

**Computer-Assisted Synthetic Analysis. A Rapid Computer Method for the Semiquantitative Assignment of Conformation of Six-Membered Ring Systems. 1. Derivation of a Preliminary Conformational Description of the Six-Membered Ring**

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The importance of conformational prediction for six-membered ring systems in computer-assisted synthetic analysis is pointed out, and a novel and appropriate means whereby this capability has been achieved in the Harvard LHASA synthesis program is outlined. In this paper the first-order conformational analysis is described. This involves assignment of one or more well-defined preliminary conformational forms and a flexibility designation to each six-membered ring system in the target molecule. The structural constraints which form the basis for these assignments are enumerated, and their various effects are described in detail. The computational method for assigning axial and equatorial labels to all stereoappendages off the six-membered rings, in a manner that leads to consistency with respect to both the structural constraints discovered and any input made by the chemist, is then detailed. It will be seen that these procedures enable the ultimate semiquantitative prediction of conformation to be made; means for accomplishing this are presented in the accompanying paper.

An essential feature of a rigorous synthetic analysis by a chemist of a target organic molecule is a clear appreciation of the nature and consequences of the three-dimensional structure of the molecule. The outcome of many reactions, whether they involve the *intra-* or *intermolecular* delivery or the removal of a molecular fragment, is to a large extent dependent on, and predictable from, the stereocharacter of the molecule about the reaction site. A key direction in the evolution of the Harvard program for computer-assisted synthetic design, named LHASA,<sup>1</sup> was therefore identified as the development of a stereochemical sophistication within the retrosynthetic analysis. The first step in this process was to establish simple means whereby three-dimensional information could be communicated to the synthesis program given the constraint of the two-dimensional graphics interface.<sup>2</sup> The solution to this problem, utilizing the commonly employed wedged and dashed bond conventions familiar to organic chemists, has been described previously.<sup>3</sup> In essence this has provided a simple yet rigorous means whereby relative stereorelationships within a molecule (e.g., the *cis* and *trans* relationships about a ring) can be distinguished and has set

the stage for more complex stereoanalysis.

A stereoanalysis will involve two distinct stages: (1) determination of the topography of the molecule and (2) assessment of its effect on the course of reaction.<sup>4</sup> This latter aspect forms the basis for a study currently underway within our research group and will be reported shortly. In this and the following paper<sup>5</sup> we describe an important aspect of the topographical question: extension of the stereochemical capabilities of the program to provide a synthetically practical description of the geometry of six-membered ring systems.

**Conformational Analysis of Six-Membered Rings.** The six-membered ring is central to organic synthesis. It is regularly invoked in the description of transition-state geometries. It not only is a most commonplace feature of every variety of naturally occurring compound but it often also figures as the central stage for synthetic operations directed toward targets of quite unrelated construction.<sup>6</sup>

The six-membered ring poses a unique geometric problem to the synthetic organic chemist. The stereochemical course of reactions at three-, four-, and five-membered rings can be reliably predicted by assuming the rings are flat and simply assessing the relative steric congestion of

(1) Corey, E. J. *Q. Rev., Chem. Soc.* 1971, 25, 455; *Pure Appl. Chem.* 1971, Suppl. 2, 45.

(2) Corey, E. J.; Wipke, W. T.; Cramer, R. D., III. *J. Am. Chem. Soc.* 1972, 94, 421.

(3) Corey, E. J.; Howe, W. J.; Pensak, D. A. *J. Am. Chem. Soc.* 1974, 96, 7724. For a discussion of machine representation and manipulation of stereochemistry using two- or three-dimensional input see: Wipke, W. T.; Dyott, T. M. *J. Am. Chem. Soc.* 1974, 96, 4825.

(4) Cf.: Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* 1974, 96, 299.

(5) Corey, E. J.; Feiner, N. F., *J. Org. Chem.*, following paper in this issue.

(6) (a) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* 1978, 100, 4618. (b) Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* 1978, 56, 1843.

the two faces. As ring size increases so does conformational mobility and hence the uncertainty of stereochemical outcome. Even with seven-membered rings<sup>7</sup> prediction is generally difficult. A synthetic chemist who takes on the three-dimensional ambiguities offered by larger rings<sup>8</sup> and acyclic systems<sup>9</sup> does so with no small peril.

Intermediate in complexity stand six-membered ring systems. The six-membered ring cannot be approximated as flat, having long been known to prefer either the chair or, less commonly, the boat and twist conformations.<sup>10</sup> As was first pointed out by Barton,<sup>11</sup> a knowledge of the conformation of a six-membered ring system, and hence its axial/equatorial substitution pattern, is crucial to an understanding of the stereochemical basis for many reactions of this ring system.

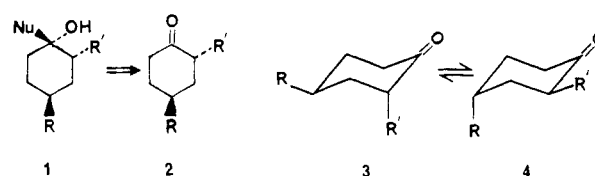
**Computer-Assisted Conformational Analysis.** In practice, the conformational analysis of six-membered ring systems has resulted in a vast amount of experimental investigation since 1950.<sup>12-14</sup> In recent years, a number of approaches have been made in the direction of computer-based prediction of conformation. These have included both *ab initio* molecular orbital<sup>15</sup> and semiempirical molecular mechanics methods; considerable excellent work has been done by Allinger<sup>16</sup> along these latter lines. This latter approach represents a quantitative and exhaustive general method of conformational analysis. The complete set of three-dimensional atomic coordinates is required to initiate an extensive calculation, generally requiring at least several minutes of computer time, which is able to compare a large number of molecular geometries, eventually becoming fine-tuned to a precisely defined conformation.

In developing an appropriate facility for conformational prediction for six-membered ring systems for the LHASA synthesis program, consideration was given to the depth of analysis required and its context within the entire synthetic analysis. In the course of the analysis of a particular target structure, many dozen synthetic precursors will be typically generated and screened by the computer.<sup>17</sup> For each, a full analysis including perception of synthetically significant features and evaluation of synthetic suitability must be carried out.<sup>18</sup> This examination requires 1-5 s of computer time per structure. Addition of a conformational analytic component to this process was seen as providing a means of swift stereoap-

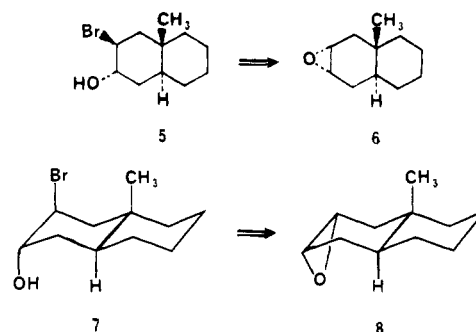
praisal, setting the stage for screening the probably or possibly acceptable from the clearly unacceptable.

It was clear from this that a new approach to the computer-based prediction of conformation of six-membered ring systems would have to be developed. The starting point for our method of conformational analysis is the expectation that, because of the 5.0-6.5 kcal/mol energy difference between the chair and the higher energy twist and boat forms of cyclohexane,<sup>19</sup> the vast majority of compounds containing a six-membered ring will tend to exist almost entirely in the chair form. If a six-membered ring system can be said to be in one chair conformation, then, for the purposes of synthetic planning, stereochemical prediction can, in many instances, be made with a considerable level of confidence.

The two simple examples which follow serve to illustrate this point and also to bring to light the two basic aspects of this approach to conformational analysis. In considering the suitability of the disubstituted cyclohexanone **2** as a



synthetic precursor to alcohol **1**, it is evident that it is not enough to assess the relative steric hindrance of each face of ketone **2** on the basis of the assumption of a flat six-membered ring; its two possible chair conformations **3** and **4** must be considered. A strong bias for conformer **3**, wherein the axial appendage  $R'$  significantly blocks the  $\alpha$  face (steroid convention) of the molecule,<sup>4</sup> will clearly favor formation of the desired alcohol **1**; a high equilibrium concentration of **4**, however, will give rise to a situation where less control of stereochemistry can be anticipated. Thus an important demand placed upon the prediction module is to establish a *basis for selection of one conformational form over another*. In the assessment of retrosynthetic generation of epoxide **6** from bromohydrin **5**,



it is insufficient simply to ascertain if the hydroxyl and bromine are trans in the target structure; these groups must be perceived as diaxial (cf. **7**  $\rightarrow$  **8**). If they are trans but diequatorial, any constraints operating on the six-membered ring to prevent it from flipping to the diaxial conformation must be identified. One such constraint is a trans fusion. This example, then, serves to illustrate the second important aspect of the analysis, namely, *the recognition of configurational constraints on the conformational options of the six-membered ring*.

Our computational method of conformational prediction is presented below in detail. In this paper we describe a first-order conformational analysis: configurational con-

(7) Conformational analysis of seven-membered rings: (a) Bocain, D. F.; Pickett, H. M.; Rounds, T. C.; Strauss, H. L. *J. Am. Chem. Soc.* **1975**, *97*, 687. (b) St-Jacques, M.; Vaziri, C.; Fremette, D. A.; Goursot, A.; Fliszar, S. *Ibid.* **1976**, *98*, 5759.

(8) Conformational analysis of medium rings: Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 7166.

(9) Conformational analysis of hydrocarbon chains: Winnik, M. A.; Lee, C. K.; Saunders, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 2928.

(10) Cf.: Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1972; Chapter 8.

(11) Barton, D. H. R. *Experientia* **1950**, *6*, 316.

(12) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Interscience: New York, 1965. Eliel, E. L. *J. Chem. Educ.* **1975**, *52*, 762.

(13) Hanack, M. "Conformation Theory"; Academic Press: New York, 1965.

(14) (a) Morris, D. G. *Aliphatic, Alicyclic, Saturated Heterocycl. Chem.* **1973**, *1* (Part III), 105; **1974**, *2*, 174. (b) Morris, D. G. *Alicyclic Chem.* **1975**, *3*, 266; **1976**, *4*, 196. (c) Brown, N. M. D.; Cowley, D. J. *Ibid.* **1977**, *5*, 191.

(15) (a) Cremer, D.; Binkley, J. S.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 6836. (b) Askari, M.; Ostlund, N. S.; Schaefer, L. *Ibid.* **1977**, *99*, 5246.

(16) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1.

(17) (a) Corey, E. J.; Cramer, R. D., III; Howe, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 440. (b) Corey, E. J.; Jorgensen, W. L. *Ibid.* **1976**, *98*, 189, 203. (c) Corey, E. J.; Johnson, A. P.; Long, A. K., submitted to *J. Org. Chem.*

(18) (a) Corey, E. J.; Wipke, W. T.; Cramer, R. D., III; Howe, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 431. (b) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Peterson, G. A. *Ibid.* **1975**, *97*, 6116.

(19) March, Jerry. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; p 228.

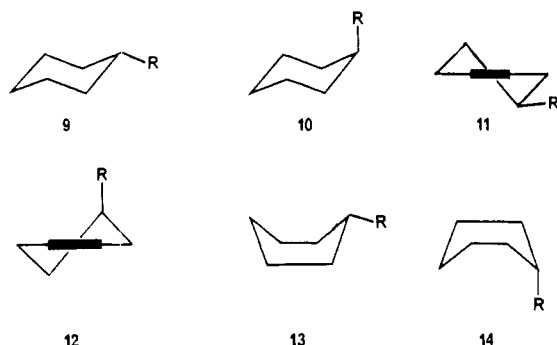
straints are identified, characterized and used to arrive at a preliminary conformational description of the six-membered ring. In the following paper<sup>5</sup> we deal with second-order effects; starting with the preliminary conformational assignment and on the basis of what is known or can be deduced about the stereoelectronic relationships of axial and equatorial substituents about six-membered rings, we arrive at a semiquantitative estimation of the energies of these preliminary forms and hence at our ultimate conformational assignments. It will be seen that the approach works directly from two-dimensional input without requiring three-dimensional atomic coordinates and that it is extremely rapid, the analysis requiring on the order of *1 s of computer time per structure*.

In order to facilitate reading of this paper a glossary of the novel terminology used is given as supplementary material.

### Preliminary Conformational Assignment

**Definitions.** Because of structural constraints, not all six-membered ring systems may adopt chair conformations, and not all chairs may freely invert. Thus, for each six-membered ring in the molecule being analyzed, it is the task of the preliminary conformational assignment module to identify those *allowable conformations* to which the ring is configurationally restricted and, further, to ascertain the *flexibility* of each such conformation.

Unless shown unattainable, each six-membered ring will be preliminarily assigned the two possible *chair* geometries 9 and 10. On the basis of certain factors of structure that

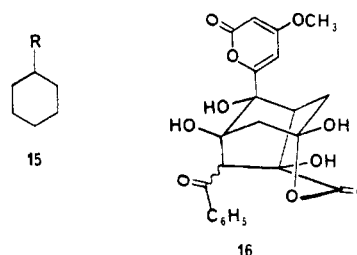


will be outlined below, however, it will be seen that certain rings must be alternatively designated. The necessity of assigning the ring a *half-chair* form (11 and/or 12), a *boat* form (13 and/or 14), or a *flat* form (15) will be recognized. If configurational constraints are discovered which make it impossible to make at least one of these preliminary assignments, then the six-membered ring will be judged conformationally ambiguous and not considered further.

The *flexibility* of a six-membered ring is an expression of the degree of conformational mobility that it is permitted. For a six-membered ring, one of three flexibility classifications will be made on the basis of structural-constraint consideration. These are (a) rigid, (b) distortable, and (c) flippable.

A *rigid* six-membered ring is permitted no conformational variation; it is held in only *one* of the forms 9–14. No additional conformational analysis is necessary for a six-membered ring once it has been found to be rigid. The six-member carbocyclic ring of vulgamycin (16)<sup>20</sup> exemplifies a rigid structural type.

A *distortable* six-membered ring is permitted some conformational variation; it may adopt one of the six forms described above, e.g., 9, 11, or 13, but, although it may



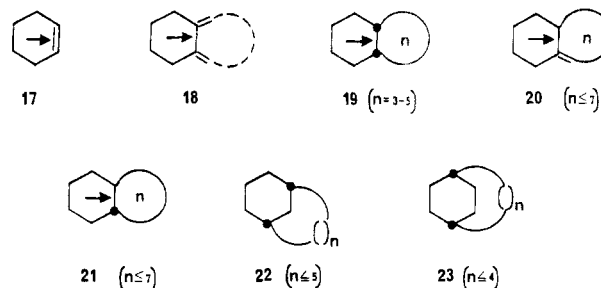
deform considerably, it may not flip over to its conformationally inverted opposite form, i.e., 10, 12, or 14. Additional conformational analysis<sup>5</sup> will be necessary for the preliminary form, 9–14, that is assigned such a six-membered ring to determine if this conformation is indeed preferable to some deformed shape. The six-membered rings of the *trans*-decalins 5 and 6 exemplify distortable structural types.

A *flippable* six-membered ring is permitted considerable conformational variation; it may adopt one pair of the geometric forms described above, i.e., 9 and 10, or 11 and 12, or 13 and 14. Additional conformational analysis<sup>5</sup> will be necessary for each form to determine which conformation will prevail. The cyclohexane systems 1 and 2 exemplify flippable structural types.

**First-Order Structural Determinants of Conformation and Flexibility.** In our analysis of the first-order structural effects on six-membered ring conformation and flexibility, we desired as general as possible a description for the benefit of the computer synthesis program. Since little relevant experimental data were available, we were obliged to turn to model building, and it is important to point out that the structural effects that are formulated below have, in large measure, been arrived at by the inspection of Dreiding-type molecular models. This is not inappropriate since our overall objective has been to provide a form of stereochemical analysis which is closely related to a chemist's problem-solving technique of model building and inspection.

In the ensuing discussion we will identify and describe those structural constraints which affect the flexibility and the conformation of the six-membered ring, serving to modify the flippable chair in the ways outlined above. We have chosen to define these constraints in terms of the bonds of the six-membered ring itself. There are three general bond types which can be considered constraining. These are (A) flattening bonds, (B) anchoring bonds, and (C) bridged bonds.

(A) **Flattening bonds** have been so designated because the presence of such a bond in a six-membered ring tends to reduce the dihedral angle between the subtended ring bonds to 0° and hence flatten the ring. Six-membered-ring bonds which are flattening include (1) bonds whose two constituent atoms are sp<sup>2</sup> hybridized (cf. 17 and 18) (these



will be referred to below as BISP2 constraining bonds), (2) *cis*-fusion bonds to three-, four-, or five-membered rings (cf. 19), and (3) fusion bonds to a ring of size seven or smaller which contains a double bond exocyclic to the

(20) Seto, H.; Sato, T.; Urano, S.; Uzawa, J.; Yonehara, H. *Tetrahedron Lett.* 1976, 4367.

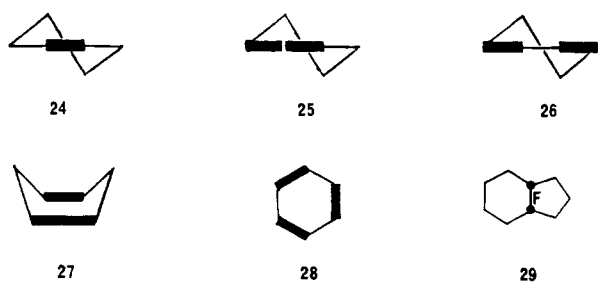
six-membered ring (cf. 20) (these will be referred to below as SP<sup>2</sup> constraining bonds).

(B) **Anchoring bonds** have been so designated because the presence of such a bond in a six-membered ring serves to impart reduced mobility to the ring, in a sense conformationally anchoring it. Six-membered-ring bonds which are anchoring include (1) SP<sup>2</sup> constraining bonds and (2) trans-fusion bonds to a ring of size seven or smaller (cf. 21).

(C) **Bridged bonds** are simply those two or three contiguous bonds in a six-membered ring that form part of a second ring. Six-membered ring bonds which are bridged include (1) two contiguous ring bonds whose termini are joined by a bridge of five atoms or fewer (cf. 22) and (2) three contiguous ring bonds whose termini are joined by a bridge of four atoms or fewer (cf. 23).

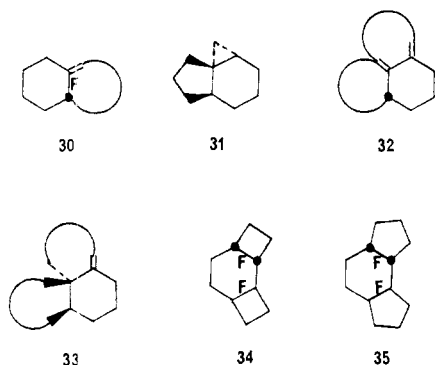
#### Effects of Constraining Bonds on Conformation.

(A) **Flattening Bonds.** The presence of flattening bonds within a six-membered ring generally removes the possibility of a full chair conformation; their specific effect depends on their number and disposition. In general, a lone flattening bond (cf. 24) or a pair of flattening bonds



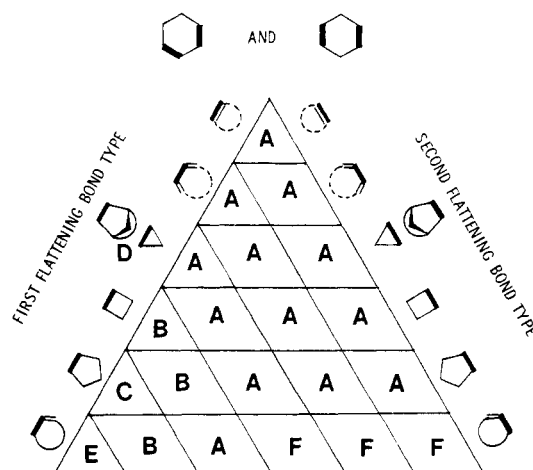
disposed in a [1,2] or a [1,3] manner<sup>21</sup> (cf. 25 and 26, respectively) gives rise to the half-chair conformation. A pair of flattening bonds disposed in a [1,4] manner (cf. 27) gives rise to a boat,<sup>22</sup> and three (or more) flattening bonds produce a flat six-membered ring (cf. 28). No further conformational analysis will be carried out on these flat rings, whose stereochemical behavior is similar to that of smaller ring systems.<sup>23</sup>

These rules hold for most of the possible arrangements of the flattening bond types defined above, although there are some exceptions. In the case of a lone flattening bond (cf. 24), either a cis-fusion constraining bond in an unbridged five-membered ring (bond F in 29) or an SP<sup>2</sup> constraining bond (bond F in 30) can be accommodated



(21) Cf.: Harvey, R. G.; Fu, P. P. *J. Org. Chem.* 1976, 41, 3722.  
 (22) (a) Paquette, L. A.; Liao, C. C.; Liotta, D. C.; Fristad, W. E. *J. Am. Chem. Soc.* 1976, 98, 6412. (b) Kumler, W. D.; Boikess, R.; Bruck, P.; Winstein, S. *Ibid.* 1964, 86, 3126. (c) Timosheva, A. P.; Vul'fson, S. G.; Sorochinskaya, E. I.; Vereshmagin, A. W.; Arbuzov, D. A. *Izv. Akad. Nauk Uzb. SSR, Ser. Khim. Nauk* 1975, 865.  
 (23) Cf.: (a) Fukuyama, T.; Kishi, Y. *J. Am. Chem. Soc.* 1976, 98, 6723. (b) DeMarinis, R. M.; Filer, C. N.; Waraszkiewicz, S. M.; Berchtold, G. A. *Ibid.* 1974, 96, 1193.

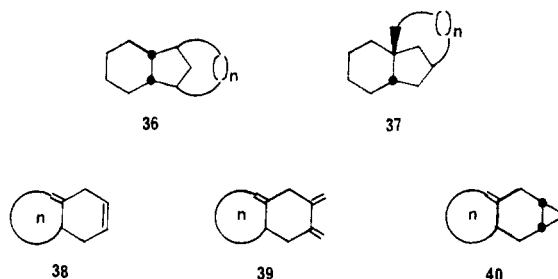
Table I. Effects of a Pair of [1,3]- and [1,4]-Disposed Flattening Bonds on Six-Membered-Ring Conformation<sup>a</sup>



<sup>a</sup> A, [1,3] disposition leads to a half-chair; [1,4] disposition leads to a boat. B, [1,3] disposition leads to a chair; [1,4] disposition leads to a boat. C, [1,3] and [1,4] disposition both lead to a chair. D, see text, note i. E, see text, note ii. F, [1,3] disposition leads to a half-chair; [1,4] disposition generally leads to a boat; however, see text, note iii.

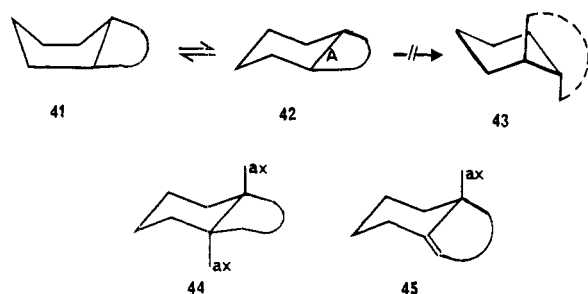
in a chair geometry. In the case of a pair of [1,2]-disposed flattening bonds (cf. 25), where such an arrangement is not precluded by ring strain (as in, e.g., 1,2-cyclohexadiene), the six-membered ring is always constrained to adopt the half-chair conformation (cf. 31-33). In the cases of [1,3]- and [1,4]-disposed flattening bond pairs (cf. 26 and 27), a complete summary of whose effects on conformation is given in Table I, a number of exceptions exist as well. Thus, for example, a pair of [1,3]-disposed cis-fusion bonds in four-membered rings (bonds F in 34) or a pair of [1,4]-disposed cis-fusion bonds in five-membered rings (bonds F in 35) can both be accommodated by a chair geometry.

A few of the structural types denoted in Table I have been singled out and must be commented upon briefly. (i) As alluded to above, if a cis flattening bond is in a five-membered ring that is bridged by a one- or two-atom arc (cf. 36 and 37,  $n = 1, 2$ ), then the effect on ring confor-



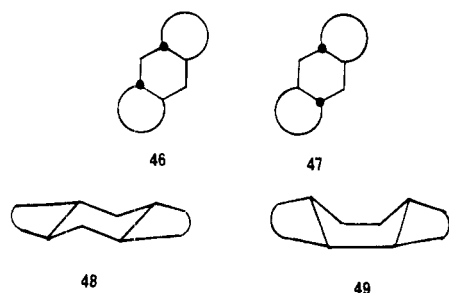
mation is equivalent to a cis flattening bond in a three-membered ring. (ii) The effect of a pair of [1,3]- or [1,4]-disposed SP<sup>2</sup> constraining bonds on six-membered ring conformation will be discussed in the following section on anchoring bonds. (iii) A six-membered ring is flat if it contains a pair of [1,4]-disposed flattening bonds, one an SP<sup>2</sup> constraining bond in a ring of size five or smaller and the other either a BISP<sup>2</sup> or a three-membered-ring cis flattening bond (cf. 38-40,  $n \leq 5$ ).

(B) **Anchoring Bonds.** The presence of a lone anchoring bond within a six-membered ring (cf. bond A in 42) reduces to one the number of possible chair, half-chair, or boat forms available to the ring, for in each case in the



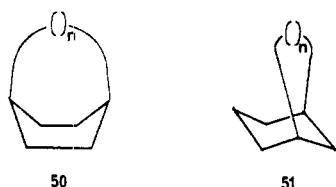
fully inverted conformation (cf. 43) the anchoring ring would have to bridge between two adjacent trans-diaxial positions, a geometric impossibility. It follows that the remaining appendages off anchoring bonds must assume an axial orientation with respect to the six-membered ring,<sup>24</sup> as shown in structures 44 and 45. It will be recognized that a partially inverted conformation is possible for an anchored chair (cf. 41); more will be said about this form shortly.

Pairs of anchoring bonds have a special effect on six-membered-ring conformation.<sup>25</sup> This may be illustrated with the six-membered ring systems 46 and 47, each of which contains a pair of [1,4]-disposed trans-fusion bonds. Although a chair conformation may obtain for the six-membered ring of 46 (cf. 48), this is not possible in 47, with



its two pairs of cis-1,4-diaxial appendages. A boat form, on the other hand, is seen to accommodate this geometry. More will be said about this latter conformation shortly.

(C) **Bridged Bonds.** As outlined above, a six-membered ring may be bridged either in a [1,4] or a [1,3] fashion. In general, [1,4] bridging leads to a single boat conformation (cf. 50), whereas [1,3] bridging leads to a

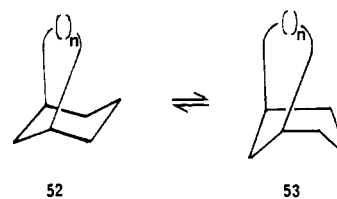


single chair conformation (cf. 51). In both cases the bridges are axially disposed with respect to the six-membered ring. The specific effect of a bridge, however, depends on its size.

A [1,4] bridge of one or two atoms (50,  $n = 1, 2$ ) results in a conformationally immobile boat. A [1,4] bridge of three or four atoms (50,  $n = 3, 4$ ) also results in a boat, although here the six-membered ring is able to distort into the so-called<sup>10</sup> twist geometry; more will be said about this conformational form shortly. A [1,4] bridge of more than four atoms (50,  $n > 5$ ) is considered structurally insignificant, since the six-membered ring is not restricted to

a boat conformation and, in fact, can adopt either chair form.

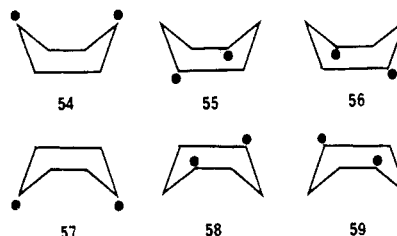
A [1,3] bridge of one to three atoms (51,  $n = 1, 2, 3$ ) gives rise to the possibility of the six-membered ring adopting either a chair or a well-defined boat conformation (cf. 52 and 53). A somewhat similar situation arises with a [1,3]



bridge of four or five atoms (51,  $n = 4, 5$ ), although more will be said shortly about the boat conformation (53,  $n = 4, 5$ ) which is less well-defined in these cases. A [1,3] bridge of more than five atoms (51,  $n \geq 6$ ) is considered structurally insignificant since the six-membered ring is able to adopt either chair conformation.

**Effects of Constraining Bonds on Flexibility.** Thus far we have shown how examination of first-order structural constraints permits the preliminary assignment of one or more of the seven conformational forms 9–15 to the six-membered ring. We have also defined three levels of conformational flexibility for six-membered rings: rigid, distortable, and flippable. It is now important to discuss ring flexibility in more detail and to show how its assignment derives from a consideration of structural constraints.

First, however, the significance of assigning a particular flexibility must be considered. The preliminary conformational assignment represents a basis for the ultimate prediction of six-membered ring geometry;<sup>5</sup> then, to the extent that uncertainty exists in the initial phase, the second-order analysis will suffer. When a six-membered ring may be assigned a chair or half-chair conformation, considerable flexibility can be tolerated without attendant ambiguity, for, due to the high degree of symmetry and the intrinsic rigidity of these forms, no more than two well-defined conformations need be anticipated. If a chair or half-chair conformation is not permitted, however, the situation becomes much more complex for all but conformationally rigid systems. The possible alternative conformations are much more mobile and much less symmetrical; six conformations are possible for a regular boat, for example (54–59), in addition to many other even less



symmetrical arrangements available to twist boats.<sup>26</sup> Since each arrangement represents a possible starting point for a second-order analysis, it can be seen that such an analysis, which, as will be outlined in detail subsequently,<sup>5</sup> depends crucially on known geometric interatomic relationships, will become untenable. In addition, it would seem that the task of distinguishing among a number of energetically similar conformations will produce results of limited synthetic utility. Thus only a small number of nonchair conformations will be treated in the analysis; most such skew forms are passed over with no axial and

(24) (a) House, H. O.; Lusch, M. J. *J. Org. Chem.* 1977, 42, 183. (b) Ficini, J.; Touzin, A. M. *Tetrahedron Lett.* 1977, 1081.

(25) (a) Johnson, W. S. *Experientia* 1951, 7, 315. (b) Johnson, W. S.; Bauer, V. J.; Margrave, J. L.; Frisch, M. A.; Deger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* 1961, 83, 606. (c) Margrave, J. L.; Frisch, M. A.; Bautiste, R. G.; Clarke, R. L.; Johnson, W. S. *Ibid.* 1963, 85, 546.

(26) Cf.: Kellie, G. M.; Riddell, F. G. *Top. Stereochem.* 1974, 8, 225.

Table II. Effects of Constraining Bonds on Six-Membered-Ring Flexibility<sup>a</sup>

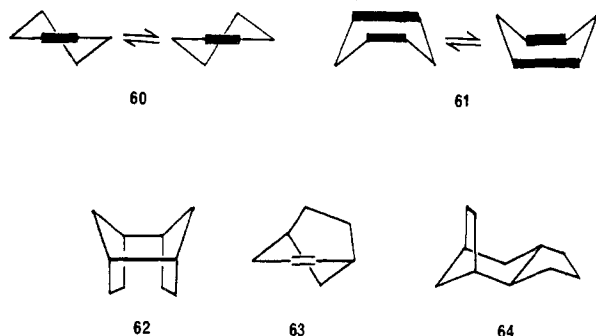
	None	F	None	
	Flattening	F	F	Flattening
	Anchoring	?	?	Anchoring
[1,3] Bridged	R	R	R	[1,3] Bridged
[1,4] Bridged	R	R	R/D	[1,4] Bridged

<sup>a</sup> F = flippable. D = distortable. R = rigid.

equatorial designations given to their appendages.

This is the fate, then, of the nonchair forms of the six-membered rings in conformations 41, 49 (certain ones), 50 ( $n = 3, 4$ ), and 53 ( $n = 4, 5$ ) described above. Examples of mobile nonchair forms that do receive a full analysis are the six-membered ring systems 27, with two [1,4]-disposed flattening bonds, and 53 ( $n = 1, 2, 3$ ).<sup>27</sup> In these cases structural constraints remove many of the conformational ambiguities described above and result in mobile though well-defined boat forms.

Prediction of the effect of constraining bonds on the flexibility of the six-membered ring is, in most cases, quite straightforward. As seen from Table II, flexibility assignments may be made directly for most possible combinations of constraining bonds within the six-membered ring. Most of the entries in Table II derive directly from the previous discussion. The absence of any constraining bonds (entry 1) permits a freely inverting chair, as does a single (entry 2) or a pair (entry 6) of flattening bonds a freely inverting half-chair (cf. 60) or boat (cf. 61).



defined above, a single anchoring bond (entry 3) or a [1,3] bridge (entry 4) gives rise to a six-membered ring that may depart from its chair or half-chair conformation but not achieve its fully inverted counterpart, and a single [1,4] bridge (entry 5) can yield a distortable or a rigid boat. If a six-membered ring is bridged and, in addition, contains a flattening (entries 8 and 9) or anchoring (entries 11 and 12) bond or a second bridge (entries 13–15), it then has no conformational mobility (cf. 62–64).

Unfortunately, prediction of the flexibility effects of combinations of anchoring bonds (entry 7) or anchoring and flattening bonds (entry 10) on six-membered rings is, as indicated in Table II, not straightforward. Whether rings so constrained are rigid or in fact retain conformational mobility is a complex function of the number, nature, and disposition of the constraining bonds about the ring. This was realized by constructing Dreiding-type models of all such possible structural combinations. For

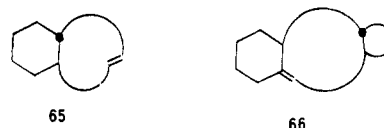
Table III. Effect on Six-Membered-Ring Flexibility of Two [1,3]- or [1,4]-Disposed Trans Constraining Bonds as a Function of the Size of the Constraining Ring

n	n'	Diagram 1	Diagram 2	Diagram 3	Diagram 4
≤5	≤5	Rigid	Rigid	Rigid	Rigid
≤5	6	↓	↓	↓	↓
≤5	≥7	↓	↓	↓	Distortable
6	6	Distortable	↓	↓	↓
6	≥7	↓	↓	Distortable	↓
≥7	≥7	↓	↓	↓	↓

this purpose, each constraining bond in each arrangement was built in turn into a five-, six-, and seven-membered ring and the flexibility of the central six-membered ring noted in each case as either distortable or rigid. A small sampling of the results, where [1,3] and [1,4] bis-trans-fused six-membered rings were examined, is noted in Table III. It can be appreciated that, in all, a large number of structural types had to be examined.

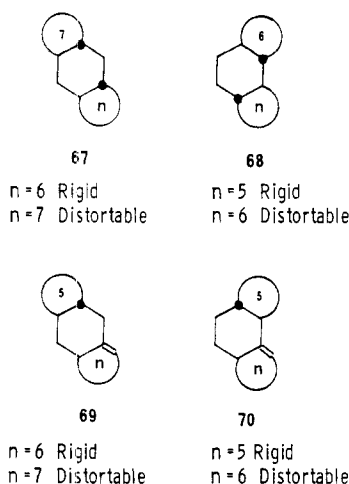
The large amount of data generated prompted a search for a conceptually unifying and computationally efficient method for predicting the six-membered ring flexibilities arrived at through the model building. A satisfying solution was found through development of an empirical predictive formula approach. In essence, the method involves assigning each of the six atoms of the ring an *atom mobility parameter* based on the type of constraining bond it is in or adjacent to, followed by obtaining an overall *ring mobility parameter* based on the disposition and the nature of the constraining bonds. Ultimately, a *ring flexibility parameter* is computed from the atom and ring mobility parameters. This number translates into a ring flexibility classification of rigid or distortable. This method is described in detail in the computation section.

**Other First-Order Conformational Effects. (1) Intrinsic Ring Size.** As mentioned above, trans and SP2 constraining bonds are only significant in the determination of six-membered ring conformation if contained in a ring of size seven or smaller. Thus, for example, trans fusion of a six-membered ring to a nine-membered ring does not, to a first approximation, conformationally restrict the six-membered ring, for a seven-carbon arc is able to reach between two adjacent axial positions. It would be anticipated that this situation would be considerably altered if various geometric constraints were placed upon the nine-membered ring. We have examined a number of molecular model systems, incorporating rings of up to size 12, to determine the effects of several different structural types on attenuating the reach of arcs of atoms. Specifically, cis double bonds, cis-fusion bonds, trans double bonds, trans-fusion bonds, and bridging bonds were considered. It was discovered that of these five only trans double bonds (e.g., 65) and trans-fusion bonds (e.g., 66) are significant. General rules for reckoning their specific effect are given in the computation section.



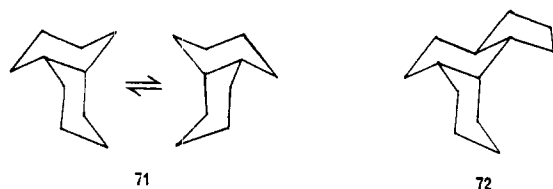
The degree to which these five structural types affect the flexibility-attenuating properties of constraining bonds was also examined. Four model six-membered ring systems (67–70) were utilized for this purpose. These are shown along with their variation in flexibility as a function of the size of the rings containing the constraining bonds.

(27) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* 1978, 100, 1765.



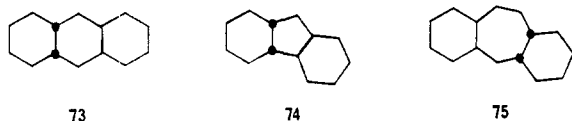
Working with these systems, we discovered that cis double bonds, cis-fusion bonds, and some bridging bonds present in the constraining ring have a significant effect on the flexibility of the central six-membered ring. General rules for reckoning this are given in the computation section.

(2) **Fusion Composites.** A final aspect of the first-order analysis concerns the cis fusion of a pair of six-membered rings. Although a cis-fusion bond obtained in a second six-membered ring is, by definition, not a constraining bond in either a flattening or an anchoring sense, it is not without a very important effect on conformation. Thus, for a pair of cis-fused six-membered rings the chair form adopted by one determines the chair form of the other. If both rings are conformationally free to flip, then they must flip simultaneously (cf. 71). If either ring is unable to



adopt its alternate chair conformation, due to the presence of a trans fusion, for example, then the other ring is likewise constrained (cf. 72). In a sense, then, a pair of cis-fused six-membered rings can be said to have a conformationally anchoring effect on each other. Groups of two or more cis-fused six-membered rings which are conformationally interdependent will be referred to henceforth as *fusion composites*.

As a means of simplifying the analysis, the assumption has been made that such conformational effects can only be transmitted across six-membered rings. Thus, while the perhydroanthracene 73 is considered a three-ring fusion



composite, the six-membered rings in its corresponding homologues 74 and 75 are viewed as conformationally independent. It is assumed that the central rings in 74 and 75 can accommodate considerable conformational variation in the flanking six-membered rings, which are then free to invert, the five-membered ring by virtue of its relatively constant flat shape and the seven-membered ring because of the significantly greater number of degrees of freedom available to it which will enable it to maintain its own low-energy arrangement independent of the six-membered rings.

### Brief Summary of Computation Techniques

The detailed information regarding various computational methods which lead to a preliminary (i.e., tentative) assignment of conformation for the individual six-membered rings in a mono- or polycyclic structure appears as supplementary material. A short and simplified outline is presented here. In the earliest phase of computation the degree of ring flexibility is calculated by an approximate algebraic method based on parametrically assigned atom and ring mobilities. The presence, nature, and position of constraining bonds underlie these mobility assignments. Special corrections are applied for rings of 6–12 members which are fused to six-membered rings to reflect the rigidifying effects of constraining bonds (e.g., trans C=C) on the geometry or “intrinsic” ring size of such 6–12-membered rings. Further conformational analysis is dependent on the following information (previously assembled during the perception phase of the processing): (1) the atom and bond connection table,<sup>1,28a</sup> derived from the two-dimensional structure that the chemist has drawn in;<sup>2</sup> (2) the basic sets containing primary atom-type and bond-type information;<sup>1,28a</sup> (3) a collection of all primary and synthetically significant secondary rings and their spiro, fusion, and bridging pairings;<sup>28</sup> (4) the identification and classification of all functional groups;<sup>18a,29</sup> (5) information on the nature and extent of all molecular appendages;<sup>17b</sup> (6) basic stereochemical information including (a) the *R* or *S* sense of each stereocenter,<sup>3</sup> (b) the cis/trans disposition of all ring appendages,<sup>3</sup> (c) the cis/trans nature of all ring fusion bonds,<sup>3</sup> and (d) the *E/Z* character of all olefinic groupings.<sup>30</sup>

A Fortran subroutine performs the necessary computation of ring conformation and flexibility so that the next task, assignment of axial or equatorial character to the substituents on a particular trial (i.e., tentative) form of a six-membered ring, can be addressed.

Once a full examination of the structural constraints associated with each six-membered ring has been completed, the stage is set for a full axial-equatorial (A/E) labeling of all the stereoappendages about these rings on a preliminary or trial basis. Care must be taken that these A/E assignments are totally self-consistent and fully in accord with all geometrical constraints that have been identified. A/E labeling is provided for the three conformations described above, viz., chair, half-chair, or boat. No special distinction is accorded the pseudoaxial and pseudoequatorial allylic cyclohexene substituents.

The general operation of the A/E assignment module proceeds along the following lines. The six-membered ring is initially given full axial-equatorial appendage assignment on the basis of an *assumed* chair symmetry. A comparison is then made between the bond labels so derived and all previous bond assignments made either during structural constraint examination or by the chemist. If any discrepancy is uncovered, an effort is made to reassign the ring on the basis of boat symmetry. In this way, A/E assignment sensitive both to the structural constraints determined by computation and to any special input from the chemist is achieved.

Once the axial or equatorial sense of a single appendage on a six-membered ring is known, all other appendages on the ring may be readily given A or E labels, *if a chair geometry is assumed*. The labeled appendage which thus

(28) (a) Pensak, D. A. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1973. (b) Corey, E. J.; Hewett, A. P. W., unpublished results.

(29) Orf, H. W. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1976.

(30) Corey, E. J.; Long, A. K. *J. Org. Chem.* 1978, 43, 2208.

serves as the point of referral for the A/E designation of all substituents about the six-membered ring is known as the *reference bond*. The assignment of a suitable bond, i.e., one which is known to have a valid A/E designation, to serve as reference is a critical task.

In many instances a bond search on six-membered ring systems rich in stereoappendages will not turn up any reference bonds. These systems have in common a lack of structural constraint and hence lack features which serve to define axial or equatorial orientations. However, since this lack of anchoring by ring fusion or bridging also has the consequence of allowing both conformational forms of the six-membered rings to exist, it is sufficient to assign *arbitrarily* a reference bond to such systems. Although this, in effect, represents an arbitrary selection of one conformation for the ring or ring system, the possibility for ring flipping which exists in these systems means that the other conformational form will be examined as well before a final conformational decision is reached.

It is computationally more efficient initially to assign each six-membered ring as a chair once a reference bond has been found, even if the ring has been determined to be a boat. Due to the high symmetry of the chair, a simple algorithm for ring assignment, based on the position and stereorelationship of each stereoappendage with respect to the reference bond, can be used. The procedure involves "growing out" from the point of attachment of the reference bond around the ring. All stereoappendages attached two atoms away and *cis* and all attached one or three atoms away and *trans* receive the same A/E label as the reference bond; all other appendages are oppositely labeled. A somewhat more complex procedure is required for the A/E assignment of a boat, where the six-membered ring atoms are not positionally equivalent. The resulting labels represent a *provisional* A/E assignment for the six-membered ring. These are compared with the results of geometric inspection, and chemist input, before the assignment can be *certified* (*vide infra*).

Since all rings initially receive an A/E assignment based on chair symmetry, the boat assignment procedure operates by chair-designation modification. The following sequence takes place for relabeling to accord boat symmetry to any ring that has been assigned as a chair. (i) The locations of the bow positions of the boat are ascertained. (ii) The *switch arc* of the ring is identified. By *switch arc* is meant that three-atom stretch of ring perimeter which consists of one bow and its two adjacent atoms that does *not* subtend the reference bond used for the A/E chair assignments. (iii) Reversal of the A/E designations for all stereoappendages off the *switch arc* takes place.

Location of the two bows of the boat forms the basis of A/E chair-to-boat switching. In some cases, a six-membered ring will be known at the outset of A/E assignment to be a boat, and its bows will thus already have been identified. Rings of this type include certain [1,4]-bridged, [1,3]-bridged, and [1,4]-flattening-bond-containing systems.

**Ring Certification.** When all stereobonds of a six-membered ring have been provisionally assigned an axial or an equatorial label by the procedures defined above, the very important process of ring certification takes place. By ring certification is meant that process wherein it is ascertained whether the provisional labels agree with valid assignments known to exist for any of these appendages. These valid assignments will have resulted from (i) designations made during the examinations for structural constraints, when some axial bonds are identified, (ii) graphical specification by the chemist, and/or (iii) the

certification of six-membered rings previously processed.

A ring-certification failure will occur if a bond-label incompatibility is discovered. If ring certification fails following chair assignment, then the possibility of a boat conformation is signaled. This is the principle means whereby the chair/boat conformational distinction is drawn.

If ring certification fails following boat assignment, two possibilities are raised. If there are no chemist-designated appendages, then a highly unusual six-membered ring geometry is signaled, and no further processing of the ring will take place. If chemist-assigned bond labels exist, however, then the possibility of a graphical input error is suggested. In this event processing is halted and the labeled bond is displayed to the chemist for correction.

After the determination of a trial conformation as chair, half-chair, or boat with the appropriate labeling of substituents as axial or equatorial, this stage of computation is concluded, and the next phase of conformational analysis, assignment of a minimum-energy conformation, is entered (see following paper).

### Conclusion

This paper has detailed the first half of a novel computer method for the prediction of conformation of six-membered ring systems, namely, the formulation of a provisional three-dimensional picture of the ring. A number of structurally significant constraints have been identified and defined, and their effect on six-membered ring conformation has been described. In what is termed a first-order conformational analysis, it has been illustrated how, starting with a two-dimensional structure which includes conventional wedged and dashed stereobonds, a preliminary three-dimensional geometry corresponding to a chair, half-chair, or boat and a qualitative description of the extent of conformational mobility, *viz.*, the flexibility, may be arrived at. Furthermore, it has been shown how a self-consistent set of axial/equatorial labels may be assigned to the appendages of each ring.

This process, which is computationally very rapid, requiring on the order of 0.5 s of computer time per target structure, leads into a second-order conformational analysis. In this phase the destabilization energy of each preliminary geometrical form assigned to each six-membered ring is computed from the assessment of through-space interactions within the six-membered ring system. A number of rapid, empirical computational procedures for carrying this out have been developed, leading, within 1 s, to a semiquantitative description of conformation for each six-membered ring in the target molecule. The second-order analysis is described in the accompanying paper.<sup>5</sup>

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**Supplementary Material Available:** Detailed information on the computation of ring flexibilities, effective ring size, machine assignment of preliminary conformation, reference bond assignment, and ring certification is presented with appropriate discussion, flow charts, and notes to the flow charts. A complete glossary of terms is included (60 pages). Ordering information is given on any current masthead page.