the Boyd-9 molecular mechanics data in Figure 4 is the best fit of the points between 118 and 135° to a cubic equation, namely

$$\text{energy} = 21.44 + 0.016\Delta\omega + 0.00023\Delta\omega^3$$

with $\Delta\omega = \omega - 124.55°$, where 124.55° is the value of ω_{4567} and ω_{8912} at the inflection point. It should be noted that no quadratic term in $\Delta\omega$ has been used and that the first and cubic powers of $\Delta\omega$ have the same signs, as required for a positive inflection point. The curve through the Boyd-9 data in Figure 4 has a negative curvature on the left at torsional angles lower than 124.55° and a positive curvature on the right at torsional angles higher than this value.

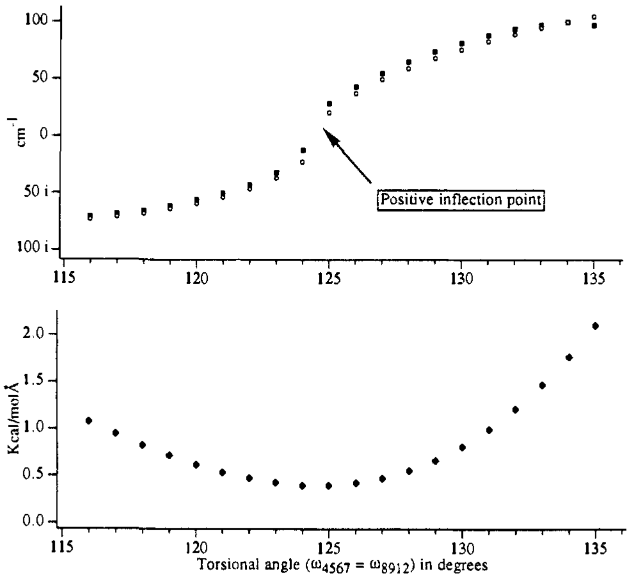


Figure 6. Properties of the cyclononane energy hypersurface near the positive inflection point (I in Figure 5) as obtained with the Boyd-9 force field. Bottom: Dependence of the largest absolute value of the first derivative of the energy with respect to the Cartesian coordinates (dE/dX_i, where X_i represents any of the $3N$ coordinaes). Top: Dependence of the symmetric (open circles) and antisymmetric (black squares) low-energy ring distortion modes on ω_{4567} and ω_{8912} (note that the frequency scale includes both real and imaginary values).

The energy hypersurface can be characterized at each point on the curve in Figure 4 by a calculation of "vibrational frequencies" via a diagonalization of the mass-weighted Hessian (second-derivative) matrix and by a calculation of the ring torsional angle displacements corresponding to each vibration normal mode.[8c] Because the molecule is not at equilibrium at any of the geometries in Figure 4 for the Boyd-9 force field, these pseudovibrational frequencies have no actual physical significance in terms of vibrational spectroscopy, but they do represent the curvature along certain directions on the energy hypersurface; they would be real frequencies if all first derivatives of the energy with respect to the cartesian coordinates were zero at the point of interest. As a result, the rotational frequencies are not exactly zero but nevertheless have absolute values less than about 5 cm^{-1}; mixed rotational and vibrational modes are obtained when the frequencies of a vibrational mode approach zero. The transitional modes are invariably pure, although they emerge from the diagonalization routine in mixed form with the rotational modes when the molecule is at equilibrium because these six frequencies are then accurately zero and are, therefore, all mutually degenerate. In the vicinity of the SCC form and irrespectively of the force field used, the molecular mechanics calculations show that there are just two low-energy vibrations with frequencies less than 150 cm^{-1}. The two modes differ in symmetry with respect to the C_2 axis and can, therefore, be labeled as symmetric and antisymmetric. These two vibrations maintain their general characteristics for ω_{4567} and ω_{8912} from 115 to 135°, as far as the associated displacements in the ring torsional angles are concerned. These displacements in ring torsional angles are essentially independent of the force field and are shown diagrammatically in Figure 5.

The symmetric vibration (Figure 5) corresponds to a distortion that leads in one direction from the SCC to the TCC form with maintenance of the symmetry axis. The antisymmetric vibration leads to a loss of the C_2 axis. Because the latter vibration is real for torsional angles greater than 123.7°, the C_2 symmetry is stable above this value, whereas it is metastable below it, the energy being lowered by a distortion in either of the two possible and equivalent directions. The dependence of the symmetric and antisymmetric low-energy modes on the torsional angles is shown in Figure 6, which also shows that the largest value of dE/dXi (i.e., the first derivative of the energy with respect to a Cartesian coordinate) is a minimum at the inflection point and is connected with the symmetrical mode. At the positive inflection point the antisymmetric vibration is real and has a value of 19.9 cm^{-1}. The molecule in this geometry has seven essentially zero frequencies corresponding to the three translational and the three rotational modes plus the zero-frequency symmetric ring distortion mode. All other frequencies are real, including that of the low-energy antisymmetric ring mode. This establishes firmly the presence of a positive inflection point in the energy hypersurface and shows that there is no energy minimum or even an energy extremum in the vicinity of the SCC form when the Boyd-9 force field is employed. Convergence to this inflection point cannot occur without introducing appropriate constraints.

A single Newton–Raphson iteration starting at ω_{4567} = 124.555°, i.e., essentially at the positive inflection point, without any constraints on the torsional angles and with no limit on the allowed corrections to the coordinates gives a "blown apart" molecule with corrections >100 Å, which is consistent with the expectations of an inflection point. The Hessian matrix of the starting geometry has then a nearly zero eigenvalue corresponding to the symmetric ring distortion mode, so the calculated corrections to the coordinates become divergently large. Iterations starting at other values of ω_{4567} (= ω_{8912}) give rise to an oscillating behavior that sooner or later becomes chaotic and results in large changes in the coordinates. The changes that take place are extremely sensitive to the precise starting geometry, just as in the case of the simple cubic equation in one-dimensional space discussed earlier. The situation is made more complex, however, because the lowest unsymmetrical ring mode is of extremely low frequency and itself becomes zero at 123.7°, so a loss of the C_2 symmetry can occur because of numerical instabilities, even when double-precision arithmetic is used in the FORTRAN calculations. Normally, the Newton–Raphson method maintains any symmetry element existing at the start of the iteration procedure,[8c] as long as the Hessian matrix is not truncated.

The energies obtained by a similar symmetric driving of ω_{4567} and ω_{8912} but with the MM2 instead of the Boyd-9 force field are also given in Figure 4 and show a local energy minimum at ω_{4567} = ω_{8912} = 130.3°, the value expected for the SCC conformation.[25] The curve through the MM2 points has been calculated from a fit of the data between 118 and 135° to a cubic equation namely

$$\text{energy} = 29.07 + 0.0040\Delta\omega^2 + 0.00027\Delta\omega^3$$

with $\Delta\omega = \omega - 130.3$, where 130.3° is the value of ω_{4567} and ω_{8912} for the SCC form. No first-power term has been employed in the fit, and as expected the quadratic term dominates and terms higher than the third are not needed, at least over the limited range of torsional angles used here. Essentially the same parameters are obtained for a fit to the data over a range of 125–135°. Calculations of the frequencies show that the SCC form is a local energy minimum with the MM2 force field, but it has two rather low frequencies (80 and 92 cm^{-1}) corresponding to the symmetric and antisymmetric vibrations, respectively, that are shown in Figure 5 and have already been discussed in connection with the Boyd force field. When ω_{4567} and ω_{8912} are decreased symmetrically, the symmetric vibration first becomes imaginary at about 125.5°, corresponding to a negative inflection point, and below about 125.5° the antisymmetric frequency becomes imaginary; i.e., an unsymmetrical geometry has then a lower energy than does the C_2 geometry. This aspect of the energy hypersurface is consistent with an unsymmetrical transition state for the interconversion of the SCC into the TCC form when the MM2 force field is used (Figure 4). Indeed, as was mentioned in the previous section, the transition state for interconversion of the SCC to the TCC conformation is close to the SCC, but unlike that conformation, it is (slightly) unsymmetrical with torsional angles corresponding to ω_{4567} and ω_{8912} of 122.9 and 125.5°. The transition state for conversion of the SCC to the TCC form involves both the symmetric and the antisymmetric low-energy vibrations, as can be seen from a comparison of the torsional angles in the (SCC–TCC)‡ and SCC geometries (Figure 3) together with the torsional angle displacements induced by these vibrations (Figure 5).

Table I also shows the energies of the global energy minimum, which is the [333] or TBC conformation (D_3 point group symmetry) for all four force fields. The transition states given in Table I have each only one imaginary frequency. As discussed previously,[15] entropy effects are important in controlling the populations of the cyclononane conformation, especially at room temperature or higher.

Discussion

The present work shows that the exploration of a conformational energy surface by methods that ignore all features other than local energy minima does not always give a satisfactory picture. The use of more than one force field can be helpful, but in general it is very desirable to determine the lowest energy transition states linking all pairs of conformations. Even if the latter is not done in a general way, the barrier separating conformations that have the same torsional sign sequence (with corresponding torsional angles of similar magnitudes) should be investigated carefully. A local energy minimum that has a very low frequency vibration is an indication that the energy surface requires careful examination. Ideally, one would like to know the energy hypersurface in terms of closely spaced grid points.

The most important point on the conformational energy surface is no doubt the global minimum. Second in importance are the various local minima that are relatively close in energy to the global minimum. Next are the lowest energy transition states between the above energy minima. Of least significance in most applications are the higher local energy minima, their associated transition states, and positive inflection and other points. The TCTC and SCC forms belong to this latter category, and they do not have the possibly redeeming feature of greater symmetry than the very closely related TCC conformation. Unfortunately, the *true* potential energy hypersurface near the SCC geometry of cyclononane is not known, so whether a positive inflection point or a local energy minimum *actually* occurs in the real molecule is also unknown. Positive inflection points can, of course, be associated with any force field if the geometrical conditions are suitable, and such conditions may not be rare. For example, a positive inflection point may be generated from a double minimum energy surface having a small barrier separating the two minima by introducing a structural perturbation that raises the energy of one of the two potential energy wells above that of the transition state, as is the case with azetidine and related molecules in comparison to cyclobutane.[26]

Raber and co-workers[3] have stated that a local energy minimum that is much higher in energy than the global minimum may become important and possibly even the global energy minimum when substituents are introduced and, therefore, feel that previously ignored conformations such as TCTC, SCC, and the twist boat–boat (TBB, or so-called skewed boat–boat,[3] SBB) in cyclononane have potential importance, even though they have a much higher energy than the global energy minimum. While this is no doubt correct, such a claim can also be made for many other points on the energy hypersurface, including points that are not energy extrema. The conformations of the cycloalkanes, with the exception of cyclopropane and chair cyclohexane, are rather flexible and, therefore, are fairly easily distorted by the presence of substituents, especially when placed unsymmetrically and in sterically hindered positions. Thus, the conformation of a substituted cycloalkane may not resemble very closely that of any

---

(25) Both paths shown in Figure 4 correspond to C_2 symmetrical geometries and must be maxima or minima with respect to any loss of that symmetry.

(26) (a) Dutley, R.; Rauk, A.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 3224–3228. (b) Moriarty, R. M. *Top. Stereochem.* **1974**, *8*, 271–421. (c) Malloy, T. B., Jr.; Bauman, L. E.; Carreira, L. A. *Top. Stereochem.* **1979**, **11**, 97–185.

local energy minimum, whether of high or low energy, in the parent cycloalkane. Indeed, it is possible for conformational transition states to become energy minima when the constraints introduced by the substituents are sufficiently strong, as with a 1,2-epoxide group in a six-membered ring. As an extreme example, consider the substitution of pairs of hydrogens in the boat form of cyclooctane by π bonds. The resulting 1,3,5,7-cyclooctatetraene is a local energy minimum in the boat form, whereas that conformation is a two-dimensional energy hill in cyclooctane. A more pertinent and typical example occurs in the conformational energy hypersurface of cyclohexene,[27] where the half-chair is a local energy minimum and the boat a conformational transition state for enantiomerization of the half-chair. In derivatives of cyclohexene, at least in the crystalline phase, and where both substituent and crystal lattice effects[28] influence the geometry of the molecule, forms (so-called sofa conformations) intermediate between the half-chair and the boat are frequently found.[27]

For cyclononane the semisystematic Dale conformational nomenclature[7,15] has some advantages over that of Hendrickson,[29] which has been used recently by Raber and co-workers.[3] The fact that the TCC, TCTC, and SCC forms all have the same name ([9] or [144]) in the Dale scheme can be an advantage because these three forms are closely related variants of one another. The Dale nomenclature is also particularly appropriate for the [333] conformation, which has D_3 symmetry, whereas Hendrickson's TBC label for this conformation does not indicate its high symmetry and is somewhat misleading because the [234] conformation (called SCB by Raber and co-workers[3]), which was not considered by Hendrickson, is a more natural candidate for the TBC label. Raber and co-workers[3] have published MM2 data on the twist boat-boat (TBB or SBB) conformation of cyclononane, which they claim has been neglected without sufficient justification. However, that conformation has been explicitly considered previously and dismissed because of its very large energy[15] and because it is not a significant intermediate in the interconversions of any of the other much lower energy cyclononane conformations.

Conclusion

Iterations using the full-matrix Newton–Raphson method without any constraints can show chaotic behavior in the vicinity of a positive inflection point. In contrast to the more usual negative inflection point, which acts as a repellent on the hypersurface, the positive type acts as an attractor and can lead to a more or less delayed and violent molecular explosion; a good analogy to the latter is the fatal attraction that a moth has to a flame. Nevertheless, convergence to such a dangerous spot on the hypersurface can be obtained with the Newton–Raphson method by suitably constraining some of the torsional angles and by monitoring the frequency and nature of the low-energy ring distortion modes. In geometries with symmetry, as in the TCC–SCC system in cyclononane, this involves a simple one-dimensional search.

We deduce that the newly discovered TCTC and SCC conformations of cyclononane have limited and questionable conformational significance for cyclononane itself. The current conformational picture of cyclononane has thus changed only a little from that described in 1980.[15] For substituted cyclononanes, many other forms potentially need to be considered apart from the local energy minima of the parent ring.

Extensive searches of the conformational energy hypersurface for local energy minima should, if at all possible, include the barriers separating pairs of conformations. If the search for local energy minima is at the limit of one's computational capacity in a given problem, then a search for transition state becomes out of the question, of course. Progress in searching for transition states and their significance is likely to be much more demanding in computer power than simply a search for local energy minima because it is not sufficient just to locate these saddle points on the energy hypersurface. It is necessary to find out how the local energy minima and the transition states are linked together, and this requires an exploration of a larger part of the hypersurface; fortunately, computing power has been continually increasing so that such a search may become practical. Once the energies and vibrational frequencies for a set of local energy minima and their associated significant transition states have been obtained for one force field, calculations for other force fields should require comparatively little extra time, provided that an appropriate program for dealing with a variety of force fields is available, because the hypersurfaces calculated with different force fields should be closely related in shape.

Acknowledgment. I thank D. J. Raber and W. C. Still for comments on the initial version of the manuscript, R. Anet, D. Farrelly, and M. Kopelevich for reading the manuscript and for valuable suggestions, and B. van de Graaf and J. M. A. Baas for providing the DELPHI program.

Registry No. Cyclononane, 293-55-0.

---

[27] Anet, F. A. L. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH Publishers: New York, 1989; Chapter 1.

[28] Pertsin, A. J.; Kitaigorodsky, A. I. *The Atom-Atom Potential Method*; Springer-Verlag: Berlin, 1987; p 193.

[29] Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7036–7043, 7043–7046, and references therein.