Molecular Geometry. VII. Modes of Interconversion in the Medium Rings[1]

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Abstract: A protocol for examining symmetrical ring conformations of six- to ten-membered cycloalkanes without recourse to models is developed and used to order their modes of interconversion and calculate the energy barriers involved, both for symmetrical modes of transition and for pseudo-rotation. The principles of conformational analysis for substituted rings are also set forth.

In order to construct a system of conformational analysis for cycloalkanes there are three basic kinds of information that must be known: (1) the detailed geometry and relative energy of each ring form which represents an energy minimum in the over-all energy profile of conformational change; (2) the modes of conformational interconversions between these forms and their associated activation energies; and (3) the strain energies associated with placing substituents on each of the various geometrically distinguishable sites of substitution on each of the rings. The great success of conformational analysis of cyclohexane derivatives[3] is founded on just this information in that, first, the energy difference between the chair and twist-boat forms is known to be about 5.5 kcal/mole, favoring the chair, and that no other form represents an energy minimum below these two; second, the barrier to interconversion between them is a little less than 11 kcal/mole and allows interconversion of equatorial and axial substituents; and finally, the only two distinguishable substituent sites, equatorial and axial, differ in energy by about 1.7 kcal/mole when substituted with methyl (and other values when otherwise substituted), with the equatorial site favored.

Larger rings than cyclohexane are more complex, partly because there are more ring forms representing energy minima of comparable magnitude and partly because these are of lower symmetry than the preferred cyclohexane chair (in which all carbons are geometrically identical) and accordingly possess more than two distinguishable substituent sites. The role of the calculations described in the preceding two papers[1] is intended to derive both the needed sets of geometry and associated energies for the possible ring conformations and the energies of methyl substitution at each site on each conformation, for cycloalkanes of six to ten carbons, thus aiming to fill the first and third prerequisite to conformational analysis described above. The present paper deals with developing an orderly system for understanding the modes of interconversion of conformers and with assigning energy values to a number of the barriers, as required by the second prerequisite above.

Since the evidence available to date implicates only symmetrical conformers as candidates for preferred energy minima,[1] the present analysis is largely confined to symmetrical forms although it also affords a framework for subsequent evaluation of asymmetrical forms. The basic symmetry elements are either a plane or a twofold axis of symmetry through the molecule, passing through an atom and the midpoint of the bond opposite in odd-membered rings, and passing either through a pair of opposite atoms or the midpoints of a pair of opposite bonds in even-membered rings. Some ring forms have only one such symmetry element, some have more; the crown forms of even rings of n-carbons, including chair cyclohexane, have $n/2$ planes through atoms and $n/2$ axes through bonds. Each definition of the symmetry element(s) in a ring produces a family of individual rings, one of which will be the energetically preferred representative. The individuals in one family may differ by variations in bond angles, θ, but experience shows[1] that these always tend to minimize around 116° in the medium rings. Much more important as characteristic of a family is the set of dihedral angles, ω, associated with the ring bonds. In families of lower symmetry one dihedral angle is independently variable within the family, resulting in a series of ring forms in one family with changing dihedral angles. However, in the neighborhood of the energy minimum the torsional strain determined by the dihedral angle set changes very little so that it is possible roughly to characterize a family by its characteristic torsional strain. Thus families with planes of symmetry bisecting bonds must have that bond eclipsed ($\omega = 0$) and have high characteristic torsional strain, and the preferred (BCB) form of cyclodecane is less strained than the all-chair form, even though it has more unfavorable nonbonded interactions, because of its substantially lower characteristic torsional strain. In the subsequent discussion reference to a ring form will be taken to mean the lowest energy individual in that family, such as the particular forms tabulated here and in ref 1. Examination of Table II, ref 1, will reveal the large differences in torsional strain characteristic of different ring families.

Characterization of Ring Forms

The fact that ring families are so characterized by their dihedral angles also allows the use of dihedral angles for their definition; in fact a family is definable by its symmetry element(s) and its sequence of signs of dihedral angles. The convention defined previously[4]

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[1] Papers V and VI (preceding papers): J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7036, 7043 (1967).

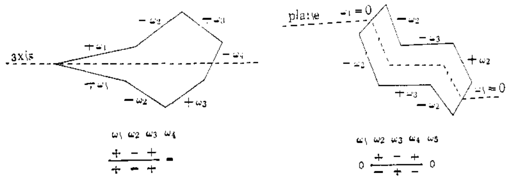
[2] Alfred P. Sloan Foundation Fellow, 1962–1966.

[3] See, for example, the review by E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, John Wiley and Sons, Inc., New York, N. Y., 1965.

[4] J. B. Hendrickson, *J. Am. Chem. Soc.*, **86**, 4854 (1964).

to describe ring families is based on this and allows all possible families to be generated.

In this convention any symmetrical ring is described by a symbol containing a horizontal symmetry line representing the symmetry element (plane or axis) passing through the ring and the cyclic sequence of dihedral-angle signs of the bonds (+, 0, −) arranged around it as in the physical ring. An atom located on the plane or axis is placed arbitrarily at the left side in the symbol. Examples of the symbols and rules for use of the convention are summarized below.



(1) Bonds opposed across the symmetry element have dihedral angles (ω_1, ω_2, etc.) equal in magnitude, and equal in sign across an axis but opposite in sign across a plane of symmetry.

(2) The symbol is equivalent to the physical ring and so may be turned over or around without changing its identity.

(3) When a symmetry element bisects a bond, the sign of its dihedral angle appears at the appropriate end of the symmetry line; it must be zero (*i.e.*, eclipsed) if the symmetry is a plane.

(4) The mirror image of a ring is generated by reversing all signs; thus it may be shown that a ring with a plane is identical with its enantiomer while one with only an axis is not.

(5) Symbols with three or more like signs in sequence are either not real rings or are very highly strained; they appear for consideration only occasionally as transition barriers.

(6) For linear presentation the symbol can be truncated by removal of the signs below the symmetry line and prefixing of A for axis or P for plane to indicate the symmetry element, since the symmetry element implies the signs below the line from those above by rule 1. The signs above the lines are put in parentheses to distinguish them from signs at the ends which represent bonds bisected by the symmetry element. Thus the two examples above are, respectively, A (+ − +)− and P 0(+ − +)0.

With this convention it is not only easy to generate all possible ring forms for consideration but it is also possible to follow the dihedral angle changes in any mode of interconversion between families. The convention symbols corresponding to each family of ring forms are shown next to the perspective drawing and name for each form in Charts I and II, which summarize the symmetrical forms. Conventional ring numbering is shown with the substituent energies and dihedral angle signs in the perspective drawings of the preceding paper.[1]

The nomenclature proposal offered before[4] for rings with a plane of symmetry is used here and extended below to include rings with only axes of symmetry (designated "T"). The proposal in brief extends our recognition of the form (/\/) as characteristic of the chair, this form being the projection of the chair ring onto its plane of symmetry as the other form (_/) is the characteristic projection of the boat. A simple extension of this projection of the ring on its plane of symmetry allows a chair–chair (CC) designation for rings of the form (/\/\) and boat–chair (BC) for (_/‾) or chair–boat (CB) for (‾_/). One more plane-symmetrical ring form for rings 8–10 must be recognized in the projection (_•‾\) which is intermediate between BC and CB forms and is tentatively labeled LC (long-chair) for identification here; a corresponding LB form also exists but is of high energy in the medium rings and so unimportant to our present discussion. In the LC (and LB) form there are six coplanar atoms in the ring (in two groups of three contiguous atoms each).

This nomenclature system is related not only to the projection of a ring onto its plane of symmetry but also to the dihedral-angle convention above, for in the latter, all-chair (C, CC, CCC, etc.) rings have fully alternating + and − dihedral angles, ignoring eclipsed (ω = 0)

Chart I. Viable Rings with Planes of Symmetry

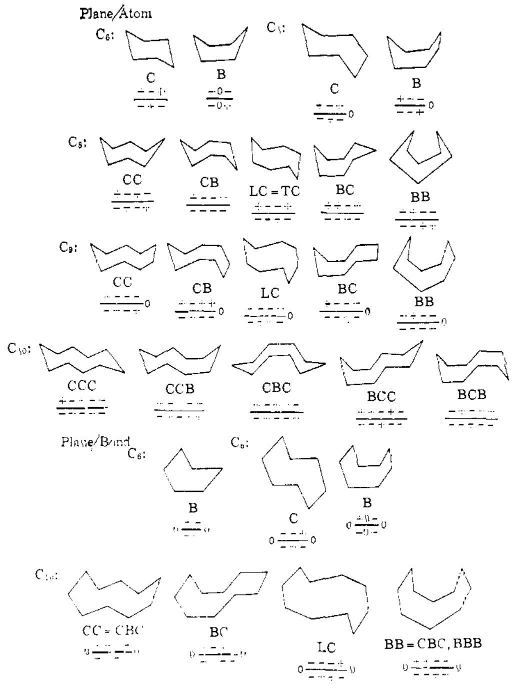
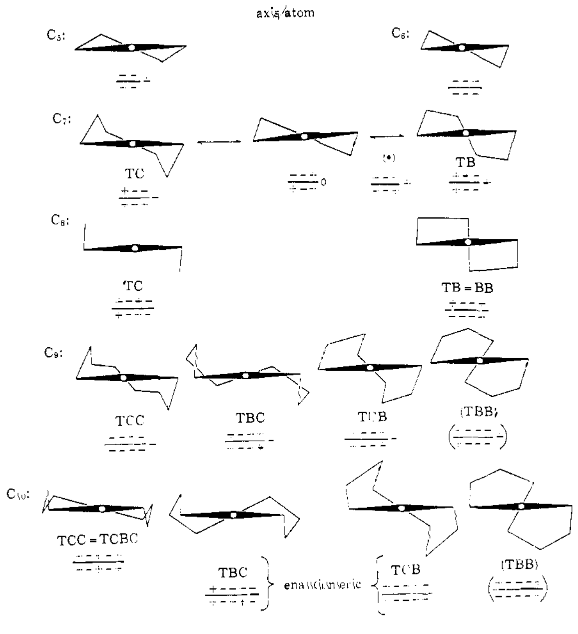
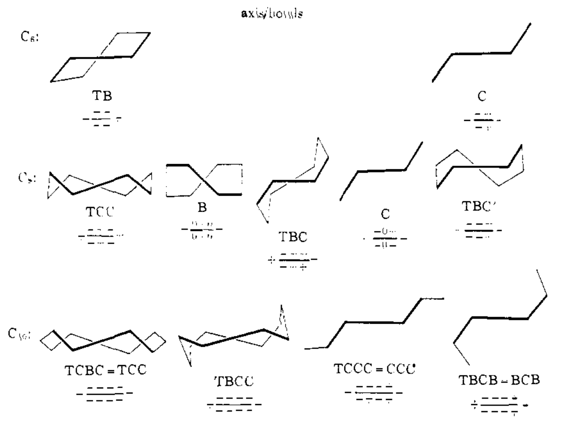


Chart II. Viable Rings with Axes of Symmetry (viewed down the axis)





bonds, and boat regions in a conformation are identified by a pair of like signs together, as can be seen in the charts.

Many of the rings have higher symmetry than merely one plane or axis in their energetically preferred forms; in most cases this consists of two perpendicular elements. For this reason, rings with both plane and axis appear in the charts twice, being shown once with respect to each symmetry element they contain. The possibility of perpendicular symmetry elements is readily discerned by passing a vertical line through the center of the ring convention symbol perpendicular to the primary symmetry line and examining the symmetry on either side of it. In the odd-membered rings it is clearly impossible; in C_8-CC, for example, a perpendicular plane is discernible, in C_{10}-BCB, a perpendicular axis. In linear representation this is also clear, *i.e.*, C_8-CC $\equiv$ P $(+ - + -)$ and C_{10}-BCB $\equiv$ P $(+ + - + +)$. The highest symmetry is found in the crown forms, of which only the cyclohexane chair is shown in the charts; for cyclooctane, the crown is a special case of the CC and TCC forms and in cyclodecane of the CCC form. Forms with perpendicular symmetry elements in the ring plane are summarized below (planes through atoms are symbolized as P/A, through bonds as P/B; axes are analogously A/A and A/B).

C_6:	C	P/A ⊥ A/B
	B	P/A ⊥ P/B
	TB	A/A ⊥ A/B
C_8:	CC	P/A ⊥ P/A
	TCC	A/B ⊥ A/B
	C	P/B ⊥ A/B
	TC≡LC	P/A ⊥ A/A
	B≡TBB	P/B ⊥ P/B
		A/B ⊥ A/B
	TB≡BB	P/A ⊥ P/A
		A/A ⊥ A/A
C_{10}:	CC≡CBC	P/B ⊥ P/A
	TCC≡TCBC	A/B ⊥ A/A
	BB≡BBB	P/B ⊥ P/A
	TBB≡TBBB	A/B ⊥ A/A
	CCC≡TCCC	P/A ⊥ A/B
	BCB≡TBCB	P/A ⊥ A/B
	LC≡TLC	P/B ⊥ A/A

Modes of Interconversion[5]

Symmetrical Mode. The modes of interconversion between ring forms can be characterized as *symmetrical* modes, *asymmetrical* modes, and *pseudo-rotation.* The symmetrical mode of transition is one in which a single symmetry element (plane or axis) is retained throughout a transition from one form or family to another, as in the change from chair to boat cyclohexane maintaining a plane of symmetry, or from the chair to the twist-boat cyclohexane maintaining an axis.[6] In such a symmetrical transition an opposing pair of dihedral angles (as ω_1, ω_2, etc.) must change from its sign(s) in one ring form, through zero, to the opposite sign(s) in the new form. In general it will be seen that the symmetrical mode tends to have a relatively high energy barrier as well as a high requirement of order, or entropy. The details of symmetrical change can be illustrated with cyclohexane: it can be seen from the symbols in Chart I that the chair (P $(+ - +)$) must pass through a form (P $(0 - +)$) with a plane of symmetry and the two bonds labeled $\omega_1 = 0$ in order to change the signs of ω_1 from the chair to the boat forms. A program can be set up to calculate this energy profile as a function of the change in the angle (ϕ) between the plane of atoms 1–2–6 and atoms 2–3–5–6. This is shown on the left in Figure 1 and the energy calculation shows that the transition does not in fact occur exactly at the form with $\omega_1 = 0$ which has five coplanar carbons but rather slightly farther toward the boat form with $\omega_1 = -6.7°$. (The forms discussed here are tabulated in detail in Tables I and II.) The energy of the transition is 11.3 kcal/mole above the chair form.

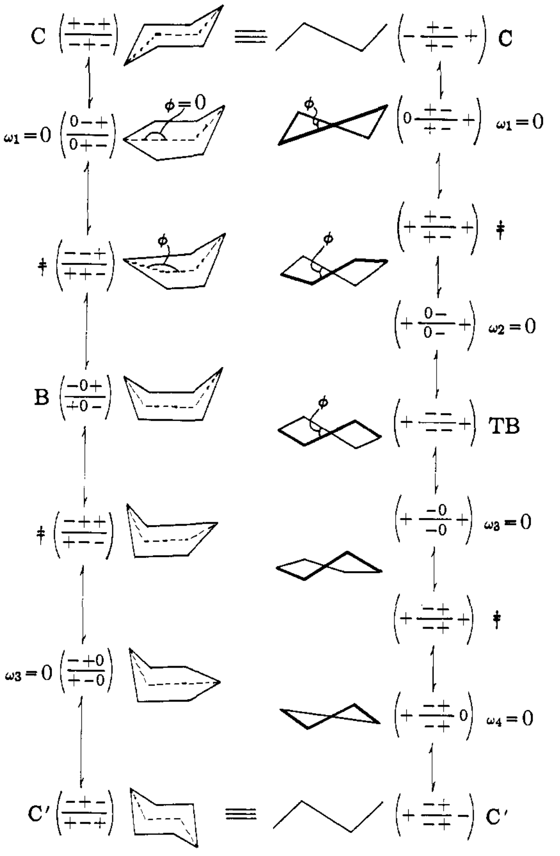


Figure 1. Symmetrical mode interconversions in cyclohexane.

A somewhat lower barrier exists in the symmetrical mode which maintains an axis of symmetry; in this

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(5) In the charts presented here the use of a half-headed double arrow has been introduced as an indication of conformational change. The rationale for this usage is that conformational change may be regarded as somewhat intermediate between resonance and chemical equilibrium (or tautomerism) and may be accorded an intermediate symbol: ↔, resonance (no movement of nuclei or breaking of bonds); ⇁, conformational change (no breaking of bonds); ⇆, equilibrium or tautomerism.

(6) (a) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961); (b) J. B. Hendrickson and K. S. Pitzer, *Nature*, **212**, 749 (1966).

Table I. Geometrical Definition of Cycloalkane Transitions

Ring[b]	Bond angles,[a] deg θ_1	θ_2	θ_3	θ_4	θ_5	θ_6	θ_7	θ_8	θ_9	θ_{10}
C_6: C/TB(a)	119	114.8	110	110	114.8	119				
C/TB(b)‡	119	114.6	110	110	114.6	119				
C/TB(c)	119	112.6	110	110	112.6	119				
C/B(d)	120	117.0	112	109	112	117.0				
C/B(e)‡	120	116.8	112	109	112	116.8				
C_7: TC/TB(a)	112	112	116.6	121	121	116.6	112			
TC/TB(b)‡	112	112	117.4	121	121	117.4	112			
TC/TB(c)	112	112	115.9	118	118	115.9	112			
C_8: BC/TC‡	118	118	118	118	118	118	118	118		
TCC($\omega_1 = 0$)	119	116	116	119	119	116	116	119		
C_{10}: BCB(ψ)‡ ≡ LC[c]	118	118	118	118	118	118	118	118	118	118

Ring[b]	Dihedral angles,[a] deg ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	ω_8	ω_9	ω_{10}
C_6: C/TB(a)	0	16.6	−49.1	65.8	−49.1	16.6				
C/TB(b)‡	12.0	8.0	−46.8	67.0	−46.8	8.0				
C/TB(c)	24.0	0	−45.3	70.5	−45.3	0				
C/B(d)	0	30.9	−62.0	62.0	−30.9	0				
C/B(e)‡	6.7	27.5	−62.0	62.0	−27.5	−6.7				
C_7: TC/TB(a)	45.1	−89.0	36.9	0	36.9	−89.0	45.1			
TC/TB(b)‡	45.6	−86.2	26.8	14.0	26.8	−86.2	45.6			
TC/TB(c)	47.5	−77.3	0	52.0	0	−77.3	47.5			
C_8: BC/TC‡	98.0	−6.3	−64.0	98.0	−98.0	64.0	6.3	−98.0		
TCC($\omega_1 = 0$)	0	−50.6	120.2	−50.6	0	−50.6	120.2	−50.6		
C_{10}: BCB(ψ)‡ ≡ LC[c]	0	112.2	−72.7	−72.7	112.2	0	−112.2	72.7	72.7	−112.2

[a] Ring numbering follows the convention in the text and in Table I, ref 1. [b] Independently variable bond angles were varied by 1° increments and are shown with no decimal; the others, with one decimal place shown, are calculated. [c] Bond angles θ not varied (see Appendix).

Table II. Energies of Cycloalkane Transitions[a]

Ring	E_θ	E_t	E_{HH}	E_{HC}	E_{CC}	E_{NB}	ΣE	E_0	ΔE
C_6: C/TB(a)	2.80	7.49	2.11	−0.99	0.13	1.35	11.54	10.4	10.4
C/TB(b)‡	2.75	8.16	2.15	−0.98	0.06	1.19	12.10	11.0	11.0
C/TB(c)	2.45	7.97	2.18	−0.93	0.15	1.40	11.82	10.7	10.7
C/B(d)	2.84	7.84	2.25	−0.97	0.15	1.43	12.11	11.0	11.0
C/B(e)‡	2.76	8.14	2.27	−0.97	0.17	1.47	12.38	11.3	11.3
C_7: TC/TB(a)	4.70	7.64	2.73	−0.70	−0.05	1.98	14.32	13.2	7.2
TC/TB(b)‡	5.07	8.25	2.72	−0.80	−0.04	1.88	15.20	14.1	8.1
TC/TB(c)	2.36	6.98	2.69	−0.63	0.13	2.20	11.53	10.4	4.4
C_8: BC/TC‡	6.62	12.67	4.47	−0.39	−0.66	3.41	22.71	21.6	11.6
TCC($\omega_1 = 0$)	5.98	11.23	5.64	−0.01	−0.36	5.27	22.48	21.4	11.4
C_{10}: BCB(ψ)‡ ≡ LC[b]	8.28	16.59	14.88	0.51	−1.33	14.05	38.93	37.8	24.6

[a] The rings are those listed in Table I. Energy designations are the same as in the comparable Table II, ref 1, preceding, which contains the rings these transitions interrelate. [b] Bond angles, $\theta = 118°$, not varied.

mode first one bond through which the axis passes goes through $\omega = 0$, then the two adjacent bonds must also pass through $\omega = 0$. If the angle ϕ between the two bonds bisected by the axis (Figure 1) is followed as a measure of the course of the transition, the barrier is found to occur at a form between these two intermediates with eclipsed ($\omega = 0$) bonds rather than at one of them, as previously thought.[7] The symbol denoting the transition barrier (Figure 1) is in fact one of those with three like signs in sequence and as such is expected to have a high energy; the geometric detail is listed in Table I. It is this barrier which corresponds to the experimental value of 10.8 kcal/mole[8] for the cyclohexane transition.

The situation in cycloheptane is similar in that the lower barrier occurs in the symmetrical transition, maintaining the axis of symmetry, from the preferred twist-chair (TC) form to the twist-boat (TB). The energy profile can be calculated as before and exhibits a maximum energy of 8.1 kcal/mole between the comparable $\omega_4 = 0$ and subsequent $\omega_3 = 0$ intermediates en route. Again, the barrier is symbolized with three (+) signs in sequence (A (+ − +)+) and its position is signalized by ‡ in Chart II. Inasmuch as the chair and boat forms of cycloheptane do not themselves represent energy minima (are rather maxima; see below), their interconversion *via* the higher energy plane-symmetry barrier is presumably not an important process.

The symmetrical conversion of one P/A (plane through atoms) ring to another by passage of the two ω_1 bonds through an eclipsed conformation with the plane of symmetry maintained, as in C_6: C ⇌ B, above, is a higher energy process with larger rings owing to more severe H–H interactions in that transition. In cyclooctane (*cf.* CC ⇌ BC ⇌ BB) this form is estimated as a barrier of at least 20 kcal/mole above the BC form; in cyclononane and cyclodecane it is probably as large. There are more symmetrical transitions possible in these larger rings, however, of the form symbolized by passage of BC ⇌ LC ⇌ CB in cyclooctane and cyclononane and occurring by changes in the signs of ω_2 and ω_3 (the middle dihedral angles).

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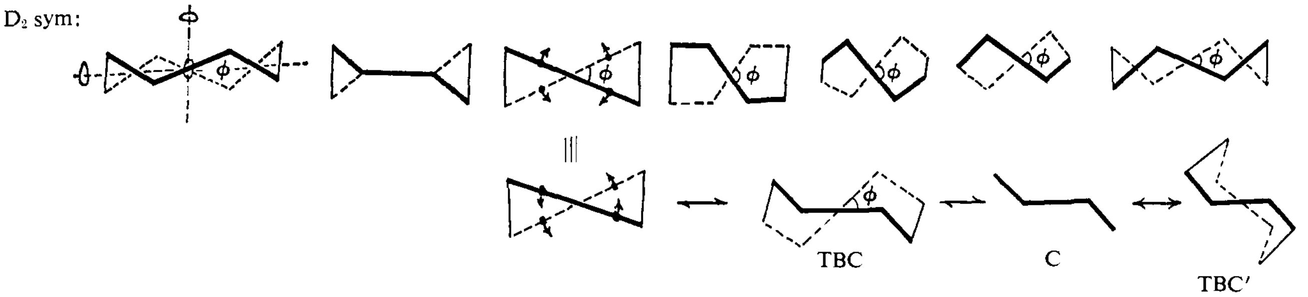
(7) This observation was independently made by Dr. H. Friebolin and his colleagues at Freiburg.

(8) F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967), and other work discussed therein.

Chart III. Cyclooctane Families with Axes through Bonds

	Crown ↔	$E_{\min}$ ↔	$\phi = 0$ ↔	$\omega_1 = 0$ ↔	Boat ($\omega_2 = 0$) ↔	$\omega_3 = 0$ ↔	$\phi' = 0$ ↔	$E_{\min}$ ↔	Crown
ϕ	−47	−15	0	46	100	98	81	72	47
ω_1	88	56	43	0	−74	−120	−120	−115	−88
ω_2	−88	−82	−76	−51	0	51	76	82	88
ω_3	88	115	120	120	74	0	−43	−56	−88
ϕ'	−47	−72	−81	−98	−100	−46	0	15	47
ΔE	2.8	1.7	2.8	11.4	10.3	11.4	2.8	1.7	2.8



The crown form of cyclooctane can be extended in a symmetrical mode either along one of its planes of symmetry into the CC forms (P (+ − + −)) or along one of its axes into the forms with D$_2$ symmetry (A + (− + −) +; two perpendicular axes in the ring and a third perpendicular to those and to the ring), which is labeled the TCC form in the pseudo-rotation discussion below; this conformation has no plane of symmetry. As with the symmetrical mode interconversions above, the passage of the crown, maintaining an axis of symmetry, through a succession of D$_2$ forms can be followed by the dihedral angle (ϕ), designated in Chart III, between the front and rear bonds and the symmetry axis which bisects them; an analogous dihedral angle (ϕ') is defined by the second axis perpendicular to the ω_3 bonds. In the crown the angle $\phi = -47°$ and passes to −15° in the most stable form (TCC), then on, through $\phi = 0°$ to a form with $\omega_1 = 0$ and $\phi = +44°$ (A 0(− + −)0). Bond angles tend to be around 116° except within the eclipsed bond where they characteristically rise to higher values (119° here; see Table I). The $\omega_1 = 0$ form represents the energy maximum (9.7 kcal/mole above the minimum TCC form) on this symmetrical route and beyond it the ring passes in the D$_2$ form to the boat (B) ring (A −(0 + 0)−) at an energy of 8.6 kcal/mole above the TCC. The boat ring is more commonly recognized by its two perpendicular planes of symmetry (P 0(+ 0 −)0) as seen in Chart I than by its three perpendicular axes (D$_2$) as portrayed here (Chart III), with a characteristic $\phi = +100°$. Continuing this mode of symmetrical conversion, maintaining the perpendicular axes, leads back to another TCC form (and crown) which is the mirror image of the original one; in the reversion to the second TCC form the two perpendicular axes (and ϕ and ϕ') have exchanged places.

Another symmetrical motion of the $\omega_1 = 0$ form retains the primary axis and destroys the perpendicular ones, leading as shown in Chart III to a family of forms, described below as TBC, having one axis only, the most stable form occurring at $\phi = 28°$ with an energy only very slightly higher than the TCC form (Table II). Continuing the symmetrical change carries this TBC form through the chair (C), $\phi = 0°$, an energy maximum 6.3 kcal/mole above the best TBC form, and then into a mirror-image (TBC′) form, and finally back to a TCC form, *via* the $\omega_1 = 0$ barrier.

Pseudo-Rotation. Pseudo-rotation (ψ) is a mode of conformational interconversion characteristically exhibiting a much lower energy barrier than that of the symmetrical mode. In the symmetrical mode most of the deformation occurs at one pair of bonds, passing from positive through zero to negative dihedral angles; this requires a high torsional strain as well as substantial bond-angle enlargement in the region of deformation. In pseudo-rotation all the bonds change dihedral angles, the deformation is roughly equalized around the ring, and only negligible if any bond-angle changes are necessary, with the result that pseudo-rotation barriers are relatively small. With Dreiding models of cycloheptane or boat cyclohexane the only conformational change possible without bending bond angles is pseudo-rotation, which gives these rings their sense of being "flexible."

Pseudo-rotation may be described as the passage of a ring with a plane of symmetry through an atom to one with an axis of symmetry bisecting the bond adjacent to that atom, and *vice versa.* Designating rings with planes through atoms or bonds as P/A and P/B, respectively, and those with axes as A/A and A/B similarly, pseudo-rotation occurs between P/A ↔ A/B or P/B ↔ P/A. The two ring forms of opposite symmetry interconverting by pseudo-rotation may be called *pseudo-rotation partners.* In odd-membered rings planes or axes necessarily pass through an atom at one side of the ring and a bond at the other but the rule is the same and is illustrated in Figure 2 for a cyclooctane and a cycloheptane. In Figure 2 the ring is shown as pseudo-rotating clockwise relative to the interchanging symmetry element (P → A → P → A → etc.). In the course of pseudo-rotation the dihedral angles of all bonds change smoothly from their values in the first (*e.g.*, plane) symmetrical ring to those which obtain in the next (*e.g.*, axis) symmetrical ring, the ring itself either being asymmetrical during the continuum of dihedral angle changes carrying it from one symmetrical form to the next or retaining an axis *perpendicular* to the ring.

An important feature of pseudo-rotation is that alternate plane rings in the sequence appear as their mirror images and alternate axis rings do the same.[9] Mirror-image rings (or positions on rings) are designated subsequently with primes (*cf.* TBC and TBC′ in

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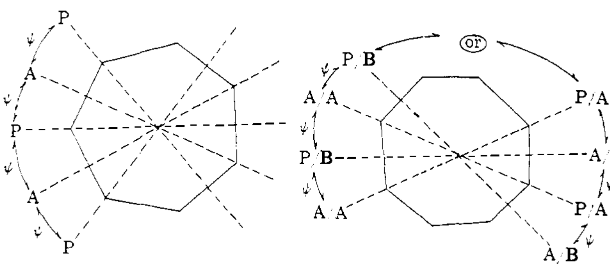
[9] Rings with a plane of symmetry of course are identical with their mirror images, but this is no longer true when they are substituted.



odd: one choice even: two choices

Figure 2. Pseudo-rotation in odd- and even-membered rings.

Chart III and the notation in Figure 4). The sequence of rings, of dihedral angles for a designated bond, or of positions of substituents is called the pseudo-rotation *itinerary*. It can easily be seen that every ring with a plane or axis of symmetry is capable of pseudo-rotation to a partner with the opposite symmetry, with the exception of the crown rings which contain in one ring the alternating axes and planes which would constitute a course of pseudo-rotation. Thus the familiar chair (crown) cyclohexane is one of the few rings which can undergo no pseudo-rotation.

A simple and useful protocol for nomenclature arises from this interrelation of rings with planes and axes of symmetry as pseudo-rotation partners. The rings with a plane of symmetry are readily named by the boat–chair convention above and their pseudo-rotation partners, the rings with axes of symmetry, may then be named the "twist" (T) counterparts, following the existing usage of twist-boat (TB) cyclohexane[10] to denote the conformation with axes of symmetry which is the pseudo-rotation partner of the boat (B) form of cyclohexane. This procedure not only provides simple names for all rings but groups them according to their natural relationships of interconversion. For example, in cyclooctane the D_2 form is the pseudo-rotation partner of the CC conformer and is named the TCC form, while the TBC form is the twist counterpart of the boat–chair (BC); the "long-chair" form is in fact the partner of the chair (C) and so is named the TC, while the BB and B forms are also pseudo-rotation partners (hence, BB ≡ TB and B ≡ TBB).

The ± convention outlined above for symbolizing symmetrical rings allows the generation of pseudo-rotation partners simply by moving each dihedral angle sign one position clockwise or counterclockwise and then converting such signs as are not symmetrically correct for the new symmetry, and in such wise that no three like signs appear in sequence if possible. Selected examples of this generation of pseudo-rotation partners are shown in Figure 3. The symbols show implicitly the nature of the symmetry element (P/A, A/B, etc.), and the alternation in the sequence of mirror image rings of the same symmetry (*cf.*, C and C′), by the reversed signs in the symbol conventions in Figure 4. The coexistence in one ring, occurring only in cyclodecane forms, of perpendicular P/A and A/B (in the CCC and BCB rings) or P/B and A/A (in the "LC" ring) implies that the two pseudo-rotation partners have the same conformation. Thus the stable BCB-cyclodecane can pseudo-rotate with itself, a situation to be distinguished from that of the crown rings (which exhibit no pseudo-rotation) since the bond dihedral angles do change in these cyclodecane cases, the ω_1 bond in one BCB ring going on to an ω_2 bond in the next BCB ring in the pseudo-rotation itinerary.

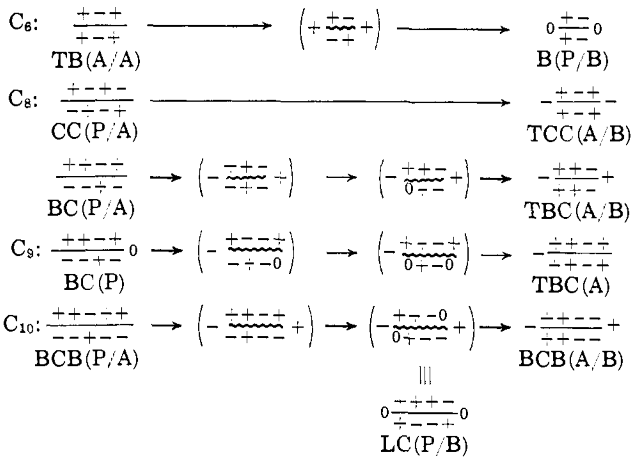


Figure 3. Examples of ring symbols in pseudo-rotation.

Thus the symbol convention allows the generation of the course of pseudo-rotation as well as the designation of which forms are pseudo-rotation partners, without recourse to the use of models. The steps in constructing a pseudo-rotation itinerary are given below and exemplified in Figure 4 for the chair–twist-chair forms of cycloheptane. Following the derivation of the successive ring symbols for the pseudo-rotation itinerary as above, a sequence of rings is drawn with the proper symmetry elements through them (four rings are enough to encompass each plane and axis case and their mirror images), and numbered clockwise from the atom on the symmetry element, identical sites being given identical numbers (across an axis) and mirror-image positions (as across a plane) labeled with primed numbers.[11] The dihedral angles (ω) are likewise numbered and given the sign called for by the ring symbol.[11]

Next, the pattern of axial and equatorial substituent positions at each atom can also be derived from the ring symbol. Looking down on the ring let the axial position be indicated by a solid bond if it is up, a dotted bond if down (and no indication at an atom lying on an axis, which will have only isoclinal[1] substituents). Such a pattern of axial sites can be written analogously to the ring symbol convention with + for an axial position up and − for an axial position down (0 to indicate an axis carbon with isoclinal sites only). It is found, in fact, that *the ring symbol, of dihedral angle signs, for any ring is the axial substituent pattern for its pseudo-rotation partner* directly following it in the itinerary.[12] This can be seen in Figure 4, it being recognized that the itinerary continues from the fourth (TC′) ring on to the first (C) again and so repeats.

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(10) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(11) The placement of atom 1 at left or right is determined by the symbol convention for the ring, which directs the placing of the several bonds relative to the symmetry element. If no atom appears on the (primary) symmetry element, the first atom clockwise from it at the left is labeled 1, and the bond on the symmetry element is labeled ω_1. The numbering convention is shown in the examples of the preceding paper.[1]

(12) A corollary of this rule is that at any carbon on a given ring the substituent which is up will be equatorial if it lies between bond dihedrals which are +− (or +0 or 0−), reading clockwise, and axial if between −+ (or −0 or 0+). Flanked by bonds with dihedral angles of the same sign, both substituents on a carbon are of equal (and equatorial or strain-free) energy; these include isoclinal substituents and those on C-2 in both C_8-BC and C_{10}-BCB and like cases.[1]

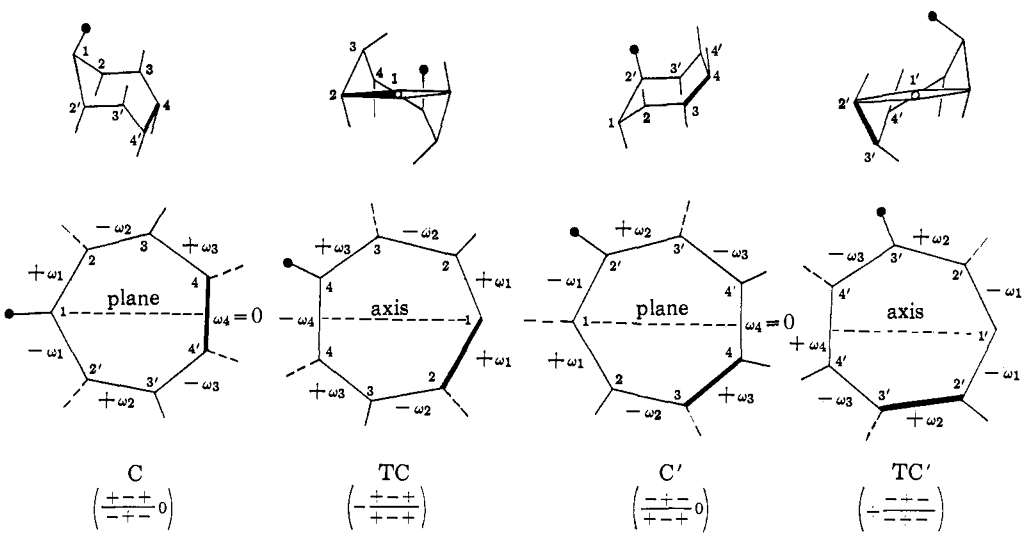

Figure 4. Pseudo-rotation itinerary for chair cycloheptane.

This construction can now be used to guide accurately the building of the corresponding molecular models (perspective drawings of the four rings and their axial positions are included in Figure 4 to show this) and also to see the complete detailed itinerary for any bond or substituent. The clockwise rotation of dihedral angle signs which makes up the symbol convention expressing pseudo-rotation is of course a reflection of the physical ring so that any given bond can be followed from one conformer to the next in its itinerary, as may be seen in the bond, designated by the heavy line in Figure 4, as it passes from ring to ring. Similarly the itinerary of a substituent, taken in the example as the substituent which is up at C-1 in the chair and labeled with a dot, can be followed as shown from ring to ring. The pseudo-rotation itinerary for this substituent will therefore be: 1a/C → 4a/TC → 2′a/C′ → 3′a/TC′ → 3a/C → 2a/TC → 4′a/C′ → 1′ (isoclinal)/TC′ → 4′e/C → 2e/TC → etc. In pseudo-rotation it should be noted that a bond changes sign when its itinerary carries it through a ring with a plane bisecting it (*cf.*, $+\omega_1$/TC → ($\omega_4 = 0$)/C′ → $-\omega_1$/TC′) and that a substituent passes from axial to isoclinal to equatorial or the reverse (*cf.*, 4e/C → 1/TC → 4a/C′).

Thus it will be clear that a pseudo-rotation itinerary is a closed cycle, that a substituent will pass through a sequence of positions as the ring to which it is attached pseudo-rotates, until it returns to its original position, and that a given ring bond will do the same with respect to the value of its dihedral angle. In most pseudo-rotation cycles (as in C/TC cycloheptane, Figure 4) the itinerary of substituent positions includes all possible positions, but in a few rings this is not the case. In the C_8CC/TCC itinerary, for example, only equatorial positions are included in one pseudo-rotation cycle and axial positions in another; for an equatorial substituent to become axial therefore requires a different kind of interconversion such as one in the symmetrical mode, as from CC → BC → TC → BC → CC. The number of positions (symmetrical rings) on the pseudo-rotation itinerary of a substituent is equal to $4n/m$ where n = ring size and m = number of symmetry elements (plane or axis) passing through atoms or bonds in the ring (m is the same for either pseudo-rotation partner). The number of positions for cyclohexane (B/TB) is therefore $4 \times {}^6/_2 = 12$ and equals the total number of possible positions in both boat and twist-boat rings. In C/TC cycloheptane it is 28, also the total possible number of distinguishable positions (mirror images counted separately). In CC/TCC, BC/TCC, or BC/TBC cyclooctanes, however, there are two independent pseudo-rotation cycles, each containing half the total number of places calculated ($4n/m = 16$). This arises in cases with no axis carbon to act as an axial–equatorial crossover for substituents and is discussed further below.

It has been assumed hitherto that in the course of pseudo-rotation, the energy profile is a simple sinusoidal one with maxima and minima represented by the two alternating (plane and axis) symmetrical forms. In cyclopentane, however, it is regarded as essentially a straight line, the two symmetrical forms being of equal energy.[6a,13] Thus, in order to test the sine-wave assumption, it was necessary to determine the energy profile of pseudo-rotation in our several cases by calculation, in particular of $E = f(\psi)$ where ψ is a hypothetical angle representing the course of pseudo-rotation and related to the geometry of the pseudo-rotating ring. This can be done by setting up a curve of sin $\omega = f(\psi)$ where ω is a ring dihedral passing through all of its possible values in the course of pseudo-rotation. The procedure is detailed in the Appendix and allows the asymmetrical intermediate ring forms and energies in pseudo-rotation to be examined. In fact these ring forms are not always asymmetrical, for in rings with an axis *perpendicular* to the ring *this* axis is maintained during pseudo-rotation, as in the case of C_6-B/TB, C_8-CC/TCC, and B/BB. The higher symmetry (D_{2d}) of the latter pair indeed is maintained in the more general S_4 symmetry throughout its pseudo-rotation itinerary.

The results of this search are to confirm that the pseudo-rotation is usually a simple sine curve with no maxima or minima other than at the symmetric forms, the form with a plane of symmetry usually being the maximum (C_6-B, C_7-C, C_8-CC), that with an axis the minimum (C_6-TB, C_7-TC, C_8-TCC), as summarized in

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(13) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959).

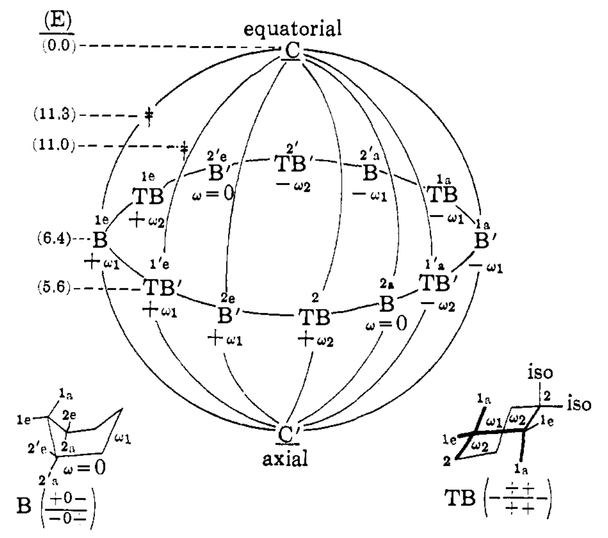


Figure 5. Map of cyclohexane interconversions (ring energies in parentheses).

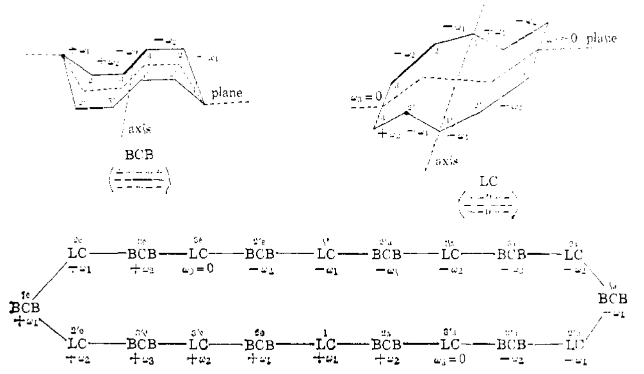
Table III. In two cases (C_7-B/TB and C_8-BC/TBC) the procedure outlined in the Appendix did not produce closed rings in the intermediate asymmetrical forms; in the cycloheptane boat family minor adjustments were adequate to show that no intermediate maxima or minima occurred between the B and TB conformers, but in the important BC/TBC pseudo-rotation of cyclooctane it was not possible to be certain of this. The data of Table III make it clear that pseudo-rotation is a viable, low-barrier transition in all cases except that of cyclodecane, discussed in more detail below, and to a lesser extent that of the B/BB forms of cyclooctane. In the latter case, uniquely, there is a minimum on the pseudo-rotation itinerary, and this is the pseudo-rotation family with the highest symmetry (S_4) throughout the cycle. The preferred S_4 form, midway between B and BB, is the "twist-tub" conformation of Roberts[14] and is detailed in Tables I and II, ref 1.

Table III. Summary of Pseudo-Rotation Energies

Ring	Plane	Int	Axis	ΔE
C_6-B/TB	6.4	...	5.6	0.8
C_7-C/TC	1.4	...	0.0	1.4
C_7-B/TB	2.7	...	2.4	0.3
C_8-CC/TCC	1.9	...	1.7	0.2
C_8-BC/TBC	0.0	?	2.0	2.0?
C_8-BB/B	1.4(BB)	0.9(S_4)	10.3(B)	9.4
C_8-TC/C	8.7(TC)	...	8.3(C)	0.4
C_{10}-BCB/LC	0.0(BCB)	...	24.6(LC)	24.6

A unique situation was uncovered in this examination of the stable BCB form of cyclodecane which pseudo-rotates with itself. It is the only ring (apart from the nonviable BB≡BBB cyclodecanes) in which *two* dihedral angle signs change during pseudo-rotation between two plane and axis forms. Since the BCB conformation has an axis of symmetry perpendicular to the ring and maintained in pseudo-rotation (like C_6-B/TB and C_8-CC/TCC), these two dihedrals (ω_2 in the original BCB) go to zero together and create an intermediate on the pseudo-rotation course between BCB forms which is in fact the LC conformer with a plane through those two eclipsed bonds (and a perpendicular axis also). The intermediacy of the LC form was shown by the equation (see Appendix) generating the geometry of conformers between one BCB ring and the next. This is illustrated in the symbols of Figure 3. This special situation arises from the fact that both the BCB and LC rings contain mutually perpendicular and opposite symmetry elements, and while they are not pseudo-rotation partners as generated by the rules above (since the changing symmetry element does not simply move to the next ring position in BCB → LC), nevertheless they do alternate in the course of pseudo-rotation. The itinerary is plotted in Chart IV, the figures showing how the change occurs (the dotted atom and solid bond are the same in each ring). The energy barrier in this pseudo-rotation is, however, relatively very large (24.6 kcal/mole) and implies that this is a very sluggish transition at room temperature, unlike all the other pseudo-rotation cycles summarized in Table III.

Chart IV. Pseudo-rotation of Cyclodecanes: BCB and LC



Interconversion Maps. These two modes of conformational interconversion (pseudo-rotation itineraries plus symmetrical changes) may now be incorporated into a map of pathways for a given substituted cycloalkane. Such a map must be three dimensional, however, and is best seen as a globe, that for cyclohexane being reproduced in Figure 5. The symmetrical changes of Figure 1 are vertical (longitudinal) and the pseudo-rotation cycle is shown as horizontal (latitudinal). Thus an equatorially substituted cyclohexane lies at the north pole and may change symmetrically by retaining any of its six planes or axes and so proceed down a longitudinal path, over a barrier (‡), to the B or TB form at the equator, where it may pseudo-rotate freely among the B/TB forms (around the globe) or pass on over another symmetrical barrier (longitudinally) to the axially substituted chair conformation, at the south pole. The boat form is the energy maximum and the twist-boat the minimum on the pseudo-rotation itinerary so that the barrier to pseudo-rotation is very low (6.4–5.6 = 0.8 kcal/mole; Table III). In principle pseudo-rotation itineraries gird the globe at all latitudes, interconnecting the symmetrical barrier forms above and below the equator, but these pathways may be disregarded since they are of high energy and contain no over-all energy minima. The surface of the globe may be seen as an energy surface with energy profiles for every pathway (energies are being plotted as radial coordinates out from the

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(14) J. D. Roberts, Chemical Society Centenary Lecture, 1966; *cf. Chem. Brit.*, 529 (1966).

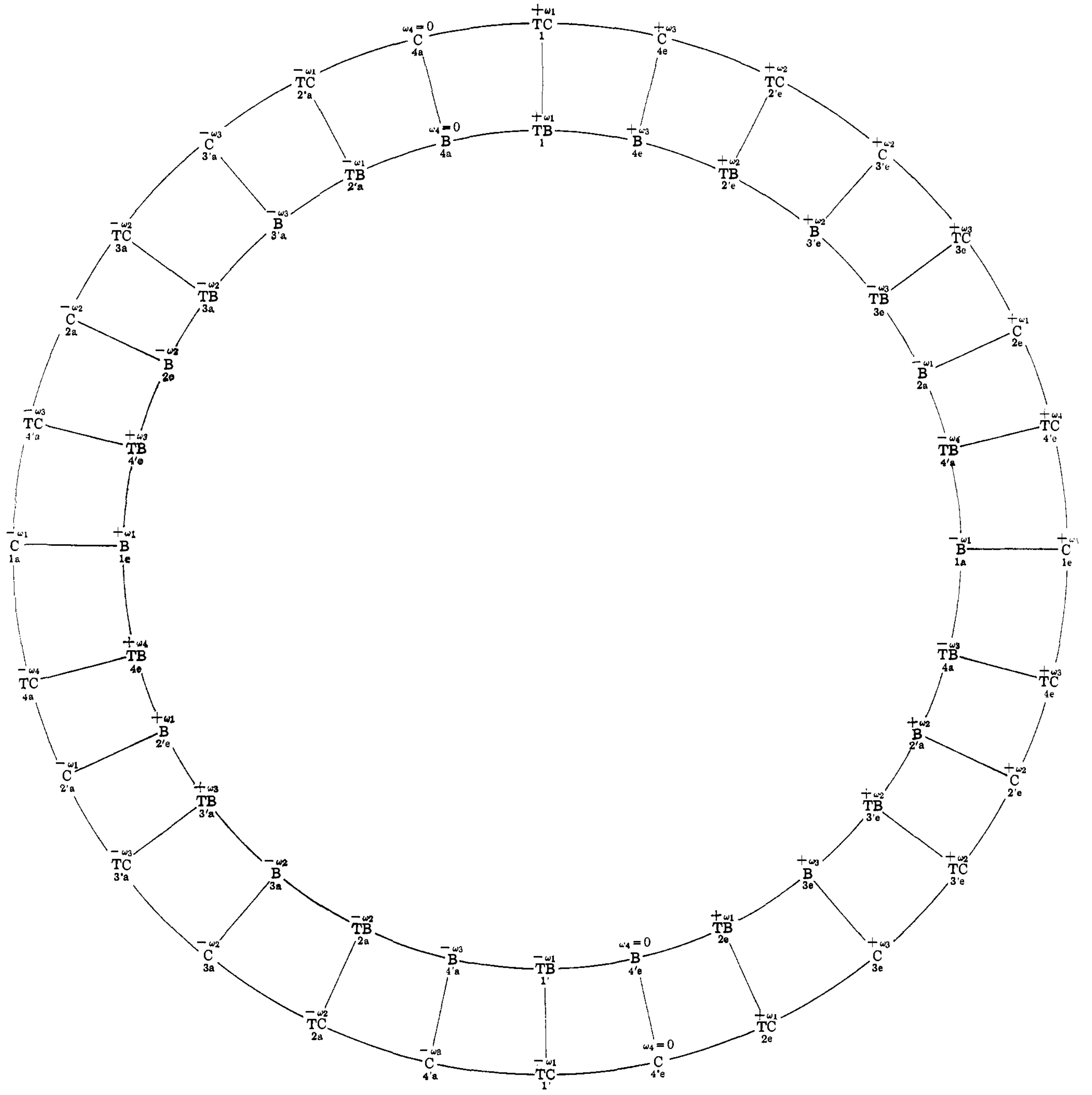

Figure 6. Map of cycloheptane interconversions.

globe surface like altitudes on the earth's surface); energies of significant points are marked in parentheses in Figure 5. The only over-all energy minima (underlined) are found at the two chair positions (poles) and the six TB positions on the equator. The boat forms represent saddles in being maxima on the horizontal pseudo-rotation itinerary but minima on the longitudinal pathways between the two barriers leading to the two chair rings.

A similar globe may be constructed for substituted cycloheptane; this has no high-symmetry form analogous to chair cyclohexane for the poles of the globe and consequently the only viable pathways are the two pseudo-rotation itineraries (C/TC and B/TB), shown as circles, and their symmetrical interconversions, shown as radial lines interconnecting them. The over-all map is then that of Figure 6 (properly representing two latitudes on a globe with its polar caps removed) with energy minima at the TC and TB positions and saddles at the C and B, as with cyclohexane.[15] The symmetrical-mode interconversions may be simplified by the general rule that exchanges between the two cycles always occur between identically labeled substituents except for 1e ⟷ 1a and 2e ⟷ 2a between C and B and 4e ⟷ 4a between TC and TB, the latter representing the more common and lower energy interchanges.

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(15) A unique feature of cycloheptane is the pseudo-rotation of its B/TB forms. The itinerary shown in Figure 6 was generated according to the rules outlined above and is physically correct, but in fact *between* each place (B or TB) listed on this itinerary the ring passes twice through symmetrical forms. The different itinerary listed in ref 6a is the more closely detailed one and it will be seen that every third place on it represents the sequence of Figure 6. Among the medium rings this abnormal itinerary is only found in cycloheptane B/TB.

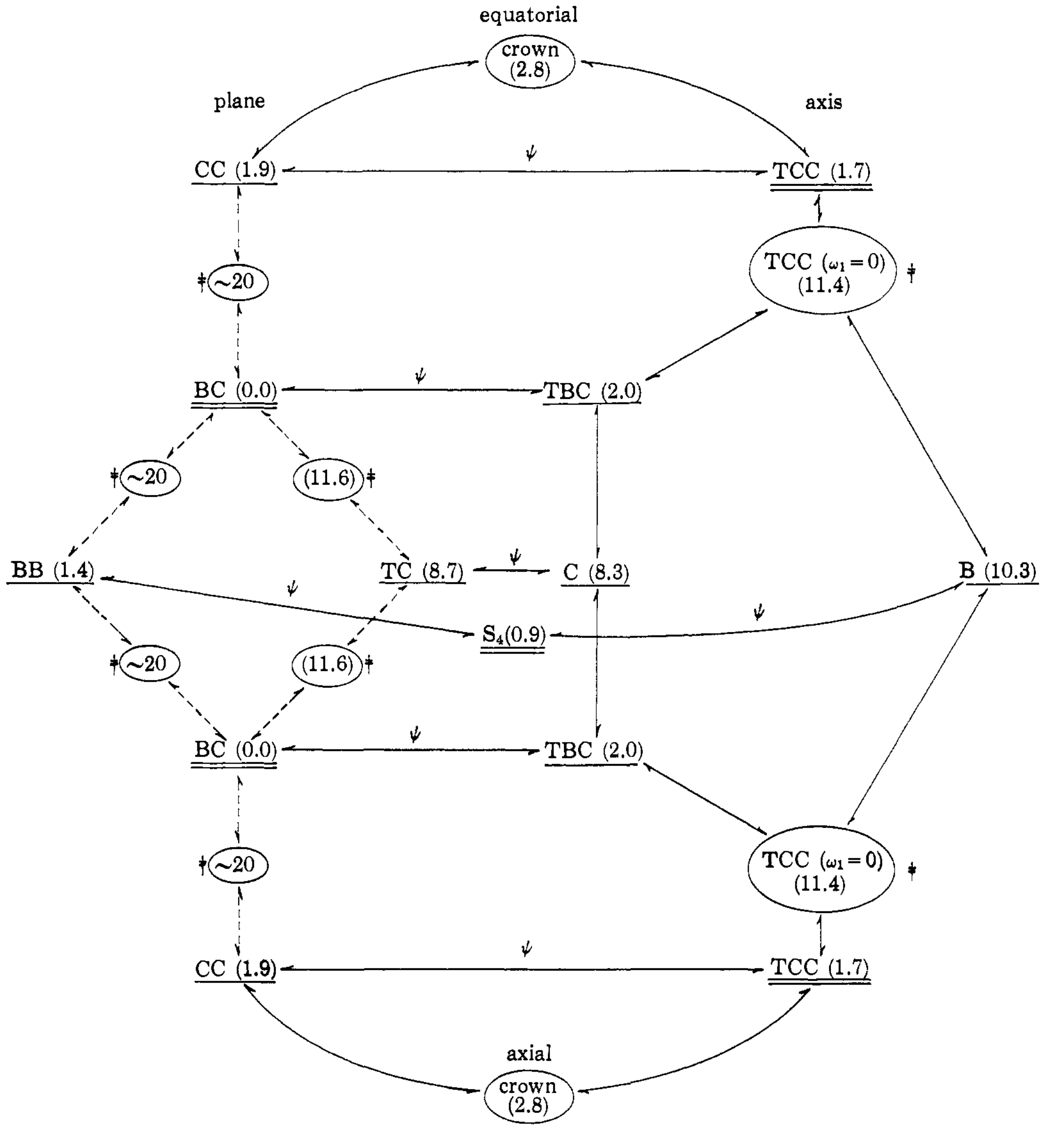

Figure 7. Interconversions of cyclooctane conformations.

For cyclooctane the situation is more complex, partly because the ring is larger and partly because there are more symmetrical possibilities in a ring with eight members. The symmetrical modes of transition for cyclooctane are coupled with its pseudo-rotation in Figure 7 which shows the crown forms at top and bottom and symmetrical-mode routes connecting them vertically, with plane of symmetry down the left and axis down the right side. Thus the two symmetries are interconnected with horizontal pseudo-rotation paths, in principle connecting every point on the two vertical routes but only shown between forms that represent energy minima or well-defined symmetries. Barriers (energy maxima) on the symmetrical pathways, discussed above, are shown with their energies in circles. Forms that represent over-all energy minima are doubly underlined (TCC, BC, and S_4); the BC form, being the preferred conformation of cyclooctane, is listed as zero and the other energies are relative to this (ΔE in Table II and ref 1). Forms that represent minima on their symmetrical interconversion routes but maxima with respect to pseudo-rotation, *i.e.*, which are saddles on the energy surface like the cyclohexane boat, are singly underlined. One exception is the chair, which is reversed, being a maximum on the symmetrical route from TBC to TBC′ but a slight minimum in its pseudo-rotation profile with the TC. Unlike the preferred crown (chair) of cyclohexane, the crown form of cyclooctane is found to represent a modest energy maximum.

The barriers on the plane symmetrical route involving flipping the end atoms on the plane ($+\omega_1 \leftrightarrow -\omega_1$, as in CC $\leftrightarrow$ BC) are high and may reasonably be ignored; such pathways are dotted in Figure 7. The over-all picture for a substituted cyclooctane is analogous to that of cyclohexane and the diagram of Figure 7 may accordingly be expanded into a globe with the crown forms at the poles, the north pole representing an equatorially-substituted crown and the south pole an axially substituted crown. The vertical symmetrical pathways connecting the poles are longitudinal routes as before, although their branching in cyclooctane complicates this visual representation. There must be as many such longitudinal routes as there are places on the pseudo-rotation itineraries which intersect them. It will be recalled that there are two pseudo-rotation itineraries for the CC/TCC forms and two for the BC/TBC forms but only one for each of the other families, and Figure 7 makes it clear why this should be. In particular the

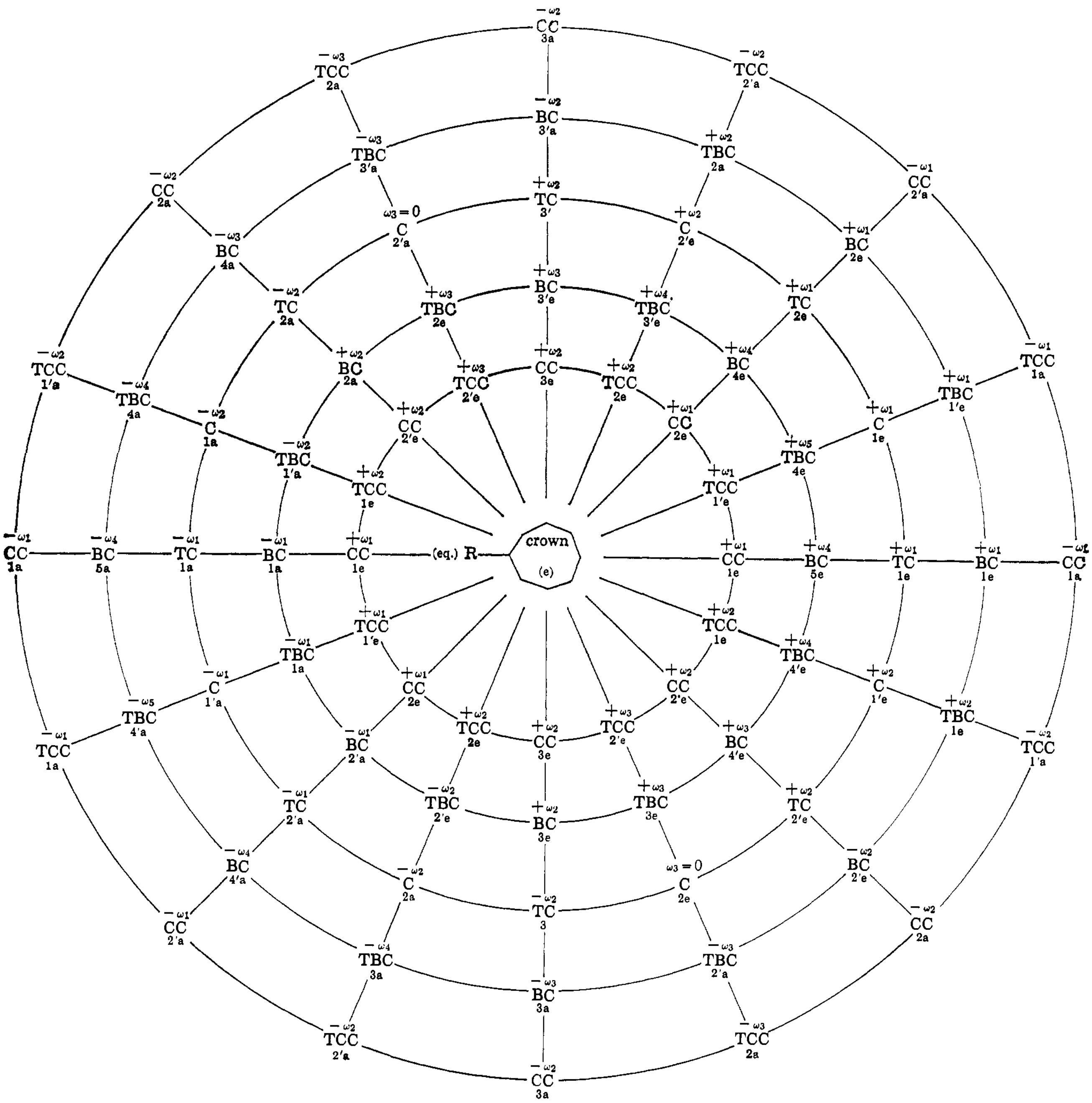

Figure 8. Map of cyclooctane interconversions.

upper CC/TCC itinerary is composed only of equatorial substituent positions, reflecting its proximity to the equatorially substituted crown at the north pole, while the lower CC/TCC itinerary is entirely of axial substituents. Both BC/TBC substituent itineraries contain both equatorial and axial positions, in a ratio of 5:3 favoring equatorial in the upper cycle and the reverse in the lower, while the C/TC cycle and the B/BB cycle at the equator carry equal numbers of axial and equatorial as is the case with the comparable B/TB cycle in cyclohexane.

The number of places on each BC/TBC itinerary (and on the C/TC cycle) is 16, thus requiring 16 longitudinal symmetrical-interchange routes on the surface of the globe. In order to simplify representation of the total interconversion globe, a map is shown in Figure 8 which is essentially a cartographer's polar projection, showing the equatorially substituted crown in the center with longitudinal (symmetrical change) pathways radiating out to the CC/TCC pseudo-rotation cycle[16] and then on to BC/TBC, TC/C, BC/TBC, and the second CC/TCC cycles with the implicit recognition that these radii then converge again at the axially substituted crown form (at the south pole). In this map the B/BB cycle, and the corresponding branching of the symmetrical-mode pathways, has been left out for several reasons: (1) the two symmetrical-mode branches do not reconverge on the same positions of the lower CC/TCC cycle thus excessively complicating the map; (2) the barriers to BC ⇀ BB interconversion are too large for

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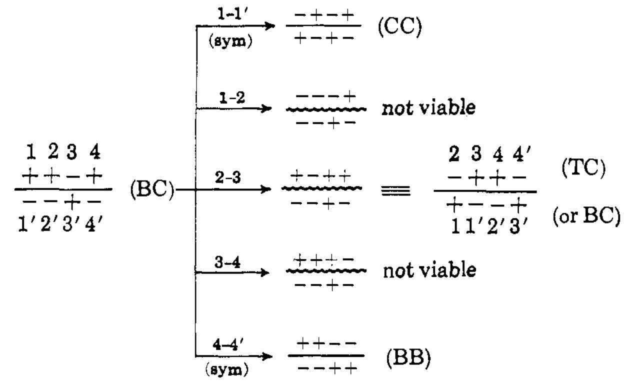
(16) Owing to the higher symmetry of its rings, each CC/TCC cycle has only eight places relative to 16 for each BC/TBC itinerary. In order to make all the connections clearly on the map it was necessary to double the CC/TCC itinerary, as will be seen by following the 1e-substituted CC ring across the crown to itself again on the other side. The normal conversion of 1e- to 3e-CC by symmetrical passage through the crown is observed by turning 90° in passing through the crown on the map.



ω changes

$\omega_1 \longrightarrow \omega_1'$
$\omega_1' \longrightarrow \omega_2'$
$\omega_2 \longrightarrow \omega_1$
$\omega_2' \longrightarrow \omega_3'$
$\omega_3 \longrightarrow \omega_2$
$\omega_3' \longrightarrow \omega_4'$
$\omega_4 \longrightarrow \omega_3$
$\omega_4' \longrightarrow \omega_4$

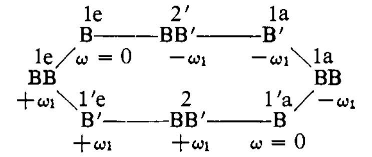
Figure 9. One-carbon wagging of BC-cyclooctane.

those routes to be viable; and (3) the high symmetry of the B and BB forms ($4n/m = 8$) would require repetition of the itinerary (as with CC/TCC) to create the 16 necessary intersections. The pseudo-rotation itinerary and symmetrical-mode changes from it are, however, summarized for the B/BB system in Table IV.

The diagram of Figure 7 with its energy profile of the parent rings and the map (Figure 8 and Table IV) expanded from it for substituents constitute a full description of the interconversions of cyclooctane in the symmetrical mode and in pseudo-rotation. The particular symmetrical forms and the relative energies of methyl substituents on them are pictured in the preceding paper.[1] One can follow a substituent from one position to any other on these maps, observing the energy barriers it encounters enroute. In effect, as in all conformation analysis, one is in fact observing changes in ring shape beneath the substituent and it is these ring changes which afford the substituent its different steric environments (characterized as CC-1e, BC-4a, TCC-2′e, etc.). For example, a crown ring with an equatorial substituent will fall to the more stable CC/TCC forms and pseudo-rotate with facility among its equatorial possibilities. Over the lower symmetrical-mode barrier (with an axis of symmetry) at TCC ($\omega_1 = 0$) the ring may drop in energy to the boat and thus onto its pseudo-rotation itinerary, finding the more stable S_4 forms between each B and BB, or it may as well fall to the TBC form and, pseudo-rotating, pass among the most stable BC forms with equatorial substituents. From the upper BC/TBC cycle the ring may rise over the various barriers represented by substituted C or TC rings to the lower BC/TBC cycle where it will reach the other possible BC/TBC substituent positions (mostly axial). Finally from either this BC/TBC cycle or from the various boat rings the substituted cyclooctane can pass again over the TCC ($\omega_1 = 0$) barrier to become an axially substituted CC or TCC, or crown.

Table IV. Interconversions of B/BB Cyclooctane Substituents

Pseudo-rotation itinerary



Symmetrical mode

TCC B TCC	BC BB BC
2e—1e—1′a	4e 2′e 2′ 2′a 4a
1′e—1a—2a	5e 3a 1a 1a 3′a
1e—1′a—2′a	4′e 4′a 2 2a 2e
2′e—1′e—1a	3e 5a 1e 3′e 1e

Asymmetrical Modes. Asymmetrical modes of conformational transformation are harder to assess with the procedures outlined above. In cyclohexane and cycloheptane there are no other modes of any energetic importance than the two described. In the larger rings, however, there can be. The simplest procedure is that in which only one side of a symmetrical ring is allowed to change, as in a wagging of a single carbon atom which in general will invert the signs of the two dihedral angles directly adjacent to it. Such transformations can be examined with the aid of the ring symbol convention as shown in Figure 9 for BC-cyclooctane, symmetrical one-carbon wagging to CC or BB having already been considered ($\Delta\omega_1$). Two other wagging motions lead to nonviable conventions while the third asymmetrical transformation (of ω_2 and ω_3) leads to a symbol with potential symmetry as a TC form (or BC near the symmetrical BC → TC barrier); the conversions that the bonds undergo are shown as well. Such asymmetrical transformations are indeed possible and offer other routes on (or through) the globe (Figures 7 and 8) interconnecting energy-minimum forms such as BC, TCC, and S_4. However, whether these routes offer competitively low-energy barriers is impossible to calculate with the procedures employed here and a detailed analysis of the possibilities has not yet been made.[17]

In cyclononane the picture is in fact somewhat simpler than in cyclooctane owing to fewer symmetrical rings and the very great strain in the BB/TBB forms which allows them to be ignored. The removal of boat forms allows single unbranched symmetrical-mode pathways to be written for each symmetry (plane and axis), re-

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(17) A study is currently underway of the best way to examine asymmetrical modes of interconversion by calculation of their barriers. As these modes become most significant in the larger rings, complete delineation of the energy profiles in cyclononane and cyclodecane awaits this clarification.

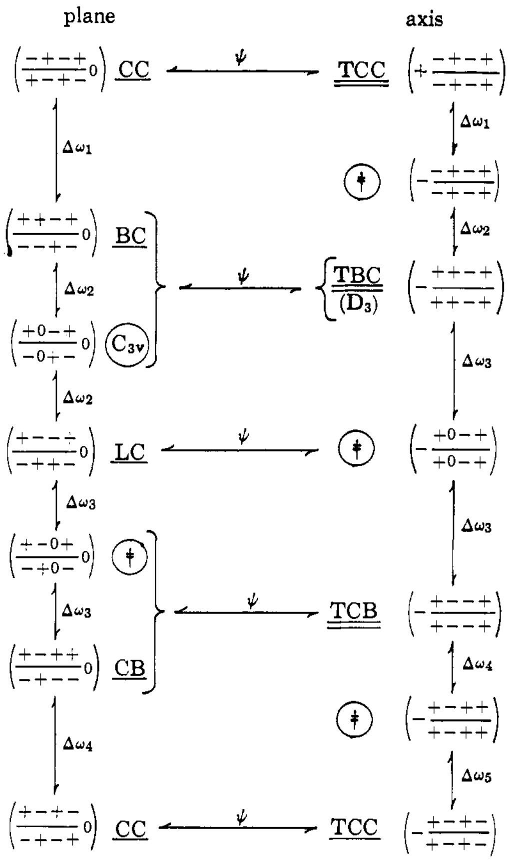

Figure 10. Interconversions of cyclononane conformations.

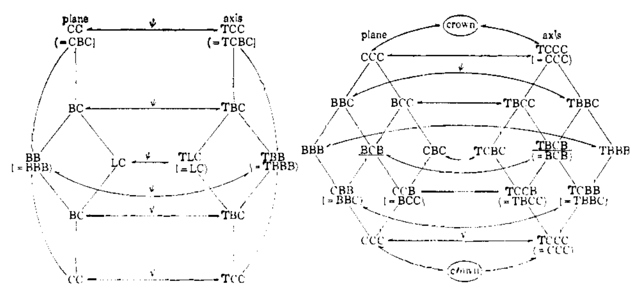

Figure 11. Interconversions of cyclodecane conformations.

sulting in a figure (Figure 10) very similar to that in cyclooctane (Figure 7) with the boat and crown forms removed. Like cycloheptane only a truncated globe, with no possible crown forms for the poles, can be constructed for this figure by expanding Figure 10, the vertical lines of which will become the $4n/m = 36$ longitudinal symmetric-mode pathways needed to connect every place on the pseudo-rotation itineraries of CC, BC, etc. In the nine-membered ring, threefold symmetry is now possible and is found in the C$_{3v}$ and TBC ≡ D$_3$ conformations, the latter being the most stable conformer of cyclononane. As pointed out previously,[4] the plane-symmetrical forms of cyclononane are energetically especially bad owing to the severe nonbonded interactions caused by the eclipsed bond so that only the axis forms represent relatively low-energy minima. Also, owing to the disparity between the energies of plane- and axis-symmetrical pseudo-rotation partners,[18] pseudo-rotation will be a less important interconversion process and asymmetrical modes will be relatively more important.[17] However, the map laid out in Figure 10 allows itineraries of substituent interconversions to be constructed, as was done above for the lower rings, and affords an over-all structure of conformer interrelations, onto which asymmetrical modes of interconversion can be overlaid.

In the more complex cyclodecane we face the need for two complete systems of description, one involving forms with planes through bonds (P/B) pseudo-rotating with partners having axes through atoms (A/A), the other involving the cases of P/A $\rightleftharpoons$ A/B. The first of these, involving CC $\leftrightarrow$ BC $\leftrightarrow$ BB forms, is completely analogous to the system of cyclooctane (Figure 7) without the crown conformations at top and bottom, and is summarized at the left of Figure 11. The ring symbols for these plane rings are identical with the corresponding ones in cyclooctane (P/A) with two added zeroes at the two ends for the eclipsed bonds in the C$_{10}$ P/B rings. On the right in Figure 11 is the comparable diagram for the pseudo-rotation system P/A $\rightleftharpoons$ A/B. The over-all picture is simplified by the mutual identity of a number of these symmetrical forms between the two systems as shown in the parentheses. This allows the combination of the two systems into a combined single map which is shown at the top of Figure 12; this map must be repeated around a globe of pseudo-rotation cycles as was done for cyclooctane and obviously becomes exceedingly complex in its complete form. However, many of the formal conformers shown are of high energy and unlikely to be important in conformational considerations. A recent study of 1,1,5,5-tetramethylcyclodecane,[19] which is constrained by axial substitution to abandon the stable BCB form, has shown that it occupies a mixture of TBC and TBCC conformations, found to be 2–3 kcal/mole less stable than the BCB conformation both by calculation and experiment. These forms are thus the next best candidates energetically for cyclodecane and the abbreviated map of interconversions involving only these forms is shown in the lower part of Figure 12, showing a part of each complete pseudo-rotation cycle horizontally and dotted, with vertical interconversions in the symmetrical mode. Figure 12 implies two separate pseudo-rotation itineraries for CCC, BC/TBC, and BCC/TBCC and only one for BCB/LC and CC/TCC, and this is in fact found to be the case when they are examined by the rules outlined above. Except for BCB/LC (Chart IV) which is abnormal ((see above), the actual itineraries have not been spelled out here but may easily be prepared by these rules.

Summary

The material presented in these three papers provides both the energies and the pathways of interconversion of substituted cycloalkanes and therefore offers the information needed to undertake the conformational analysis of particular compounds. The general procedure is to locate the substituent(s) on equatorial positions of the most stable conformer, if possible, or, failing that, to assess the energetic preferences between axial substitution on the most stable ring and equatorial substitution if possible on a less stable conformation. Then

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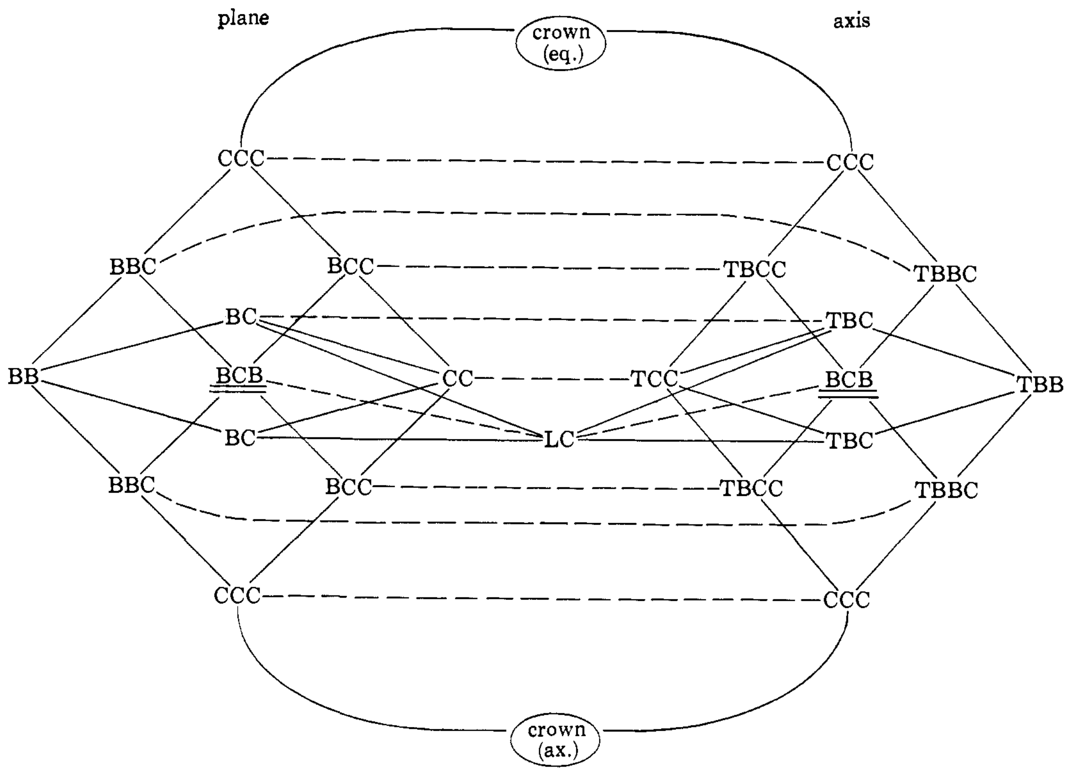
(18) These can for the present[17] be roughly assessed from the energy differences offered in ref 4 for various cyclononanes; the general trends in the tables there remain valid.

(19) M. Bixon, H. Dekker, J. D. Dunitz, E. Eser, S. Lifson, J. Sicher, and M. Svoboda, *Tetrahedron*, in press.



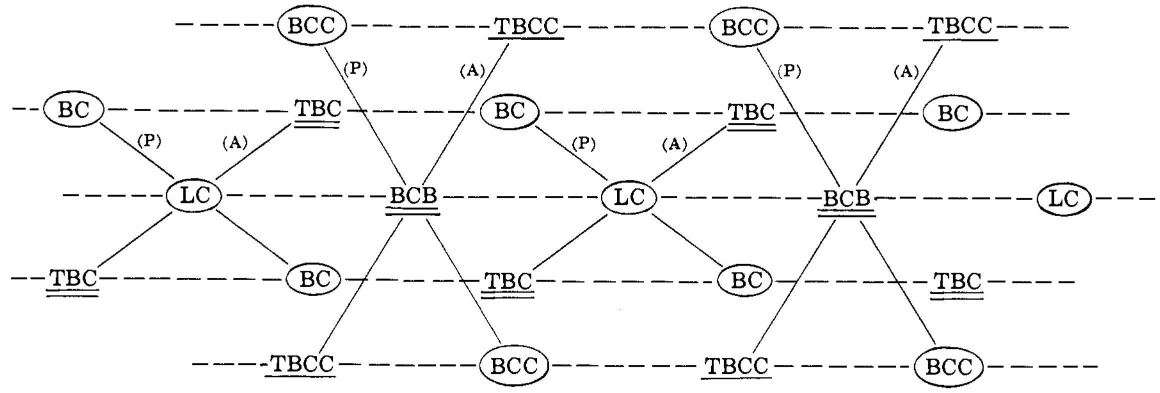


Figure 12. Condensed map of cyclodecane interconversions: ———, symmetrical; A = axis; p = plane; -----, ψ.

it is necessary to locate that substituted conformer on the appropriate over-all interconversion map and to follow all the interconversions possible from that location, recording the relative energies of other energy-minimum conformations which it may reach and the barriers it must cross to reach them. This should simulate the possibilities open to the molecule itself, which will interchange among all the lowest energy conformers which are separated by barriers low enough to pass at the temperature in question. While the barriers to interconversion of the parent rings are usually not high (<12 kcal/mole), they may become much higher with substituents or fused rings attached to the parent ring. Such substitution can effectively bar certain interconversion pathways and limit the number of possible conformers. Some cycloheptane examples have been discussed before[20,21] and the approach has been used by Jones in steroid examples with marked success.[22] In cyclooctane one would expect a monosubstituted cyclooctane to be largely a mixture of the five equatorial-substituted **BC** conformers and lesser amounts of the equatorial-substituted S_4 or TCC forms. *gem*-Disubstituted cyclooctane should, however, exist largely as the BC conformer disubstituted at the 2 position, at which both substituent sites are unstrained, and this is confirmed in Groth's X-ray study of dimeric cyclooctanone peroxide.[23]

In other disubstituted cycloalkanes examination of pseudo-rotation itineraries is simplified by the recognition that (if the substituents fall on the same itinerary, as in most rings) *cis* substituents pseudo-rotate in the same direction, *trans* substituents in opposite directions. Thus it is relatively easy to follow the double itinerary of two *cis* substituents, and with *trans* substituents it is

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(20) J. B. Hendrickson, *J. Am. Chem. Soc.*, **84**, 3355 (1962).

(21) J. B. Hendrickson, *Tetrahedron*, **19**, 1387 (1963).

(22) J. B. Jones, J. M. Zander, and P. Price, *J. Am. Chem. Soc.*, **89**, 94 (1967).

(23) P. Groth, *Acta Chem. Scand.*, **19**, 1497 (1965); see also ref 1.

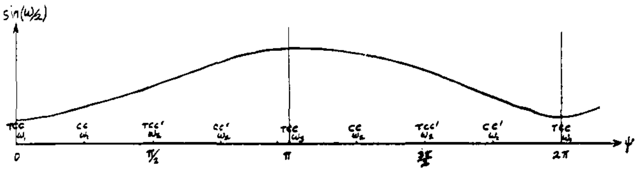
easier to follow the epimer of one substituent (so that *cis* groups are being followed in parallel).

In conclusion it may be noted that the chemical fraternity has been fortunate in having so uniquely simple a situation as that of chair cyclohexane on which to learn and practice the principles of conformational analysis; we are also fortunate that most occasions for that practice arise in cyclohexane derivatives. However, as work in this area develops more strongly into the medium rings, it will be necessary to invoke the more complex interrelations outlined here. The principles discussed here hold equally well for other substituents than alkyl groups, and the detailed conformational site energies quoted for methyl groups may be at least qualitatively followed for other substituents, having regard for their relative steric bulk. The fact that in these rings bond angles are commonly 115–118° implies that the same forms will hold for carbonyl groups with little change in geometry. The major effect of sp^2 carbons of this kind in a ring should be the elimination of serious nonbonded hydrogen interactions and this implies that carbonyl groups will prefer positions (such as C-1 or C-3 in C_8-BC or C_{10}-BCB) which in the saturated ring have the most seriously strained axial hydrogens.

Acknowledgment. The author wishes to record his warm appreciation to Professor E. Grunwald of Brandeis University and Dr. H. Friebolin of the Institut für Elektrowerkstoffe at Freiburg for stimulating discussions and the National Institutes of Health for their generous support of the work. The privilege of using the Brandeis University and Massachusetts Institute of Technology computer centers is also gratefully acknowledged.

Appendix

In general, as noted previously,[4,5] the computation procedure using internal coordinates involves determining the number of independent variables (most or all symmetrically distinguishable bond angles, θ, and usually one dihedral angle, ω, or none at all in cases of high symmetry) which define individual rings in the family under consideration. These are then independently varied through a range of values in a nest of DO loops in the computer program. With the independent variables so defined, the remaining angles (θ and ω) of the ring are computed from them by the equations characteristic of the ring family (C_8-CC, C_9-TBC, C_{10}-BCB, etc.) in question[24] and the ring checked for closure by determining the distance from one atom around the ring to itself again, which should be zero. In rings with only axes of symmetry it is easier to determine the ring by varying a second dihedral angle, ω, until this closure distance goes to zero. A subroutine then operates on all the calculated angles of the ring to compute their associated energies ($E_\theta = f(\theta)$ and $E_t = f(\omega)$), as well as the set of nonbonded distances (HH, HC, and CC) and their associated nonbonded interaction energies, and sums these to obtain the energy of the individual ring. The energies so obtained for each individual ring in the grid of independently variable angles are automatically compared to select energy minima. In obtaining symmetrical-mode barriers, energy maxima are observed instead and are, in particular, maxima with respect to change in ω but minima with respect to θ.



$$\sin(\omega/2) = 0.66971 - 0.1778\cos\chi - 0.00122\cos 2\psi + 0.00291\cos 3\psi + 0.00019\cos 4\psi)$$

Figure 13. Pseudo-rotation of dihedral angles in cycloctane (CC/TCC).

For pseudo-rotation profiles values of $\sin\omega$ for a single bond at each successive symmetrical ring on its itinerary were plotted against an angle, ψ, varying from 0 to π for a full sequence of changes in ω, and the constants of an interpolation curve, $\sin\omega = K_1 + K_2\cos\psi + K_3\cos 2\psi + K_4\cos 3\psi + \ldots$, were obtained by matrix inversion on the computer. These equations then allowed calculation of values of ω intermediate to those of the symmetrical forms on the itinerary and thus determination of an energy profile for that itinerary. The case of cyclooctane-CC/TCC is shown as an example. There are five different values for ω_1 in symmetrical rings, through which the bond passes in its itinerary ($TCC/\omega_1 \leftrightarrow CC/\omega_1 \leftrightarrow TCC'/\omega_2 \leftrightarrow CC'/\omega_2 \leftrightarrow TCC/\omega_3$). This plot is shown in Figure 13.

It can be seen that an interval of 180° in ψ contains all the dihedral angles of a given ring, the symmetrical forms being represented (*e.g.*, by C or TC) by alternate points on the graph. In the course of pseudo-rotation, then, each ω moves along the graph curve to the next point, representing the next symmetrical form of opposite symmetry. Some of the curves cross the abscissa within the 180° interval, implying a ring in which one dihedral angle changes sign between symmetrical rings; as is the case with C_7-B/TB and C_8-BC/TBC (in C_{10}-BCB/LC, this crossing occurs at the LC form) and is discussed in the text (*cf.* Figure 3). The intermediate asymmetrical rings so obtained on the various itineraries were of course all checked by ring closure and found to be true rings in every case except that of C_8-BC/TBC. In these calculations of rings on the pseudo-rotation itinerary the bond angles (θ) were all set equal to the mean value for the two symmetrical rings.

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(24) Such equations, for equal-angle rings, are listed in the Appendix of ref 4.