Computer-Assisted Synthetic Analysis. A Rapid Computer Method for the Semiquantitative Assignment of Conformation of Six-Membered Ring Systems. 2. Assessment of Conformational Energies

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The description of a new semiquantitative computer-based method to be used in synthetic planning for the prediction of the conformation of six-membered ring systems is carried on in this paper through the final stages of assignment. Starting with specific geometries from preliminary assignment (i.e., chair, half-chair, boat) which are deduced from the first stage of analysis, simple empirical procedures are applied to calculate approximate conformational destablization energies of each of the preliminary (i.e., tentative) geometries. These procedures are based upon consideration of the disposition of axial and equatorial appendages and do not rely on three-dimensional atomic coordinates. The quantification of interatomic interactions depends on sets of appendage interaction values, the derivation of which is described. Rules for identifying destabilizing interactions between appendages within the same ring and on adjoining rings are given. The destabilization energies so obtained lead to the final conformational decision. Comparisons are made between the results of the present method and those obtained both by more complex molecular mechanics calculations and by X-ray crystallographic analysis.
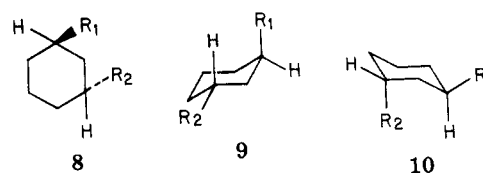
The importance of stereochemical factors in the analysis of complex synthetic problems cannot be exaggerated. In the accompanying paper[1] we have outlined the plan of development of such an aspect of the Harvard LHASA computer program for synthetic analysis and have discussed the initial steps for predicting conformations of six-membered ring systems. In this paper we provide a description of the last stages of conformational determination and the implementation of a computationally efficient method of execution.

The preceding paper dealt with a *first-order* conformational analysis of six-membered ring systems wherein each six-membered ring was scrutinized for a number of predefined configurational constraints. The results were threefold. First, each six-membered ring system received, if possible, a preliminary conformational assignment in harmony with these constraints. The assignment corresponded to one or both of the well-defined chair (1, 2), half-chair (3, 4), or boat (5, 6) geometries or to the flat geometry 7. If no such assignment could be made the ring
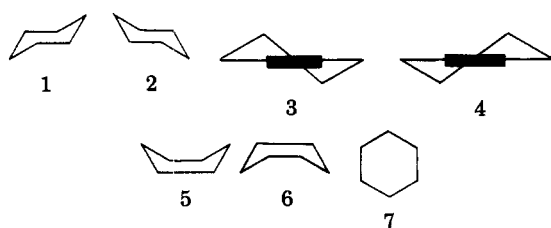
was deemed conformationally ambiguous and was disqualified from any further consideration. Second, each six-membered ring system received a flexibility assignment of either *rigid, distortable,* or *flippable,* reflecting, respectively, negligible conformational mobility, the ability to deform out of the well-defined assigned geometry, or the freedom to interconvert between two well-defined assigned geometries. Third, for each preliminarily assigned form, each stereoappendage attached to the six-membered ring received a stereolabel of either axial or equatorial.

Thus the first-order analysis performs an important task. This can be viewed as taking two-dimensional structures (e.g., 8)[2a] with conventional wedged and dashed stereo-

bonds (to indicate specific stereorelationships at chiral centers) which the chemist draws into the computer[2b] and rendering them effectively three-dimensional (e.g., 9 and/ or 10). Although a formal three-dimensional representation of structure is not actually generated, the information provided by the first-order analysis is in many ways equivalent to what would be gleaned from a 3-D representation.

The conformation that is assigned during the first-order analysis is provisional and is refined as described in this paper to obtain a final conformational decision. Unless a six-membered ring system has been found to be either flat, ambiguously constrained, or conformationally rigid, each of its provisionally assigned forms is examined, and, *on the basis of assessment of nonbonded interatomic interactions, a total destabilization energy* E_D^{SYS} *is computed.* This energy value is taken to reflect the tendency of the six-membered ring to depart from its provisionally assigned conformation and, in addition, permits prediction of the relative populations of a pair of energetically acceptable conformers. The conformational energies given by our method are only approximate, and the conformational assessment to which they lead is utilized in connection with screening out stereochemically inappropriate chemistry during the performance of a full antithetic analysis. The specific context of the conformational analysis was outlined at the outset of the accompanying paper.[1] The refinement and precision of a molecular-mechanics calculation[3] has not been the goal of our method.

Interatomic interactions are estimated from a consideration of the disposition of the axial and equatorial ap-

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

(2) (a) Corey, E. J.; Howe, W. J.; Pensak, D. A. *J. Am. Chem. Soc.* 1974, *96*, 7724. (b) A structure is quickly input by using an electronic drawing tablet and stylus[2c] or via cross-hair cursor positioning of the atoms. (c) Corey, E. J.; Wipke, W. T.; Cramer, R. D., III. *J. Am. Chem. Soc.* 1972, *94*, 421.
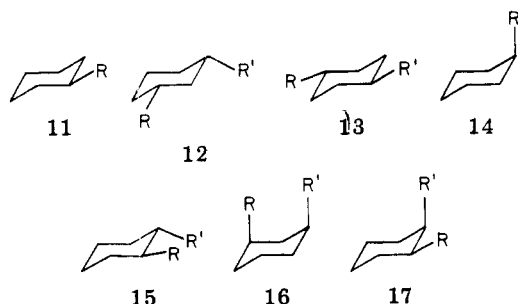
(3) (a) Allinger, N. L. *J. Am. Chem. Soc.* 1977, *99*, 8127. (b) Allinger, N. L. *Adv. Phys. Org. Chem.* 1976, *13*, 1.

pendages about the ring; three-dimensional atomic coordinates are not required. We have developed a series of simple empirical computational procedures for tallying the interactions, drawing on the results of inspection of Dreiding-type molecular models and the available experimental data. Two types of destabilizing interaction are differentiated: *intra*-ring, those between a pair of appendages on the same six-membered ring, and *inter*-ring, those between two appendages or atoms on adjoining rings. In this way a means of *rapid*, semiquantitative conformational analysis is achieved; the computational procedures described below require on the average *only 1 s of computer time per target structure*.

Intra-ring Interactions in Chairs

A monoequatorially substituted cyclohexane (**11**) or a 1,3- or 1,4-diequatorially substituted cyclohexane (**12** or **13**) is considered to have minimal through-space substit-

uent interactions and is hence assigned a total destabilization energy of zero; i.e., these ring systems are considered, for all R, to be perfect chairs. In our analysis, four types of *intra*-ring arrangements which can destabilize the chair are recognized. These include (1) the presence of a single axial appendage (**14**) and the interaction of a pair of appendages in either (2) 1,2-trans-diequatorial (**15**), (3) 1,3-cis-diaxial (**16**), or (4) 1,2-cis-axial/equatorial (**17**) disposition.

In practice only *three* of these interaction types, those in **14, 15**, and **16**, are counted as actually raising the energy of the chair conformation. No effective destabilization is counted for the 1,2-cis-axial/equatorial interaction in **17**. This simplifying procedure is followed even though appendage pairs here bear the same spatial relationship as do two trans-diequatorially situated appendages (**15**), with a dihedral angle of separation, ϕ, of 60° (**18**);[4] it is justified
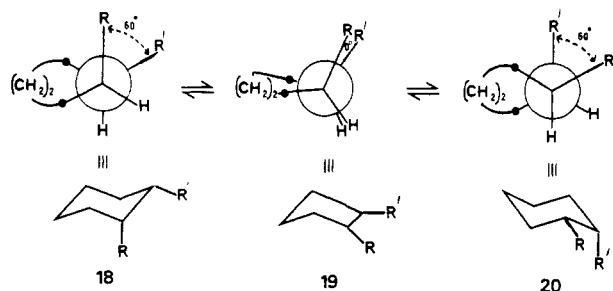
(4) In reality cyclohexane has been shown to adopt a distorted chair conformation which serves to bring A/E substituent pairs in somewhat closer proximity (ϕ in i = 55°) than E/E pairs (ϕ in ii = 65°), resulting in enhanced A/E interactions. Cf.: (a) Aycard, J.-P.; Bodot, H.; Lauricella, R. *Bull. Soc. Chim. Fr.* **1969**, 3516. (b) Wohl, R. A. *Chimia* **1964**, 219. (c) Sicher, J.; Tichy, M. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3687.
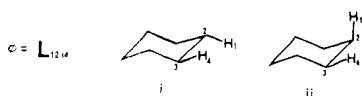

Table I. Set of Computational *A* Values

H	0	NH$_3^+$	2.0
		NR$_2$	2.1
F	0.2	NHR	1.3
Cl	0.4	N=	0.5
Br	0.4	N≡	0.2
I	0.4	NO$_2$	1.1
PR$_2$	1.6	C≡	0.2
SR	0.8	aryl	3.0
S(O)R	1.9	CO$_2^-$	2.0
S(O$_2$)R	2.5	CHO	0.8
		C=	1.3
OR	0.8	CR$_3$	6.0
		CHR$_2$	2.1
		CH$_2$R	1.8

by reasoning that, in general, axial/equatorial interactions, unlike their 1,2-E/E counterparts, cannot be relieved in departing from the chair: initial chair deformation leads to increased interaction (**19**), while a full conformational inversion returns an equivalently disposed A/E pair (**20**).[5]

An important simplifying assumption used throughout is that conformational effects are additive, i.e., that various destabilizing interactions identified within a six-membered ring system operate independently of each other. Thus, for example, it is assumed that the position of the equilibrium between **21** and **22** can be determined simply from

$$E_D{}^R = A_R \ (1) \qquad E_D{}^R = 0 \ (2)$$
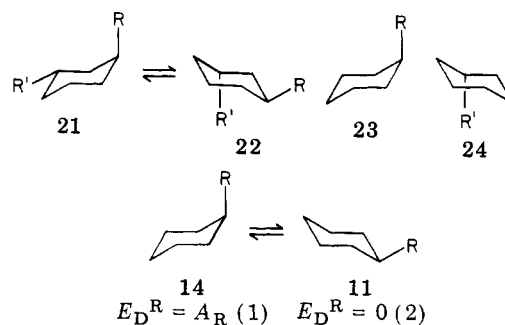
the difference in the conformational energies of the systems **23** and **24**. Although the additivity principle has been shown to be not always valid,[6c,7a,b] it is frequently usefully applied[7c] and is felt to be a satisfactory approximation for our purposes.

Axial Interaction. For a monosubstituted cyclohexane, the negative of the free energy difference associated with its conformational equilibrium (**14 ⇌ 11**) is defined as the *A* value[8] of the substituent R. In a monosubstituted cyclohexane, the greater the *A* value of an appendage R the greater the driving force to adopt the R-equatorial chair

(5) (a) Strictly speaking, real differences can exist between 1,2-cis-disubstituted cyclohexane conformers (**18** vs. **20**), reflecting specific rotational preferences of R and R' in their respective axial and equatorial environments.[6] (b) This rationalization breaks down in the relatively uncommon instances when half-flips of chairs give well-defined boats. Thus R/R' destabilizations are tallied for boat conformers ii and iv but not for chair conformers i and iii.
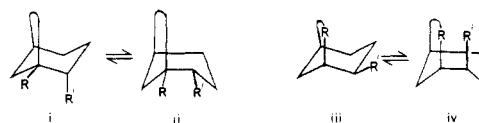
(6) (a) Stolow, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 2170. (b) Tichy, M.; Vasickova, S.; Vitek, A.; Sicher, J. *Collect. Czech. Chem. Commun.* **1971**, *36*, 1436. (c) Eliel, E. L.; Schroeter, S. H.; Brett, T. J.; Biros, F. J.; Richer, J.-C. *J. Am. Chem. Soc.* **1966**, *88*, 3327.
(7) (a) De Beule, H.; Anteunis, M. *Tetrahedron* **1974**, *30*, 3573. (b) Eliel, E. L.; Enanoza, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 8072. (c) Rej, R. N.; Bacon, E.; Eadon, G. *Ibid.* **1979**, *101*, 1668.
(8) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.

form. In our computation, the A value of R, A_R, is thus considered to be the destabilization energy imparted to a monosubstituted six-membered chair by an axial appendage R (14); an equatorial appendage R (11) contributes a destabilization energy of zero (eq 1 and 2).[9]

The A values for a large number of monosubstituted cyclohexanes are on record.[10] We have observed that, to a first approximation, the A value of an appendage is chiefly determined by the nature of its *connecting atom* (i.e., the atom which is bonded to the six-membered ring), specifically by the atomic type, degree of hydrogen attachment, and hybridization of this atom. On this basis a relatively short list of A values that are of general use within the analysis was drawn up. This is presented in Table I.

Estimation of Diaxial and Diequatorial Interactions. Although the conformational energies for many monoaxially substituted cyclohexanes are known, there is a surprising paucity of energy data available in the literature for pairs of interacting cyclohexane substituents. Thus it was anticipated that in many instances during a conformational analysis the value for an unmeasured interatomic interaction of either the 1,2-diequatorial (15) or the 1,3-diaxial (16) type would be required. Since there exists no simple method for the general estimation of the magnitudes of such interactions, we were obliged to devise means of doing so.

Two simple approaches, which eventually had to be rejected, are as follows. First we describe an approach with 1,2-diequatorial interactions. Our basis for the prediction of the magnitude of these came from a simple analysis of the destabilizing factors in monoaxially substituted cyclohexanes. It is commonly believed[11a] that the destabilization caused by an axial substituent is due its interaction with the two syn-1,3-diaxial hydrogens on the ring (25).[12]

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26   27
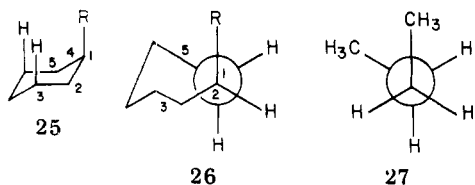
$$E_D{}^R = A_R = g[1,2,3] + g[1,4,5] \ (3)$$

Each of these interactions is of the same type as that in the gauche rotamer of butane (26, R = Me, and 27). Thus it was thought that the contribution to the destabilization energy made by a lone axial group R, $E_D{}^R$, could be set equal to the sum of the energies of its two equivalent gauche interactions $g[1,2,3]$ and $g[1,4,5]$ (25); since the A value of R is a measure of this destabilization, A_R was equated to this sum (eq 3).

On the basis of this simple relationship the *gauche interaction value* (g value) of a cyclohexane appendage was defined as equal to half its A value. The g value was then

Table II. Reported 1,2-Diequatorial R/R Interaction Energies (kcal/mol)

entry	R_1	R_2	energy	ref
1	F	I	0.1	13
2	Cl	Cl	0.7-1.4	14-17
3	Cl	Br	1.1-1.5	14
4	Cl	I	1.2	18
5	Cl	OMe	0.5-1.2	15, 17
6	Cl	Me	0.2	14
7	Br	Br	1.2-2.0	14-17
8	Br	I	1.9	19
9	Br	OMe	0.4-1.0	15, 17
10	Br	Me	0.25	14
11	I	I	1.9	20
12	OMe	I	0.4-0.8	17
13	OH	OH	0.35	20, 21
14	OH	OMe	0.64	15
15	OH	NH_2	-0.9	22
16	OH	NMe_2	-0.6	22
17	OMe	OAc	0.2-1.0	17
18	OTs	OTs	1.8	20
19	OAc	OAc	0.2	20
20	SMe	Cl	1.2-2.2	17
21	SPh	Cl	0.7-0.9	23
22	SMe	Br	1.5-2.5	17
23	SMe	OMe	0.6-1.8	17
24	SMe	OAc	0.6-1.8	17
25	SMe	SMe	1.5-2.9	17
26	Me	Me	0.75-0.80	14, 22
27	Me	OH	0.38	5, 24
28	Me	CO_2Et	0.2	24
29	Me	$CO_2{}^-$	0.9	24
30	Me	CN	0	24, 25
31	Me	NHR	0.7	26
32	t-Bu	OH	2.5	27
33	t-Bu	OMe	2.5	27
34	CO_2H	CO_2R	0.3	4a

used to derive an expression for approximating the magnitude of the 1,2-diequatorial *intra*-ring interaction as follows. The connecting atoms (vide supra) of a pair of 1,2-diequatorially arranged appendages bear the same spatial relationship as the terminal carbon atoms in the gauche rotamer of butane (27 and 28). The case was thus

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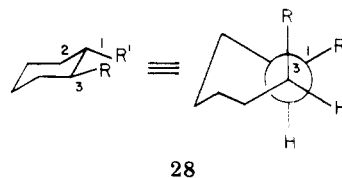
$$E_D{}^{R/R'} = g[1,2,3] = (A_R + A_{R'})/4 \ (4)$$

made that, to a simple first approximation, the 1,2-diequatorial destabilization could be considered to arise from a "shared" gauche interaction between the two appendages, in other words one whose magnitude is given by the average of the g values of the two groups, i.e., $^1/_2(A_R/2 + A_{R'}/2)$. A possible general expression for estimating the 1,2-diequatorial interaction energies of structural type 15 was thus formulated; this is given in eq 4.

To ascertain the degree to which this formula provided energies in accord with experimental results, we plotted all such data known to us, tabulated in Table II, against

(9) In this paper $E_D{}^R$ and $E_D{}^{R/R'}$ denote contributions to the total destabilization energy $E_D{}^{SYS}$ of a particular conformer made by a single appendage R and a pair of appendages R/R', respectively.

(10) (a) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. (b) Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139. (c) Morris, D. G. *Aliphatic, Alicyclic, Saturated Heterocycl. Chem.* **1973**, *1* (Part III), 105; **1974**, *2*, 174. (d) Morris, D. G. *Alicyclic Chem.* **1975**, *3*, 266; **1976**, *4*, 196. (e) Brown, N. M. D.; Cowley, D. J. *Ibid.* **1977**, *5*, 191. (f) The first A values for phosphorus have been obtained recently: Gordon, M. D.; Quin, L. D. *J. Am. Chem. Soc.* **1976**, *98*, 15.

(11) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Interscience: New York, 1965; p 43. (b) *Ibid.*, pp 113-4. (c) *Ibid.*, p 11.

(12) An alternative explanation for the equatorial bias among six-membered-ring substituents hinges on the gauche H/H interaction. Cf.: Wertz, D. H.; Allinger, N. L. *Tetrahedron* **1974**, *30*, 1579. Cf. also ref 17.

(13) Hall, L. D.; Jones, D. L. *Can. J. Chem.* **1973**, *51*, 2914 and references therein.

(14) Buys, H. R.; Havinga, E. *Tetrahedron Lett.* **1968**, 3759.

(15) Subbotin, O. A.; Sergeev, N. M.; Zefirov, N. S.; Gurvich, L. G. *J. Org. Chem. USSR (Engl. Transl.)* **1975**, *11*, 2265.

(16) Reeves, L. W.; Stromme, K. O. *Trans. Faraday Soc.* **1961**, *57*, 390.

(17) (a) Zefirov, N. S.; Gurvich, L. G. *Tetrahedron* **1976**, *32*, 1211. (b) Bairamov, A. A.; Mursakulov, I. G.; Guseinov, M. M.; Zefirov, N. S. *J. Org. Chem. USSR (Engl. Transl.)* **1978**, *14*, 903.
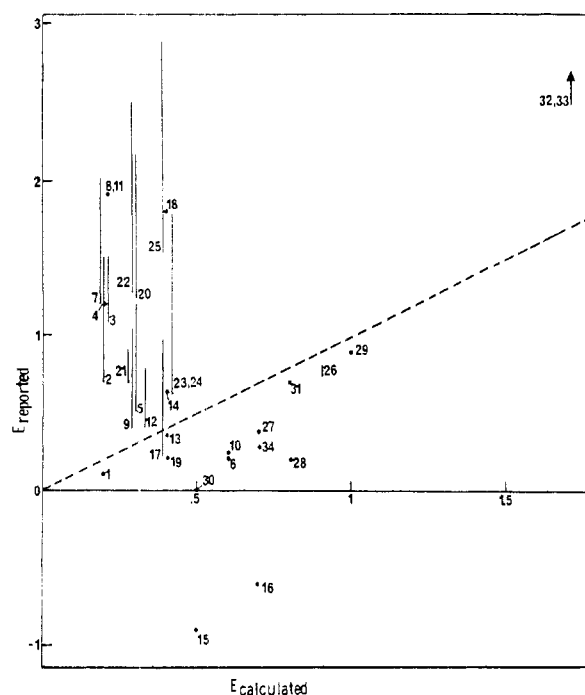
Figure 1. Reported 1,2-diequatorial interaction-energy values and ranges (Table II) plotted against values calculated with A values (Table I) by using eq 4. The numbers in the plot correspond to the entry numbers of Table II. The dashed line denotes ideal correspondence. All energies are in kcal/mol.

the predicted values computed from eq 4 (Figure 1). It was immediately obvious from this plot that, in spite of the wide range of some of the reported values, the deviation from an ideal correspondence (indicated by the straight line through the origin) is large. It was clear that a reasonable approximation of 1,2-diequatorial interactions is not to be had through utilization of A values.

Next we describe a simple but unsuccessful approach to the derivation of the magnitude of 1,3-diaxial interactions using A values. Two cis-1,3-diaxially oriented substituents on a six-membered ring (**16**) bear a unique and


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$$E_D{}^{R/R'} = A_R + A_{R'} \quad (5)$$

special geometric relationship to each other: as will be demonstrated in the ensuing discussion, this interaction will serve as an ideal geometric model for many of the less commonly considered *inter*-ring destabilizing arrangements possible in six-membered ring systems. In order to derive

(18) Pan, Y.-H.; Stothers, J. B. *Can. J. Chem.* **1967**, *45*, 2943.

(19) Torgrimsen, T.; Klaeboe, P. *Acta Chem. Scand.* **1971**, *25*, 1915.

(20) Lemieux, R. U.; Lown, J. W. *Can. J. Chem.* **1964**, *42*, 893.

(21) Angyal, S. J.; McHugh, D. J. *Chem. Ind. (London)* **1956**, 1147.

(22) Tichy, M.; Vasickova, S.; Arakelian, S. V.; Sicher, J. *Collect. Czech. Chem. Commun.* **1970**, *35*, 1522.

(23) Zefirov, N. S. *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 1768.

(24) Tichy, M.; Sicher, J. *Collect. Czech. Chem. Commun.* **1968**, *33*, 68.

(25) LaFrance, R.; Aycard, J.-P.; Berger, J.; Bodot, H. *Org. Magn. Reson.* **1976**, *8*, 95.

(26) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1977**, *42*, 51.

(27) (a) Stolow, R. D.; Groom, T.; Lewis, D. J. *Tetrahedron Lett.* **1969**, 913. (b) Stolow, R. D.; Gallo, A. A.; Marini, J. L. *Tetrahedron Lett.* **1969**, 4655. (c) Stolow, R. D.; Marini, J. L. *Ibid.* **1971**, 1449. (d) Pasto, D. J.; Rao, D. R. *J. Am. Chem. Soc.* **1970**, *92*, 5151.

Table III. Reported 1,3-Diaxial R/R Interaction Energies (kcal/mol)

entry	R_1	R_2	energy	ref
1	Me	Me	3.7	28
2	OH	OH	1.9	29
3	Me	OH	1.9–2.7	29, 30
4	OAc	OAc	2.0	29
5	Cl	Cl	5.5	29, 31
6	Me	Br	2.2	29
7	Me	F	0.4	29
8	Me	CO_2Et	2.8–3.2	29, 30
9	Me	Ph	2.9	32
10	Me	CN	2.7	30
11	Me	$CO_2{}^-$	3.4	30
12	CN	CN	3.0	30
13	CO_2CH_3	CO_2CH_3	1.7	33
14	CO_2H	CO_2H	1.1	33
15	$CO_2{}^-$	$CO_2{}^-$	4.2	33
16	$NH_3{}^+$	$CO_2{}^-$	–1.8	33
17	$NH_3{}^+$	CO_2H	0.5	33
18	OMe	CH_2R	1.9	34
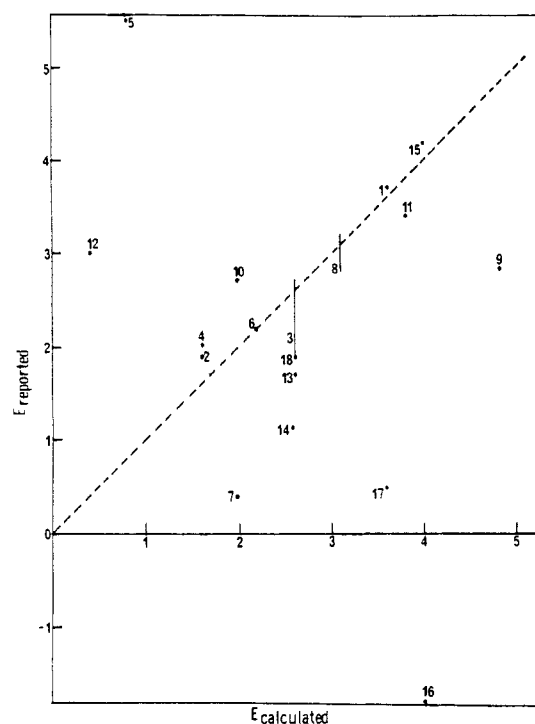
Figure 2. Reported 1,3-diaxial interaction-energy values and ranges (Table III) plotted against values calculated with A values (Table I) by using eq 5. The numbers in the plot correspond to the entry numbers of Table III. The dashed line denotes ideal correspondence. All energies are in kcal/mol.

a general predictive expression for the destabilizing interaction between a 1,3-diaxial pair, initial recourse was made to the known conformational energy value of 3.7 kcal/mol for diaxial 1,3-dimethylcyclohexane (**16**, R = R′ = CH_3).[28] Since this value is almost equivalent to twice the A value of the methyl group itself, it was tempting to consider all 1,3-diaxial interactions between two six-membered ring appendages as imparting destabilizations roughly equal to the sum of the A values of the two appendages.

A potentially general expression, then, which was formulated to estimate the 1,3-diaxial component of the destabilization energy of structural type **16**, is given in eq 5. To our knowledge only a modest number of 1,3-diaxial interaction energies have been measured experimentally

(28) Allinger, N. L.; Miller, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 2145.

(Table III); these data were plotted against the corresponding values predicted by eq 5 (Figure 2); again the straight line drawn through the origin represents an ideal correspondence. Examination of this plot revealed a less than satisfactory agreement between prediction and observation. It was once again clear that appendage A values cannot be reliably drawn on to provide assessment of appendage/appendage 1,3-diaxial interactions.

We now discuss a more productive empirical approach to the prediction of appendage/appendage interaction destabilization energies. We were not particularly surprised by the shortcomings of the early attempts described above. The lack of a simple relationship between the conformational bias recorded for isolated cyclohexane appendages, as measured by their A values, and the energies of interaction recorded between pairs of cyclohexane appendages has been commented upon by several investigators;[17,30,34] the difficulty lies in consideration of the A value as an inherent property of the appendage itself, rather than of the monosubstituted cyclohexane system for which it was measured. However, it seemed that it might be possible to utilize the energy data collected from the literature to generate empirically sets of reasonably self-consistent *appendage interaction values* which would be useful, to a first approximation, in predicting 1,3-diaxial and 1,2-diequatorial interactions. This proved to be the case. Our method for assessing the three basic types of *intra*-ring destabilization interactions defined above for six-membered chairs is as follows. Each appendage type R listed in Table I has associated with it three appendage interaction values: (1) an A value,[8] A_R, as defined above, for monoaxial interactions, (2) a G value,[35] G_R, for 1,2-diequatorial interactions, and (3) a U value,[36] U_R, for 1,3-diaxial interactions. Monoaxial interactions (14) are computed as already described (eq 1). A group pair interaction is simply obtained by summing the appropriate G or U values for diequatorial (15) and diaxial (16) interactions respectively (eq 6 and 7). The successful derivation of the sets of G and U values is now described.

$$E_D^{R/R'} = G_R + G_{R'} \quad (6) \qquad E_D^{R/R'} = U_R + U_{R'} \quad (7)$$
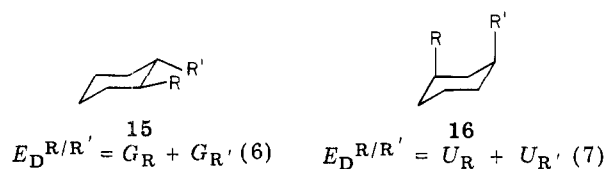
In order to obtain the desired G values, we used the set of published diequatorial interaction energies collected in Table II. Since roughly half of the appendage types which had been defined (Table I) are represented in this col-

Table IV. Set of Computational G Values

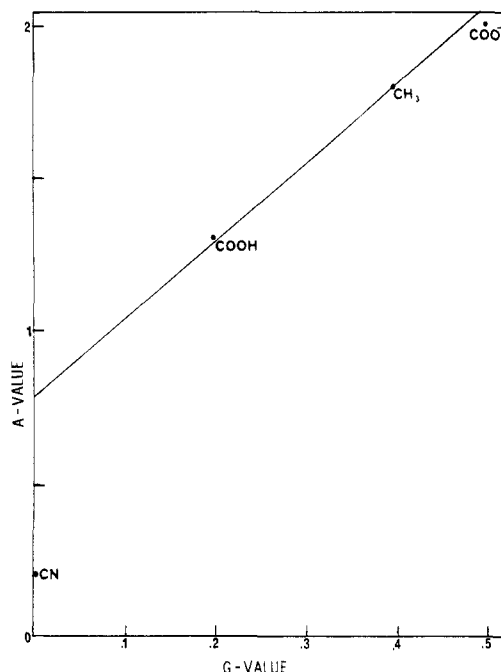|			
H	0	NH_3^+	0.5
		NR_2	0.5
F	0	NHR	0.3
Cl	0.5	N=	0.1
Br	0.8	N≡	0.1
I	1.0	NO_2	0.3
PR_2	1.6	C≡	0
		aryl	1.2
SR	1.1	CO_2^-	0.5
S(O)R	2.7	CHO	0.3
$S(O_2)R$	3.5	C=	0.2
		CR_3	2.5
OR	0.2	CHR_2	0.8
		CH_2R	0.4

Figure 3. Correlation of A (Table I) and G values (Table IV) for some appendages with carbon connecting atoms. The relationship $G_C = 0.4A_C$ derives from the slope of the line drawn.

lection, it proved possible to use these data to extract a fairly complete set of G values by proceeding as follows. G values were first assigned to those appendages R for which R/R diequatorial interaction energies ($E_{R/R}$) were known (Table II, entries 2, 7, 11, 13, 25, 26, and 34). In these cases G_R was set equal to half of $E_{R/R}$ or to half of the median $E_{R/R}$ if a range of values had been reported. Thus, for example, the G value for iodine was assigned a value of 1.9/2 = 1.0 (Table II, entry 11). In this way, G values were extracted for the following appendage types: Cl, Br, I, OR, SR, C≡, and CHR_2. The assignments are given in Table IV. The G value assigned OR (0.2) represents an arbitrary choice, for it will be noted that widely divergent energy values for three OR/OR diequatorial interactions have been reported (Table II, entries 13, 18, and 19). G values were then assigned to those appendages R' for which R/R' diequatorial interaction energies were known, i.e., energies reported involving two different appendages R and R' where R was an appendage whose G value had been assigned as described above (Table II, entries 1, 29–31). Subtracting G_R from $E_{R/R'}$ gave $G_{R'}$; when a negative number resulted, a $G_{R'}$ value of zero was assigned to R'. Thus G values were obtained for the following appendage types: F, CO_2^-, CN, and NHR. The assignments appear in Table IV. In order to complete the assignment of G values, we made the assumption that

(29) Allinger, N. L.; Graham, J. C.; Dewhurst, B. B. *J. Org. Chem.* **1974**, *39*, 2615 and references cited therein.

(30) Tichy, M.; Orahovats, A.; Sicher, J. *Collect. Czech. Chem. Commun.* **1970**, *35*, 459.

(31) Schwabe, V. K. *Z. Elektrochem.* **1956**, *60*, 151.

(32) (a) Shapiro, B. L.; Chrysam, M. M. *J. Org. Chem.* **1973**, *38*, 880. (b) Shapiro, B. L.; Johnson, M. D., Jr.; Shapiro, M. J. *Ibid.* **1974**, *39*, 796. (c) Allinger, N. L.; Tribble, M. T. *Tetrahedron Lett.* **1971**, 3259.

(33) Armitage, B. J.; Kenner, G. W.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 747.

(34) Tavernier, D.; DePessemier, F.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1975**, *84*, 333.

(35) The term "G value" to denote the nonbonded interaction free energy of the hydroxyl group in 1,2-diequatorial relationships was coined by Lemieux.[20]

(36) We suggest the particular alphabetic designation "U" in lieu of the perhaps more obvious but already spoken for "A". This derives from the term "upright" which was originally[37] used to describe what later[38] came to be known as "axial" bonds.

(37) Hassel, O. *Tidsskr. Kjemi Bergves. Metall.* **1943**, *3*, 32; *Acta Chem. Scand.* **1947**, *1*, 149.

(38) Barton, D. H. R.; Hassel, O.; Pitzer, K. S.; Prelog, V. *Nature (London)* **1953**, *172*, 1096.
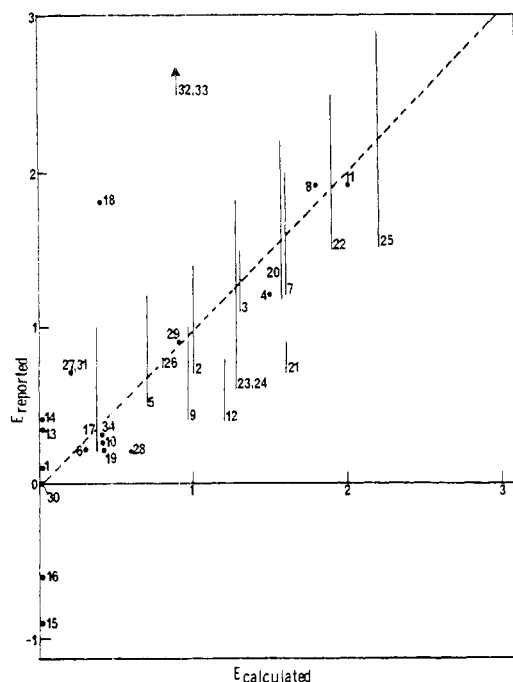
Figure 4. Reported 1,2-diequatorial interaction-energy values and ranges (Table II) plotted against values calculated with G values (Table IV) by using eq 6. The numbers in the plot correspond to the entry numbers of Table II. The dashed line denotes ideal correspondence. All energies are in kcal/mol.
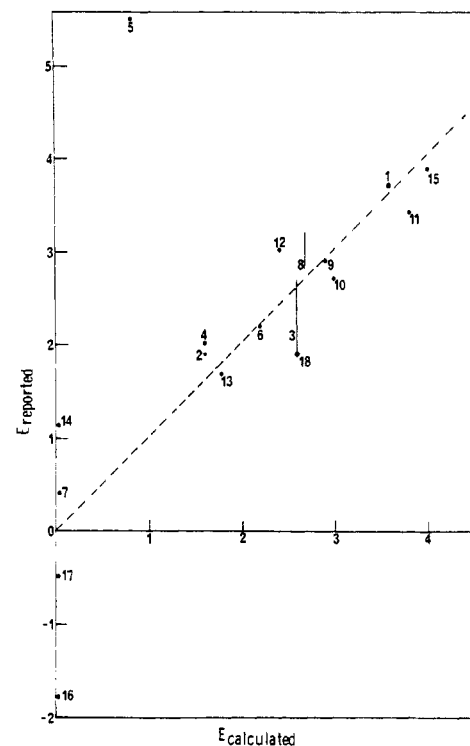
Table V. Set of Computational U Values

|			
H	0	NH_3^+	2.0
		NR_2	2.1
F	0	NHR	1.3
Cl	0.4	N=	0.5
Br	0.4	N≡	1.2
I	0.4	NO_2	1.1
PR_2	1.6	C≡	1.2
SR	0.8	aryl	1.1
S(O)R	1.9	CO_2^-	2.0
$S(O_2)R$	2.5	CHO	0.8
		C=	0.9
OR	0.8	CR_3	6.0
		CHR_2	2.1
		CH_2R	1.8

Figure 5. Reported 1,3-diaxial interaction-energy values and ranges (Table III) plotted against values calculated with U values (Table V) by using eq 7. The numbers in the plot correspond to the entry numbers of Table III. The dashed line denotes ideal correspondence. All energies are in kcal/mol.

within a group of appendages with the same connecting atom (vide supra) there exists a rough linear correspondence between the G and A values. Thus when the G values computed by using the technique described above for the four carbon appendages CN, CO_2H, CH_3, and CO_2^- were plotted against the corresponding A values, a satisfactory linearity was observed (Figure 3). From this plot, which gives $G_C = 0.4A_C$, G values for aryl, CHO, CHR_2, and CR_3 were obtained. Similarly, on the basis of the single G values computed above for NHR and SR, it followed that $G_N = 0.24A_N$ and $G_S = 1.4A_S$. This technique established G values for all the remaining appendage types except PR_2, which was arbitrarily assigned a G value equal to its A value. Our complete set of G values appears in Table IV.

In general, the use of G values to give 1,2-diequatorial interaction energies appears to work satisfactorily; the correlation achieved is illustrated in Figure 4 by using data drawn from Table II. We have analyzed the results in terms of appendage types and found that although there is usually very good agreement between prediction and observation for the pairings halogen/halogen, halogen/oxygen, oxygen/oxygen, sulfur/halogen, and sulfur/oxygen, the predicted carbon/heteroatom values are consistently high. Thus we have adopted the empirical practice of reducing to one-third all 1,2-diequatorial gauche interactions computed between carbon and heteroatom appendages by G-value summation. It will also be noted from the plot in Figure 4 that zero destabilization energies have been computed for the interactions between OH and a second OR or NR appendage. As will be discussed in more detail shortly, this follows our practice of counting no net stabilization or destabilization for appendage pairs that can hydrogen bond.

In contrast to the estimation of G values, obtaining a set of U values was a simpler task. As noted above, there is a fairly direct relation between 1,3-diaxial interaction energies and A value, and it seemed that in most cases the U value of an appendage could be set equal to its A value. Our empirical U-value assignments are listed in Table V.

There are a few instances where the A value has been modified, namely, for the appendage types F, aryl, C=, C≡, and N≡. Fluorine is apparently of very little steric consequence in transannular appendage interaction (Table III, entry 7) and has been assigned a zero U value. We have also chosen to assign a somewhat reduced U value to sp²-hybridized carbon and to phenyl (Table III, entries 13 and 9); the conformational peculiarities of this latter substituent have been discussed.[32] On the other hand, as has been noted,[30] the "small" cyano group can display significant 1,3-diaxial interaction with groups larger than hydrogen (Table III, entry 10). Accordingly, this group and the isoelectronic isocyanide have been assigned enhanced U values. The good correlation which results when U values are used to predict 1,3-diaxial interaction energies is shown in Figure 5. This plot includes corrections for electrostatic phenomena, which will be described shortly.

Modified *Intra*-ring Interactions. In the assessment of conformational destabilization due to *intra*-ring interactions it is important to be aware of those general structural features which will lead to a reduction in the normally computed interaction energies. Both steric

modifications, which result in the partial or complete absence of one component of a 1,3-diaxial interaction, and electronic factors, which lead to stabilizing interactions, must be considered.
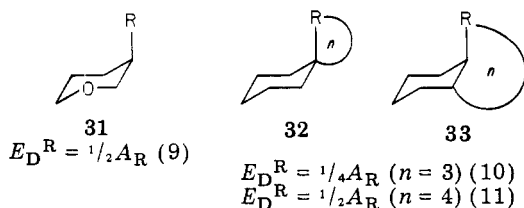
In the discussion of interatomic interactions in chairs, the conformational destabilization caused by a lone axial appendage was attributed to its repulsive interaction with the two syn-axial hydrogens (**29**). In the absence of one
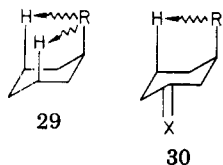
$$E_D{}^R = [(3 - n)/3]A_R \quad (8)$$

of these syn-axial hydrogens, as, for example, in 3-substituted cyclohexanones or methylenecyclohexanes (e.g., **30**, X = O or CH_2), one might thus anticipate the destabilization caused by an axial appendage to be reduced by half. Conformational studies on such systems have provided varied results. For alkyl-group appendages the total destabilization due to axial R has been found to range from $^1/_2A_{Me}$ for 3-methylmethylenecyclohexane (**30**, R = CH_3, X = CH_2)[39] to $^3/_4A_{Me}$ for 3-methylcyclohexanone (**30**, R = CH_3, X = O).[11b] For polar appendages (**30**, R = OR or SR, X = O), however, either an increase or decrease in axial population has been observed, depending on solvent polarity.[39] Therefore the following computational practice has been adopted: for axial appendages with carbon connecting atoms the destabilization contribution is given by the A value of the appendage, diminished by $^1/_3$ times the number, n, of β sp^2 centers (eq 8).[40] If the appendage has a heteroatom origin, no special effect of β sp^2 centers is counted.

A great deal of investigation has focused on the conformational behavior of six-membered heterocycles.[41-46] In our general treatment it has not been possible to make provision in the computational procedures for the variety of phenomena that have been observed, although a very important feature of the analysis allows the chemist to specify the effect of many of these during a specific analysis; this feature is described briefly below. Heterocyclic systems are simply treated in the computation as follows. A zero steric interaction is counted between any axial appendage and a β-situated heteroatom in the six-membered ring. Thus in the 3-substituted tetrahydropyran **31**, for example, the destabilization due to axial R is computed as half of the A value of R (eq 9).

$$E_D{}^R = ^1/_2A_R \quad (9)$$

$$E_D{}^R = ^1/_4A_R \quad (n = 3) \quad (10)$$
$$E_D{}^R = ^1/_2A_R \quad (n = 4) \quad (11)$$

Reduced axial interaction might also be anticipated for appendages in small rings where the geometric constraints tend to bend the appendage R away from the β syn substituents. Conformational preferences have been measured for the spirooxirane **32** ($n = 3$, R = O)[47] and for the spiroaziridine **32** ($n = 3$, R = NH).[48] In both systems the heteroatom was found to be axial, and A values of 0.16 and 0.27 kcal/mol, respectively, were reported. On the basis of these results the empirical practice has been adopted of reducing the destabilizing contributions of axial substituents in spiro-coupled (**32**) or fused (**33**) small rings to one-fourth (for three-membered rings) or half (for four-membered rings) of their customary A value (eq 10 and 11); U and G values are likewise decremented.

The possibility is also recognized of instances when, because of a stabilizing electrostatic interaction between two groups, simple summation of the corresponding pair of U or G values will give an inappropriately high $E_D{}^{R/R'}$. The following computational provisions have been adopted as empirical but simple means of handling these situations. (i) If the two interacting groups bear opposite charges, a stabilization (i.e., a negative $E_D{}^{R/R'}$) equal to half the sum of the appropriate U or G values is tallied.[49] (ii) If the two interacting groups bear the same charge, the interaction is computed by summing the appropriate U or G values; no extra destabilization is counted. (iii) If the possibility for hydrogen bonding between the two interacting groups exists, with such bonding limited to hydrogen bridging between elements of the set fluorine, oxygen, and nitrogen,[50] no destabilizing interaction is computed.

One further instance where electrostatic effects result in a conformational stabilization is exemplified by the diaxial forms of *trans*-1,2- and -1,4-dihalocyclohexanes (**34** and **35**). In these molecules a considerably greater pro-

$$E_D{}^{SYS} = ^1/_2(A_X + A_Y) \quad (12)$$

portion of diaxial population than would be expected from A-value additivity considerations is often observed.[51] This phenomenon has been attributed to a more favorable electrostatic interaction between the dipoles in the diaxial conformation.[52] In our assessment of interatomic destabilization interactions, this effect is allowed for by halving the destabilization contribution computed for [1,2]- or [1,4]-disposed diaxial heteroatomic appendage pairs through A-value summation (eq 12). In the absence of information on other heteroatoms this procedure is restricted to halogen appendages.

It remains to comment on the fact that, as a result of the complexity intrinsic in the operation of electrostatic forces of both an *intra*molecular and a solvent-involving nature upon the conformational behavior of six-membered ring systems, a wide variety of subtle geometric results beyond the scope of our simple general treatment can be anticipated. Descriptions detailing the operation of special effects of a stereoelectronic origin, such as interactions

(39) Lambert, J. B.; Clikeman, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 4203.
(40) For one β sp^2 center (e.g., **30**) $E_D = ^2/_3A_R$. Since the 1,3-diaxial H/R interaction is given by $^1/_2A_R$, it follows that the 1,3-diaxial orbital/R interaction is given by $^1/_6A_R$.
(41) Eliel, E. L. *J. Chem. Educ.* **1975**, *52*, 762.
(42) Lambert, J. B.; Featherman, S. I. *Chem. Rev.* **1975**, *75*, 611.
(43) Blackburne, I. D.; Katritzky, A. R. *Acc. Chem. Res.* **1975**, *8*, 300.
(44) Hirsch, J. A.; Havinga, E. *J. Org. Chem.* **1976**, *41*, 455.
(45) Robinson, M. J. T. *Tetrahedron* **1974**, *30*, 1971.
(46) Claus, P. K.; Rieder, W.; Vierhapper, F. W. *Tetrahedron Lett.* **1976**, 119.

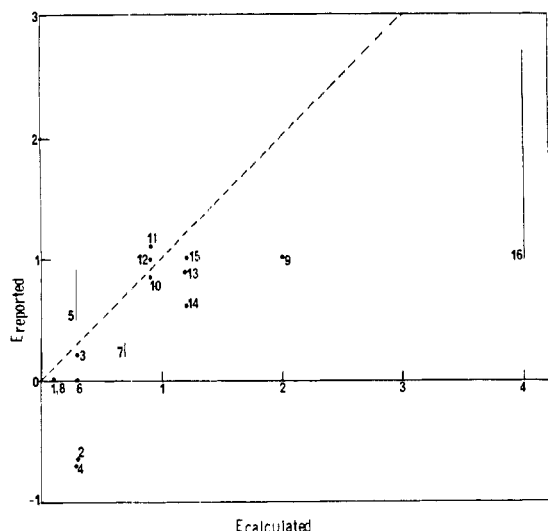(47) Carlson, R. G.; Behn, N. S. *Chem. Commun.* **1968**, 339.
(48) Buchanan, G. W.; Kohler, R. *J. Org. Chem.* **1974**, *39*, 1011.
(49) Kung, T. C.; Gutsche, C. D. *J. Org. Chem.* **1978**, *43*, 4069.
(50) Morrison, R. T.; Boyd, R. N. "Organic Chemistry", 2nd ed.; Allyn and Bacon: Boston, 1966; pp 503–4.
(51) Cf. ref 10b, pp 185 ff.
(52) Wood, G.; Woo, E. P.; Miskow, M. H. *Can. J. Chem.* **1969**, *47*, 429.

Figure 6. Reported conformational energies of 3- and 4-mono-substituted cyclohexenes (Table VI) plotted against values calculated with A values (Table I) by using eq 13. The numbers in the plot correspond to the entry numbers of Table VI. The dashed line denotes ideal correspondence. All energies are in kcal/mol.

within 4-oxycyclohexanones,[53] solvent effects on halocyclohexanes[54] and 2-halocyclohexanones,[18,32a,55] or results of *intra*molecular hydrogen bonding,[56] serve to illustrate the range of these phenomena. Fortunately, due to the highly interactive nature of the LHASA program, the chemist is readily able to specify conformation at the outset of the analysis, as described in the accompanying paper,[1] and can thereby include special conformational effects in the antithetic analysis.

Intra-ring Interactions in Non-Chairs

In the accompanying paper,[1] first-order structural constraints were described which led to well-defined and conformationally mobile half-chair (36) and boat (37) conformations. During the second-order conformational


36

37
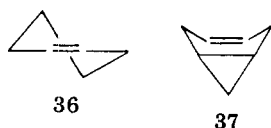
analysis it is therefore necessary to be able to assess interatomic interactions within these ring systems. Since there are considerably less data available on the conformational behavior of half-chairs and boats, our treatment of them is necessarily empirical, drawing from the examination of Dreiding-type molecular models and the computational procedures which have been developed for chairs.

Half-Chairs. The conformational equilibrium for a monosubstituted cyclohexene (38a ⇌ 38b) is known to be less biased against the axial conformer than is the case with its saturated analogue; this may, at least in part, be attributed to the absence of one 1,3-diaxial hydrogen in-

Table VI. Reported Conformational Energies of 3- and 4-Monosubstituted Cyclohexenes (kcal/mol)

| entry	R	energy	ref
1	4-F	0.01	10b
2	3-Cl	-0.64	61
3	4-Cl	0.2	10b
4	3-Br	-0.70	61
5	4-Br	0.5-0.9	10b
6	4-I	-0.02	10b
7	4-NO$_2$	0.2-0.3	63
8	4-CN	0	58
9	4-Ph	0.99	10b
10	4-CO$_2$Me	0.84	63
11	4-CO$_2$Et	1.1	59
12	4-COOH	1.0	63
13	4-CH$_2$OH	0.9	60
14	3-Me	0.6	58
15	4-Me	1.0	61, 62
16	3-t-Bu	1.0-2.7	58

teraction for either an axial (38b) or pseudoaxial[57] (39) appendage.[10b] As a first approximation, then, a desta-

38a 38b

39
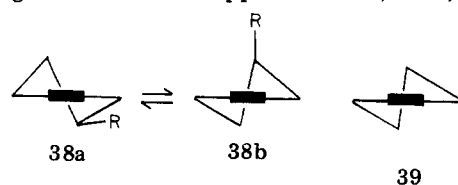
$$E_D{}^R = {}^2/_3 A_R \quad (13)$$

bilization energy of two-thirds the A value of the appendage R is assigned to the monoaxially substituted conformers 38b and 39 (eq 13), in close analogy with the case described above of cyclohexane systems with an exocyclic double bond (30). A small number of reported conformational preferences for monosubstituted cyclohexenes have been collected in Table VI. A plot of the free-energy differences observed for these systems vs. the corresponding destabilizations which result from computations employing eq 13 appears in Figure 6.

For the half-chair three types of destabilizing interactions have been identified for pairs of appendages: 1,3-axial/pseudoaxial (40), 1,2-equatorial/pseudoequatorial (41), and 1,2-diequatorial (42). There have been very few

40 41

$$E_D{}^{R/R'} = U_R + U_{R'} \quad (14)$$

42
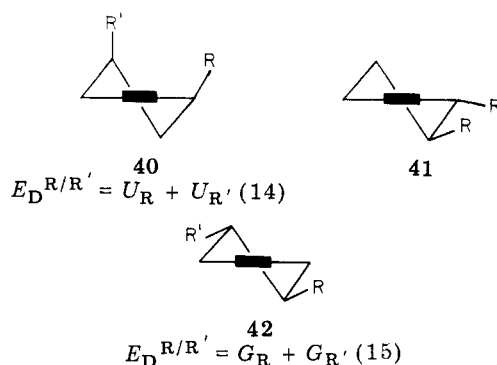
$$E_D{}^{R/R'} = G_R + G_{R'} \quad (15)$$

values published for these types of interactions,[58,60,63,64]

(53) (a) Stolow, R. D.; Giants, T. W. *Chem. Commun.* **1971,** 528. (b) Stolow, R. D.; Groom, T. *Tetrahedron Lett.* **1968,** 4069.

(54) (a) Bodot, H.; Dicko, D. D.; Gounelle, Y. *Bull. Soc. Chim. Fr.* **1967,** 870. (b) Abraham, R. J.; Rossetti, Z. L. *Tetrahedron Lett.* **1972,** 4965. (c) Abraham, R. J.; Siverns, T. M. *J. Chem. Soc., Perkin Trans. 2* **1972,** 1587.

(55) (a) Jantzen, R.; Tordeux, M.; de Villardi, G.; Chachaty, C. *Org. Magn. Reson.* **1976,** *8,* 183. (b) Cantacuzene, J.; Jantzen, R. *Tetrahedron* **1970,** *26,* 2429. (c) Cantacuzene, J.; Atlani, M. *Ibid.* **1970,** *26,* 2447. (d) Catacuzene, J.; Jantzen, R.; Ricard, D. *Ibid.* **1972,** *28,* 717.

(56) (a) Tichy, M. *Adv. Org. Chem.* **1965,** *5,* 115. (b) Tichy, M. *Collect. Czech. Chem. Commun.* **1973,** *38,* 3631.

(57) Using Fieser molecular models, we have measured the 1,3-diaxial separation in the chair (d in i) and the 1,3-diaxial/pseudoaxial separation in the half-chair (d in ii) *both* to be 125 mm.


i ii
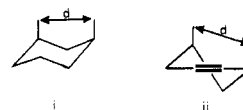
(58) Aycard, J.-P.; Bodot, H. *Org. Magn. Reson.* **1975,** *7,* 226.

(59) Aycard, J.-P.; Bodot, H. *Can. J. Chem.* **1973,** *51,* 741.

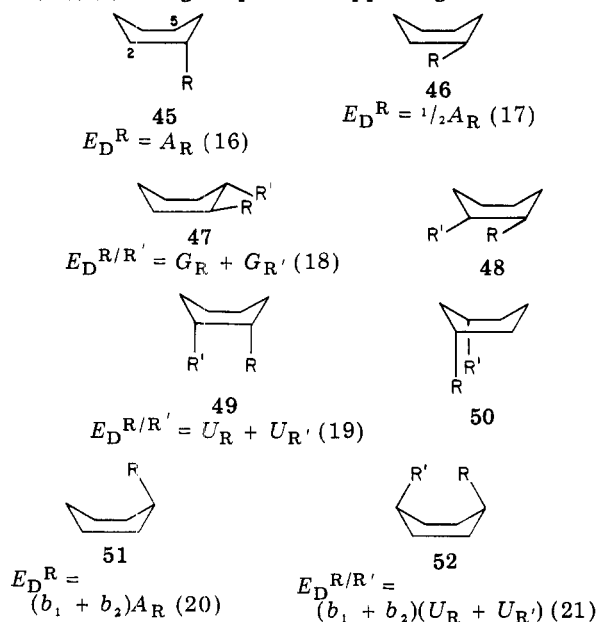(60) Aycard, J.-P.; Geuss, R.; Berger, J.; Bodot, H. *Org. Magn. Reson.* **1973,** *5,* 473.

certainly not enough data to develop a separate semi-empirical treatment for appendage-pair interactions in half-chairs. Therefore, recourse has been taken to the computational practice adopted for chairs: the R/R' destabilization contribution for structures **40-42** is obtained by simply adding the appropriate pair of U^{57} or G values (eq 14 and 15).

Boats. We are aware of no substantial body of work that has explored the energetics of substituted six-membered rings in boat conformations. However, in order to assess conformational equilibria in systems such as **43** and **44**, we found it necessary to formulate empirical rules for
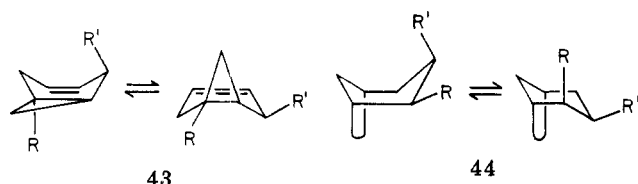
computing the destabilizing interactions that can take place in these systems.

In our analysis eight types of *intra*-ring arrangements which can destabilize the boat are recognized. These include (1) a single axial appendage on the bottom of the boat (**45**), (2) a single equatorial appendage on the side of

$$E_D^R = A_R \ (16)$$

$$E_D^R = {}^1/_2 A_R \ (17)$$

$$E_D^{R/R'} = G_R + G_{R'} \ (18)$$

$$E_D^{R/R'} = U_R + U_{R'} \ (19)$$

$$E_D^R = (b_1 + b_2)A_R \ (20)$$

$$E_D^{R/R'} = (b_1 + b_2)(U_R + U_{R'}) \ (21)$$

the boat (**46**), a pair of appendages in (3) 1,2-diequatorial (**47**), (4) 1,2-diequatorial eclipsed (**48**), (5) 1,2-diaxial (**49**), or (6) 1,3-diaxial (**50**) disposition, (7) a single axial appendage on the top of the boat (**51**), and (8) a pair of axial appendages on the top of the boat (**52**).

From inspection of Dreiding-type models it is apparent that most of these arrangements find close parallels in those already encountered in chair systems; expressions for the resulting destabilization energies follow directly. Thus a single axial appendage on the bottom of a boat (**45**) encounters two axial hydrogen atoms, on C_2 and C_5, in

(61) Rickborn, B.; Lwo, S. Y. *J. Org. Chem.* **1965**, *30*, 2212.
(62) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773.
(63) Zefirov, N. S.; Chekulaeva, V. N.; Belozerov, A. I. *Tetrahedron* **1969**, *25*, 1997.
(64) Viktorova, N. M.; Knyazev, S. P.; Zefirov, N. S.; Gavrilov, Y. D.; Nikolaev, G. M.; Bystrov, V. F. *Org. Magn. Reson.* **1974**, *6*, 236.
(65) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; pp 204 ff.
(66) (a) Carriera, L. A.; Carter, R. O.; Durig, J. R. *J. Chem. Phys.* **1973**, *59*, 812. (b) Paschal, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 272.

Table VII. Bowsprit-Flagpole Distances, d, and Flatness Parameters, b, Associated with Several Boat Conformers

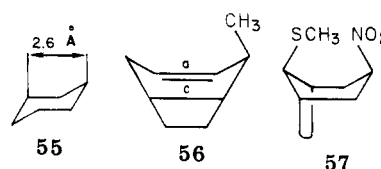| boat type	flattening bond type	d, Å	b
	BISP2	2.9	0
	cis-3	2.7	0.25
	SP2	2.6	0.50
	cis-4	2.1	0.60
	cis-5	1.9	0.70
	none	1.8	0.75

much the same spatial relationship as does a monoaxial appendage the two 1,3-diaxial hydrogens in the chair (**25**). Hence for conformer **45** the destabilization due R is set equal to the A value of the appendage counted (eq 16). A pair of 1,2-diequatorial appendages in the boat (**47**) are arranged identically with the corresponding pair in the chair (**15**); the resulting destabilization is thus assigned by summing the appropriate G values (eq 18). Furthermore, it seems reasonable to consider both the 1,2-diequatorial eclipsed (**48**) and the 1,2-diaxial (**49**) appendage-pair interactions as closely analogous to the 1,3-diaxial appendage-pair interaction in the chair (**16**). Therefore, for these two situations, as well as for the 1,3-diaxial interaction (**50**), which is exactly the same as its chair counterpart, the destabilization component due the R/R' pairing is computed through U-value summation (eq 19). For a single equatorial appendage on the side of the boat (**46**), which is a special instance of the 1,2-diequatorial eclipsed arrangement **48**, a destabilization given by half of the A value of R is assigned (eq 17).

Axial appendages on the top of the boat (**51**, **52**), however, are in unique geometrical arrangements with no close analogy to chair systems. Therefore, in order to compute the conformational destabilizations caused by the interaction of such substituents, a simple and clearly approximate method was developed by using eq 20 and 21. The b values derive from comparing the bowsprit-flagpole distances measured by using Dreiding-type models for a number of boat types (**53** and **54**) against the 2.6-Å 1,3-
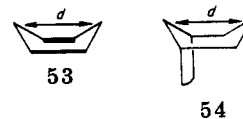
diaxial distance measured in the chair (**55**) (cf. Table VII). Because they are rough estimates, these b values are subject to change in the face of any experimental data that may be forthcoming.
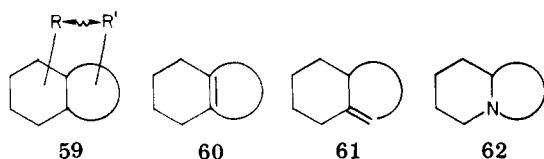

Thus, for example, the destabilization computed for system **56** due to the lone axial methyl group is initially set equal to A_{Me}, i.e., 1.8 kcal/mol. In this particular system $b_1 = 0$ (for bond a) and $b_2 = 0.60$ (for bond c), giving

a correction factor of 0.60 and hence a destabilization energy of $0.60 \times 1.8 = 1.1$ kcal/mol for **56**. Similarly, the energy of interaction arising from the [1,4] SMe/NO_2 interaction in **57**, where there are no flattening bonds and hence where $b_1 = b_2 = 0.75$, is found to be $1.5(0.8 + 1.1)$ = 2.9 kcal/mol.

Inter-ring Interactions

The conformation adopted by a six-membered ring will be greatly influenced by interaction between appendages on the six-membered ring itself and appendages attached to a second fused ring (**59**); a major feature of our sec-

ond-order analysis is, therefore, the identification and estimation of *inter*-ring interactions. Unfortunately, there are little quantitative data available on interactions between appendages subtended by different rings.[26,34,67] In order to put the assessment of such *inter*-ring interactions on a semiquantitative basis, we have utilized the empirical models developed above for *intra*-ring appendage repulsions. The treatment described below is divided into four categories: (1) interactions within the *cis*-decalin cavity, (2) 1,3-diaxial-like interactions in *cis*- and *trans*-decalins, (3) interactions in other fused $6/n$ (six-membered/n-membered) ring systems, and (4) chair/boat interactions.

A few simplifying assumptions govern our computation of *inter*-ring interactions. (i) No *inter*-ring interactions are computed between rings whose fusion includes any sp^2 centers (**60** and **61**). (ii) No *inter*-ring interactions are computed between a pair of rings whose fusion involves a heteroatom (**62**). The conformational complexities involved in such cases, whereby the character of the fusion can change through heteroatom inversion,[68] cannot currently be properly analyzed by the program. In these situations it is necessary for the chemist to specify graphically the conformation of each ring.[1] (iii) No *inter*-ring interactions are computed between a pair of six-membered rings if either ring is of ambiguous conformation, although if the ring pair is cis fused, an arbitrary *inter*-ring interaction destabilization is assigned; this will be illustrated presently.

cis-Decalins. Prior to describing our method for computing interactions between *cis*-decalin appendages, it is necessary to consider *cis*-decalin itself (**63**) and to compare the conformational strain obtained against that computed for *trans*-decalin (**64**) (Figure 7). In *cis*-decalin (**63**) two 1,3-diaxial appendage/hydrogen interactions are found in each ring. In ring 1 these are between C_5 and the axial hydrogens off C_1 and C_3; the resulting destabilization is given by the A value of C_5, i.e., 1.8 kcal/mol. In ring 2 the interaction is between C_1 and the axial hydrogens off C_5 and C_7; it is given by A_1, i.e., 1.8 kcal/mol. The resulting total destabilization energy, E_D^{SYS}, is thus 3.6 kcal/mol. In *trans*-decalin (**64**) there are only 1,2-diequatorial interactions, and these are not recorded because the ap-


Figure 7. Destabilizing interatomic interactions and total conformational energies tallied for *cis*- and *trans*-decalin. As described in the text, failure to take common interactions into account leads to an inflated energy difference found between the two systems.

pendage connecting atoms (C_5/C_8 and C_1/C_4) are joined;[69] thus $E_D^{SYS} = 0$. The energy difference between *cis*- and *trans*-decalin is therefore computed to be 3.6 kcal/mol. This is significantly higher than the 2.55 kcal/mol reported[67c] as the theoretical energy difference between these two systems.

This discrepancy is due to the fact that in the computation employed, in which the interaction energies of each ring were simply summed in order to obtain the total destabilization for the decalin system, *common interatomic interactions* were ignored; these were thereby counted *twice*. Thus, with *cis*-decalin (**63**) the destabilization attributed to axial atom 5, which was viewed as involving the two axial hydrogens off C_1 and C_3, would have been better described in terms of its gauche components, i.e., the C_1/C_5 and the C_3/C_5 interactions. Similarly, the axial C_1 destabilization is seen to consist of the C_1/C_5 and the C_1/C_7 gauche interactions. By computing E_D^{SYS} by simply summing the A values of C_1 and C_5, one then observes that a double counting of the C_1/C_5 gauche interaction (worth $^1/_2 A_{C_1}$ or 0.9 kcal/mol) results. The destabilization energy of the *cis*-decalin system, properly computed, then works out to be $3.6 - 0.9 = 2.7$ kcal/mol, and the energy difference found with *trans*-decalin (**64**) becomes reasonable. It is, therefore, the computational practice to record the gauche interaction components of each destabilization counted and to subtract the shared interactions to arrive at a total destabilization energy for a conformationally interdependent group of rings. A detailed example of this practice will be given below.

Severe *inter*-ring interactions can take place within the concavity of a *cis*-decalin system (**65**). Two types of po-
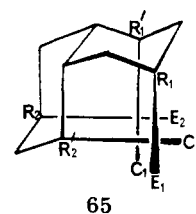
$$E_D^{C_1/R_2} = U_{C_1} + U_{R_2} \quad (22a)$$
$$E_D^{C_2/R_1} = U_{C_2} + U_{R_1} \quad (22b)$$
$$E_D^{E_2/C_1} = U_{E_2} + U_{C_1} \quad (22c)$$
$$E_D^{C_1/C_2} = U_{C_1} + U_{C_2} \quad (22d)$$
$$D_D^{C_2/E_1} = U_{C_2} + U_{E_1} \quad (22e)$$

tentially interacting axial appendages can be identified:

(67) (a) Cf.: Ficini, J.; Touzin, A. M. *Tetrahedron Lett.* **1977**, 1081. (b) Cf. ref 45. (c) Cf. ref 11, pp 226–43. (d) Laing, M.; Burke-Laing, M. E.; Bartho, R.; Weeks, C. M. *Tetrahedron Lett.* **1977**, 3839. (e) Masaki, N.; Niwa, M.; Kikuchi, T. *J. Chem. Soc., Perkin Trans. 2* **1975**, 610. (f) Rogers, D.; Williams, D. J.; Joshi, B. S.; Kamat, V. N.; Viswanathan, N. *Tetrahedron Lett.* **1974**, 63.

(68) Cf.: Blackburne, I. D.; Katritzky, A. R.; Read, D. M.; Chivera, P. J.; Crabb, T. A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 418.

(69) No destabilization is counted in the analysis for any appendage pair that is joined by a chain of fewer than four atoms.

a "central" appendage (C_1, C_2) and an "edge" appendage (E_1, E_2). Two types of interaction are possible: (i) an appendage/ring interaction involving the C_1/R_2 or C_2/R_1 atoms and (ii) an appendage/appendage interaction involving the E_2/C_1, C_1/C_2, or C_2/E_1 atoms.

The appendage/ring interaction is completely analogous to the 1,3-diaxial interaction within the chair. Appendage C_1, for example, bears the same spatial relationship to ring atom R_2 as it does to ring atom R_2'; the C_1/R_2' pairing is, in fact, assessed during examination for 1,3-diaxial *intra*-ring interactions. Thus, in the computation, the appendage/ring *inter*-ring interaction is tallied by summing the U values of the appropriate connecting atoms (eq 22a and 22b).

The appendage/appendage interaction is more difficult to quantify. Inspection of Dreiding-type molecular models reveals that in such an arrangement each pair of appendage connecting atoms (i.e., E_2 and C_1, C_1 and C_2, or C_2 and E_1 in **65**) is forced exceedingly close together. We are aware of no measured value for this type of interaction, although the possibility for such a clash, specifically for a methyl/methyl edge/center interaction (**65**, $E_2 = C_1 = $ Me, $C_2 = E_1 = $ H), is exemplified within the D and E rings of the friedelin system.[67d-f] In the computation, a *cis*-decalin edge/center or center/center appendage/appendage interaction is empirically assigned a destabilization contribution equal to the sum of the U values of the two appendages involved (eq 22c–e).[70] Thus for *cis*-decalin **65** with $E_2 = C_1 = $ Me and $C_2 = E_1 = $ H, the system destabilization energy, E_D^{SYS}, computed for the conformation shown will be very high and will include (i) the intrinsic *cis*-decalin interaction (vide supra), (ii) the interaction of the central methyl group (C_1) with a 1,3-diaxial hydrogen (E_1), a 1,3-diaxial ring carbon atom (R_2'), and a 1,3-diaxial-like ring atom (R_2), (iii) the interaction of the edge methyl group (E_2) with a 1,3-diaxial hydrogen (C_2) and a 1,3-diaxial ring carbon atom (R_1'), and (iv) the C_1/E_2 clash itself.

A description of our computational treatment of 1α-methyl-*cis*-decalin (**66** ⇌ **67**) now follows (cf. Figure 8). It is important to consider this system in some detail to illustrate fully the subtleties involved in computing these types of *inter*-ring interactions. The total destabilization energy for the equatorial methyl conformer **66** will be computed at 2.7 kcal/mol, the same as that found for *cis*-decalin itself (**63**) above; as outlined in the Intra-ring Interactions in Chairs section, the additional axial/equatorial gauche interaction between C_8 and C_{11} is not included in the tally. The situation is more complex for axial methyl conformer **67**. *Intra*-ring interactions are first picked up. In ring 1 these include (i) gauche interactions between axial appendages C_5 and C_{11} each with C_3 [the 0.9 kcal/mol destabilizations each derive from the appropriate A values ($^1/_2A_5$, $^1/_2A_{11}$)] and (ii) a 1,3-diaxial interaction (3.6 kcal/mol) between C_5 and C_{11} given by $U_5 + U_{11}$. It is important that this latter interaction be described in terms of its two gauche components as well as the "extra"[71]

Figure 8. Destabilizing interatomic interactions and total conformational energies tallied for the two chair/chair conformers of 1α-methyl-*cis*-decalin. The conformational analysis is fully described in the text.

C_5/C_{11} interaction itself, as will be seen shortly.

The sole *intra*-ring destabilization within ring 2 involves the axial C_1 appendage. As outlined above, the resulting energy, which involves the two gauche interactions C_1/C_5 and C_1/C_7, is obtained from the A value of C_1. This is given in Table I as 2.1, corresponding to the CHR_2 classification C_1 has received. But it will be appreciated that this assignment represents an implicit counting of the C_{11} methyl group at a premature stage of the analysis, and it will lead to a double counting when *inter*-ring interactions are picked up. Thus, at this point, a *base* A value for C_1, i.e., the A value for the substituent with all sp^3-attached groups considered to be hydrogen (in this case 1.8), is used.[72] Therefore, 0.9 kcal/mol is counted for each gauche interaction.

Inter-ring examination will reveal an interaction between C_7 and C_{11} of the appendage/ring type described above. Destabilization is recorded for ring 2 only since it complements the entry for the C_5/C_{11} diaxial interaction made earlier for ring 1. The energy value is obtained by adding the U values for C_7 and C_{11}. Again, it will be appreciated that a base U value for the ring atom (in this case C_7) must be employed in this type of summation; thus a destabilization of 1.8 + 1.8 = 3.6 kcal/mol is found. In addition, however, it will be noted from Figure 8 that among the gauche components recorded for the C_7/C_{11} destabilization is the C_8/C_{11} equatorial/axial gauche interaction worth $G_8 + G_{11} = 0.8$ kcal/mol. Since 1,2-cis-axial/equatorial interactions are not counted as destabilizing (cf. 17), a reduced C_7/C_{11} destabilization energy of 2.8 kcal/mol is tallied.

Total destabilizations of rings 1 and 2 are thus found to be 5.4 and 4.6 kcal/mol, respectively. The energy of the *cis*-decalin system **67** is obtained by summing these values and subtracting the doubly counted gauche interactions for C_1/C_5 and for C_1/C_7, giving 8.2 kcal/mol. Therefore, 5.5 kcal/mol separates conformers **66** and **67**.

It was of interest to compare this result with the quantitative treatment of this system by the comprehensive

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(70) When appendage/appendage interactions of this type are tallied, no check for double counting takes place. Clearly this would be inappropriate given the approximating required for assessing such interactions.

(71) In the computation, a 1,3-diaxial interaction (i) is viewed as being composed of two gauche butane-like interactions (C_1/C_4 and C_2/C_3) analogous to a lone axial appendage interaction (e.g., C_1/C_5) plus an extra interaction between the appendage origins themselves (i.e., C_1/C_2).
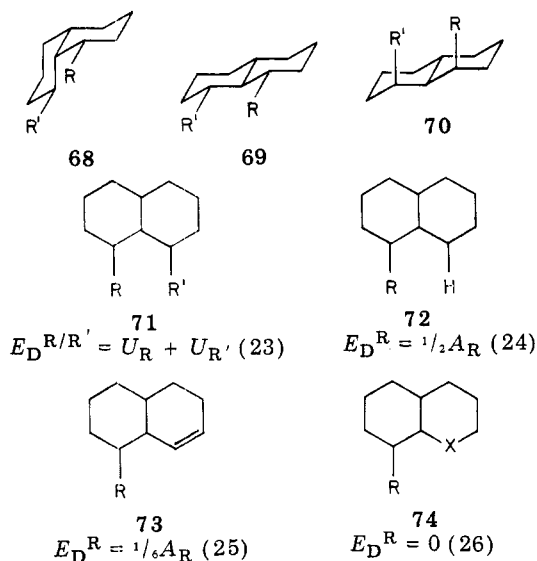
(72) In the computation, any axial or equatorial carbon appendage that is in a ring of size less than nine-membered that is fused to the six-membered ring under consideration is assigned A and U values of 1.8 each and a G value of 0.4; these are its base appendage interaction values.

Table VIII. Conformational Energies (kcal/mol) for
Monomethyl-*cis*-decalins Computed by the Method
Described in This Paper and by the
Molecular-Mechanics Method of Allinger[3,74]

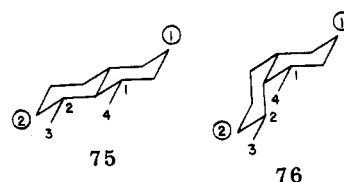| *cis*-decalin	LHASA	Allinger
1α-Me	5.5	5.29
2β-Me	1.8	1.68
3α-Me	3.6	3.76
4β-Me	0.9	0.46

semiempirical molecular mechanics conformational analysis method developed by Allinger.[3,73] His computer program determines an energy difference between the two 1α-methyl-*cis*-decalin conformers **66** and **67** of 5.29 kcal/mol.[74] A similar comparison between our treatment and the Allinger method for the remaining monomethyl-*cis*-decalins is presented in Table VIII. Very good agreement in all but the 4β-methyl-*cis*-decalin case is reached.

***cis*- and *trans*-Decalins.** There exists a second type of *inter*-ring interaction which may take place between pairs of appendages (R/R′) situated on opposite sides of a *cis*- or *trans*-decalin fusion bond; this is illustrated with structures **68**, **69**, and **70**. The R and the R′ appendages

68   **69**

$E_D^{R/R'} = U_R + U_{R'}$ (23) $E_D^R = {}^1/_2 A_R$ (24)

71   **72**

$E_D^R = {}^1/_6 A_R$ (25) $E_D^R = 0$ (26)

73   **74**

in these systems bear the same spatial relationship to each other as the members of a 1,3-diaxial appendage pair on a cyclohexane chair. Thus the same procedures used in computing 1,3-diaxial-interaction destabilizations, described above, are employed here. This simply involves summing the U values for R and R′ (**71**) or utilizing the appropriate A value expression when R′ is replaced by a hydrogen atom (**72**), an sp²-hybridized center (**73**), or a heteroatomic center (**74**) (eq 23–26).

When using these procedures for computing *inter*-ring interactions, a repeated counting of 1,2-diequatorial *intra*-ring interactions is incurred. Thus the 1,2-diequatorial interactions between C_2 and C_4 on ring 1 and between C_1 and C_3 on ring 2 in *trans*-decalin **75** and those between C_1 and C_3 on ring 2 in *cis*-decalin **6** form part of the *inter*-ring destabilizations just described. However, since the gauche components of each *intra*-ring or *inter*-ring interaction are

(73) The Allinger program was made available through the courtesy of Dr. D. A. Pensak, E. I. duPont de Nemours and Co.

(74) As pointed out in the accompanying paper,[1] the Allinger program requires the precise three-dimensional coordinates of every atom in the system, including each hydrogen, and the calculation requires on the order of 3 min. By comparison, the computation described in these papers starts with a two-dimensional structure sketched quickly by the chemist and requires less than 1.5 s of computer time.


75   **76**

recorded, as described above, this duplication will be detected and corrected.

Other Fused-Ring Systems. Significant interatomic interactions may also take place between six-membered ring systems and the appendages on smaller or larger fused rings. Although it is difficult to analyze such interactions with as much precision as has been done with decalin systems, due to the wide range and variability of the possible spatial relationships, simple empirical ways of assessing such interactions have been formulated.

As a first approximation it is considered that there are no *inter*-ring interactions between ring systems smaller or larger than six-membered which are trans fused to six-membered rings. Cis-fused ring systems, on the other hand, must be dealt with.

In general, cis-fused rings of size other than six-membered can have the effect of positioning an appendage under the six-membered ring in much the same way that an axially oriented *tert*-butyl appendage disposes one of its methyl groups with respect to the ring (**78** and **79**).

78   **79**   **80**

$E_D^R = U_R$ (27) $E_D^{R/R'} = U_R + U_{R'}$ (28)
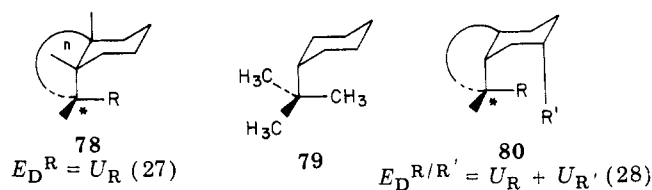
Specifically, such interactions are tallied only for rings smaller than nine-membered (i.e., **78**, $n \leq 8$ and $\neq 6$) and only when they bear an appendage R (i) that is attached "α-axial" with respect to the six-membered ring [i.e., attached to that atom of the fused ring (C* in **78**) that is both α to the six-membered ring and is the connecting atom of an axial appendage] and (ii) that is syn to the six-membered ring (i.e., trans, with respect to the *n*-membered ring, to the appendages off the two 6/*n* fusion atoms). The magnitude of the extra destabilization imparted by the presence of R in structure **78** is taken simply as the U value of R (eq 27). This is added to the destabilizing contribution made by axial C*.

For cases where there is also present a syn-axial appendage off the six-membered ring (R′ in **80**), a situation quite similar to the appendage/appendage *cis*-decalin concavity arrangement (**65**) is encountered. In these circumstances the destabilization energy for the appendage/appendage interaction is obtained by summing the U values of the two appendages involved (eq 28).[70] Thus, for conformation **80**, with R = R′ = Me, the contributors to the total destabilization (kcal/mol) include the following: (i) axial C* (0.9),[72] (ii) axial R′ (0.9), (iii) 1,3-diaxial C_7/R′ (3.6),[72] and (iv) R/R′ (3.6). Thus E_D^{SYS} for conformer **80** is 9.0 kcal/mol.

Chair/Boat Interactions. The final type of *inter*-ring situation which is considered involves two fused six-membered rings, with one a chair and the other held in a boat conformation. Due to the reduced symmetry of the boat, the possible fusion arrangements are more complex than for chair/chair pairings. Below we outline how the fused chair/boat systems are handled, first describing chair/boat cis fusions and then chair/boat trans fusions. For both it has been possible to describe the various structural

situations in terms of the models developed above; hence, the computation of the destabilizing interactions that can arise is carried out in a completely analogous manner, and no new destabilization energy equations are required.

Four types of chair/boat cis fusions are possible, involving attachment of the chair to the (1) "end/bottom" (81), (2) "end/top" (82), (3) "side/top" (83), or (4) "side/
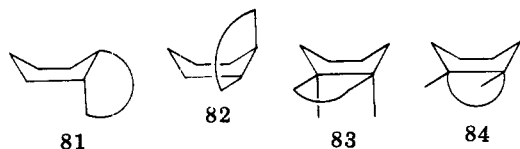
bottom" (84) of the boat, as schematically illustrated. It was hoped that *inter*-ring interactions for all these situations might be handled by the analytical method developed for other cis-fused $6/n$ pairs. Here, as described above, only the syn appendage subtended by that atom in the n-membered ring that is "α-axial" to the six-membered ring is capable of interacting with the six-membered ring (78). This guide does, in fact, usefully apply to the two cis-fused chair/boat systems 81 and 83 (85), but for the other two systems the steric arrangement is so modified that only that syn appendage subtended by the "β-axial" atom in the boat ring may interact (86). Destabilization contributions for the appendage R in systems 85 and 86 are computed by using eq 27.[70]
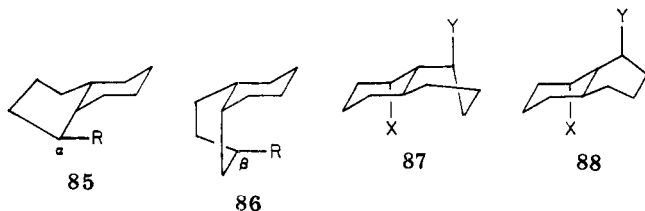
Two types of chair/boat trans fusions are possible, with the fusion involving either an end (87) or a side (88) of the boat. In either case, the *inter*-ring appendage/appendage interactions are almost completely analogous to those described above for *trans*-decalins (69 and 70), where, it will be remembered, two axial/axial and two equatorial/equatorial appendage pairings are possible. For chair/boat *trans* fusions, however, two equatorial/equatorial pairings are possible, but only one axial/axial pairing is possible; members of the other axial appendage pair are on opposite sides of the ring systems (X and Y in 87 and 88). For the interacting pairs, destabilization energies are obtained by using eq 23–26.

Final Conformational Assignments

Once all the interatomic interactions associated with each of the assigned conformations have been assessed for each of the six-membered rings in the molecule, it is possible to address the question of final conformational assignment. Two criteria must be met in order to assign a unique and well-defined conformation to a six-membered ring: (i) the total computed destabilization $E_D{}^{SYS}$ of the lowest energy conformation must be *significantly* lower than the energies of all other conformations considered, and (ii) the destabilization of the minimum-energy conformer must be less than an *energy cutoff value*. Both these points will be discussed presently.

Ring Flexibility. First, however, it is important to refocus attention on the *flexibility* designation which accompanied the preliminary conformational assignment made for each six-membered ring during the first-order analysis.[1] Although it has been amply demonstrated how the preliminary conformation has formed the basis for the

second-order analysis described in this paper, little has been said to this point about ring flexibility. The significance of this parameter is now discussed briefly.

It will be recalled that each ring received one of three flexibility designations: *rigid, distortable,* or *flippable.* Rigid rings are those found structurally constrained to a single geometric form (one of structures 1–6) with no conformational variation allowed; for these systems second-order analysis is clearly inappropriate, and a final assignment conformation is possible immediately after the first-order analysis. Flexible six-membered rings represent the opposite situation. For such systems configurational constraint is minimal, and two well-defined conformations, corresponding to two chairs (1 or 2), two half-chairs (3 or 4), two boats (5 or 6), or sometimes to a chair and boat (1 or 5), can exist. By comparison of the relative energies of the two geometries during the second-order analysis, the basis for a conformational decision can be reached. The third flexibility designation, distortable, accounted for intermediate structural situations. Distortable six-membered rings, like rigid systems, are limited by configurational constraint to adopt a single well-defined conformation; however, like flippable systems, they may depart from this conformation. The unique aspect of distortable rings is that when they leave the well-defined conformational form they can only enter into a distorted geometry, assumed to be of intrinsically higher energy, and they may not achieve a second well-defined form. For such ring systems a second-order analysis is crucial, for it must be determined whether the energy of the well-defined form is low enough to discourage the ring from availing itself of the distorted geometry.

Significant Energy Difference. A *significant* energy advantage for a conformer is considered to be 1.2 kcal/mol; this corresponds to roughly a 90% preponderance of this conformer at room temperature.[11c] Thus conformational homogeneity would be predicted, for example, for 2-methylcyclohexanone (89), where the two possible con-

89, R = H
90, R = Ph
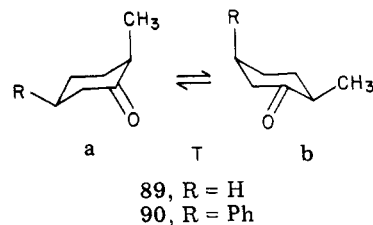
formers differ in destabilization energy by $A_{Me} = 1.8$ kcal/mol, but would not be expected for cis-2-methyl-5-phenylcyclohexanone (90), where $E_D{}^{SYS}$ is computed at $^2/_3(3.0) - 1.8 = 0.2$ kcal/mol (cf. eq 8), favoring 90a. Thus a definite stereoassignment corresponding to the chair geometry of 89b would be made for system 89. For system 90, however, since only a slight preponderance (i.e., about a 60/40 excess[11c]) of the minimum-energy conformer can be expected, no assignment of geometry or axial/equatorial labeling would be made. These same considerations apply to fusion composites,[1] i.e., to conformationally interdependent groups of six-membered rings. Thus, for the monomethyl-*cis*-decalins discussed above (Table VIII), conformational assignments can be made for the 1α, 2β, and 3α systems, where in each case $E_D{}^{SYS}$ is more than 1.2 kcal/mol, but not for the 4β compound, where the two conformers are found to be separated by only 0.9 kcal/mol.

The distinction between configurationally locked vs. conformationally free well-defined geometries is important when the results of the analysis are applied to the evaluation of chemical transformations in the antithetic analysis.[75] Thus the six-membered rings in 91 and 89 both
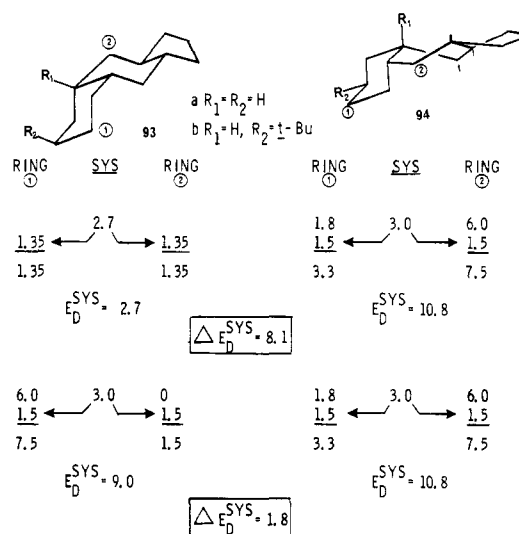
91   **92**
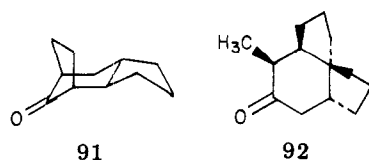
receive unambiguous chair assignments. In **91** this assignment represents the only geometry available to the ring, since through first-order analysis it is shown to be rigid.[1] System **89**, on the other hand, is flippable, and the ring is free to depart from the geometry of **89b**; although strongly predominating in equilibrium concentration, this conformer is rapidly interconverting with **89a**.[65]

A parallel distinction can be made between configurationally vs. conformationally ambiguous ring systems, as exemplified by **92** and **90**, respectively. System **92** is shown during first-order analysis to be incompatible with any well-defined geometry.[1] Thus no axial or equatorial labels can be assigned. No A/E labels may be assigned either in system **90** where the second-order analysis showed the energy separation between the two chair forms to be insignificant. Only lenient stereochemical screening will be applied in transform evaluations involving both these types of systems.[75]

Cutoff Energy. As stated at the outset the basis for our method of conformational analysis is the strong tendency of configurationally unconstrained six-membered ring systems to adopt the well-defined chair or half-chair conformations. If, however, the resulting interatomic appendage/appendage interactions are large enough, the energy advantage of the conformation may be lost, and the six-membered ring will possibly opt for an ill-defined skewed or twist geometry.[76] Although a well-defined geometry may still, in fact, represent the energy minimum for such a system, our method does not permit an accurate appraisal of this possibility. It is, therefore, the practice in our analysis to compare the total destabilization energy E_D^{SYS} computed for a given conformation against an arbitrary absolute standard termed the *cutoff energy*. If the E_D^{SYS} values computed for the available well-defined forms are each found to exceed the cutoff value, no conformational assignment is made for a ring system. In principle three cutoff-energy values were required, corresponding to the chair, half-chair, and boat geometries. The derivation of these parameters is described below.

We were led to a cutoff-energy value for the chair geometry by consideration of two sets of experimental data. The energy difference between the chair and twist-boat geometries of cyclohexane has been measured to be 5.5 kcal/mol;[77] it was tempting directly to utilize this value as the cutoff energy for all chairs. X-ray crystallographic structures have been published for a number of natural products with a common structural feature: each contains at least one conformationally independent six-membered ring in which there is a single destabilization—a syn-1,3-diaxial methyl/methyl interaction.[78-80] For each of these systems the six-membered rings were found to be just commencing to depart from the chair. We compute the total conformational destabilization for the methyl/methyl 1,3-diaxial interaction to be 5.4 kcal/mol (U_{Me} + U_{Me} +

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Figure 9. Destabilizing interatomic interactions and total conformational energies tallied for the substituted *cis*-decalin conformers **93** and **94**. The conformational analysis is fully described in the text.

$^{1}/_{2}A_{Me}$ + $^{1}/_{2}A_{Me}$). On the basis of these data the cutoff energy for the chair has been assigned a value of 6.0 kcal/mol. This energy value was also assigned as the A value of the *tert*-butyl group; *trans*-1,3-di-*tert*-butylcyclohexane is known to exist in a twist conformation.[81]

The activation barrier between cyclohexene and its twist geometry has been measured at about 5.3 kcal/mol.[82] The corresponding barrier for cyclohexane is 10.8 kcal/mol.[77] On the basis of these values the cutoff energy for the half-chair has been assigned a value of 3.0 kcal/mol. This cutoff is also applied to chair systems with a single sp[2] center in the ring, on the basis that the energy barrier between the chair and twist forms in the cyclohexanone system is reported to be 2.5–3.3 kcal/mol.[27a,83,84]

In practice, no cutoff-energy value has been assigned to the boat conformation. It will be remembered that boat geometries are only considered in the second-order analysis when the conformational possibilities are restricted to a choice between two well-defined boats (**43**) or between one such boat and a chair (**44**). Since no twisting of the ring from the boat form is permitted by the constraints of configuration in such situations, it is not appropriate to compare the destabilization energy computed for a particular conformation against an absolute cutoff energy. Of course, comparison of the destabilization energies for available conformers with each other is still important, and the same significance is attached to energy differences here as in the case described above.

A second use is also made of the cutoff-energy values; this pertains to distortable ring systems, i.e., those limited to a single well-defined geometry but for which skewed conformations are available. For such systems the skewed form that the six-membered ring can adopt is assigned a destabilization energy equal to the cutoff value of the basic ring system, as defined above, *without regard to the specific substitution pattern of the ring*.

Two examples are now presented which will illustrate the utility of the cutoff energy and, in addition, amplify

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the treatment of *inter*-ring interactions. The conformational equilibrium between systems **93** and **94** is analyzed as follows (Figure 9). During first-order conformational analysis[1] flexibility assignments of flippable and distortable are made for rings 1 and 2, respectively; this follows from the single configurational constraint on the ring system: the trans fusion with the five-membered ring. Thus, both six-membered rings may adopt chair conformations in **93**; in **94** only twist geometries are available to ring 2, although a chair form is possible for ring 1.

We first consider the unsubstituted system **93a** ⇌ **94a**. In conformation **93a** an unsubstituted *cis*-decalin system is present. Thus, as described above, following consideration of first *intra*-ring and then *inter*-ring interactions, a system destabilization energy, E_D^{SYS}, of 2.7 kcal/mol will be computed for the pair of rings. In conformation **94a**, on the other hand, the situation is quite different. In ring 1, a provisional chair, the monoaxial $C_1/H,H$ interaction contributes 1.8 kcal/mol of destabilization. Ring 2 is a twist conformer and is thus assigned its cutoff energy of 6.0 kcal/mol. No specific *inter*-ring interactions are assessed between rings 1 and 2 because, as stated at the outset of the discussion of *inter*-ring interaction computation, one of the rings is of ambiguous geometry. However, an arbitrary destabilization of 3.0 kcal/mol (i.e., 1.5 kcal/mol/ring) is assigned to the ring 1/ring 2 system to take *inter*-ring interatomic interactions into account. This practice is adopted in all such 6/6 fusion situations when the conformation of one ring is not known. Thus the total destabilization energies for rings 1 and 2 compute at 3.3 and 7.5 kcal/mol, respectively, and for system **94a** E_D^{SYS} = 10.8 kcal/mol. The difference in the total destabilization energies between systems **93a** and **94a**, which is found to be 8.1 kcal/mol, then leads to unambiguous assignment of conformation **93a**.

Next we consider the monosubstituted system **93b** ⇌ **94b**. In conformer **93b** both rings are provisional chairs; *intra*-ring interactions are looked at first. Ring 1 will be assigned a destabilization of 6.0 kcal/mol for its axial *tert*-butyl group; no destabilizing interactions are found within ring 2. Since the destabilization assigned to ring 1 is equal to its cutoff-energy value, the provisional assignment of the chair geometry for the ring must thus be abandoned at this stage in the computation. Therefore, no specific *inter*-ring interactions are computed between ring 1 and ring 2, and an arbitrary destabilization energy of 3.0 kcal/mol is assigned the ring system. Thus the total destabilization energies for rings 1 and 2 are computed to be 7.5 and 1.5 kcal/mol, respectively, and E_D^{SYS} is 9.0 kcal/mol. In conformer **94b**, ring 1 is a provisional chair and ring 2 a twist. Since the *tert*-butyl group is now equatorial and hence noninteracting, this system is computed to have the same destabilizations as system **94a**. As a result, E_D^{SYS} for the **93b** ⇌ **94b** equilibrium is computed to be 1.8 kcal/mol in favor of **93b**. This energy difference is considered to significantly favor conformer **93b**. Thus a chair geometry may be assigned ring 2. Ring 1, on the other hand, is not assigned a geometry since its total destabilization was found to exceed the cutoff-energy value.

Conclusions

In this and the accompanying paper[1] we have formulated a number of general guidelines to enable the prediction of the consequences of structure on the conformation of six-membered rings. The response to the effects of both configurational constraint and nonbonded interatomic interaction has been treated. These guidelines have been utilized in the preparation of a computer program[85] de-

signed to serve as an adjunct in the computer-assisted generation of synthetic routes to complex organic molecules.[1] The results of the conformational analysis described herein are obtained sufficiently rapidly and with enough reliability to be of value in LHASA. In essence the stereochemical information so obtained permits the screening of many organic transformations which retrosynthetically remove stereocenters from a six-membered ring so that a rating of acceptable or not acceptable is generated. Thus a service comparable to that provided for an organic chemist consulting a Dreiding-type molecular model is performed. Various stereochemical aspects of antithetic analysis by computer are currently under development[75] and will be reported on in future publications.

We close by providing a number of examples of the results of our computations for a variety of six-membered ring systems whose conformations have been determined by X-ray crystallographic analysis. The aphidicolin (**95**)

95[86]   96[87]   97[88]
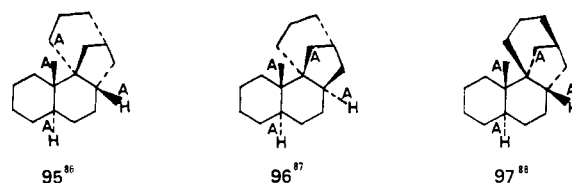
and related 8-epiaphidicolin (**96**) and stemodin (**97**) ring systems provide interesting illustrations of the variation of six-membered ring conformation with configurational constraint. In each system the conformation of the B ring follows from the axial appendage assignments made on the basis of the trans fusions identified during first-order analysis. In systems **95** and **97** a chair geometry can be assigned, but this is found not possible in **96**. The X-ray data support these conclusions.

A number of reported systems of natural or synthetic origin follow, each of which can be assigned a ring flexibility designation of flippable. These include the chair ⇌ chair (C/C) systems **98–100**, the half-chair ⇌ half-chair

98[89]   99[90]   100[91]

$\Delta E_D = 3.8$ (C/C) $\Delta E_D = 1.3$ (C/C) $\Delta E_D = 2.7$ (C/C)
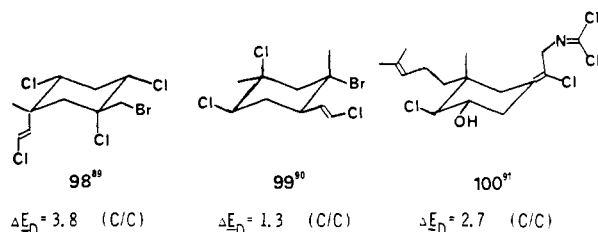
(85) A listing of this computer program is available from one of the authors (E.J.C.).

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(96) Neoconcinndiol: Howard, B. M.; Fenical, W.; Finer, J.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 6440.

(97) Corylifuran: Burke, B. A.; Chan, W. R.; Prince, E. C.; Eickman, N.; Clardy, J. *Tetrahedron* **1976**, *32*, 1881.

(HC/HC) system **101**, the half-chair ⇌ boat (HC/B) system **102**, and the chair,chair ⇌ chair,twist (CC/CT) fusion composite system **103**. For each of these systems

$\Delta E_D = 1.4$ (HC/HC) $\Delta E_D = 2.0$ (HC/B) $\Delta E_D = 4.6$ (CC/CT)
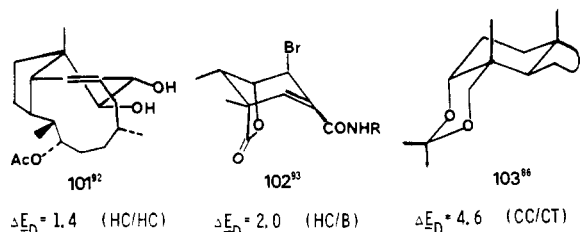
is shown the conformation predicted and the computed total destabilization energy (ΔE_D, kcal/mol) found to favor this conformation over its well-defined alternative. In each case the significant energy difference computed leads to prediction of the geometry actually established by the X-ray data.

Finally, several naturally occurring systems (**104–107**) are shown, each of which contains one or a pair of six-membered rings with a flexibility classification of distortable. For each of these is shown the total destabilization energy (E_D, kcal/mol) computed for the single well-defined chair conformation available. In each case this number is below the appropriate energy cutoff value and leads to acceptance of the chair geometry shown.
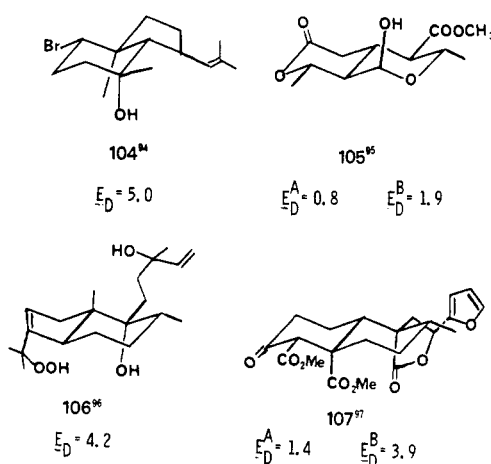
Again, these assignments are supported by the X-ray data.

Indole-3-sulfonium Ylides and Related Sulfonium Salts. Chemical and Physical Properties

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Acid–base titration of the sulfonium salt–sulfonium ylide pair dimethyl(1*H*-indol-3-yl)sulfonium 3-(dimethylsulfonio)indolide, the corresponding 2-methyl or 2-phenyl analogues, or the homologous 3-diethylsulfonium compounds resulted, in each case, in a hysteresis; i.e., titration of the sulfonium ylide with acid gave a different set of pH values from those observed upon titration of the sulfonium salt with base. In related studies comparison of ultraviolet spectra of the sulfonium salts and ylides in anhydrous dioxane and in water revealed significant differences. ¹H NMR spectra of sulfonium salts in aqueous or aqueous trifluoroacetic acid solutions revealed the formation of a new species which (a) exhibited an acid–base titration hysteresis indistinguishable from that of the precursor salt, (b) exhibited ions in the mass spectra corresponding to a sulfonium salt plus a molecule of water, and (c) reverted to the precursor salt upon attempted purification. These results are consistent with covalent hydration across the highly polarized C-2, C-3 double bond of the indole ring.

We have reported that 3-(dimethylsulfonio)indolide (**1a**),
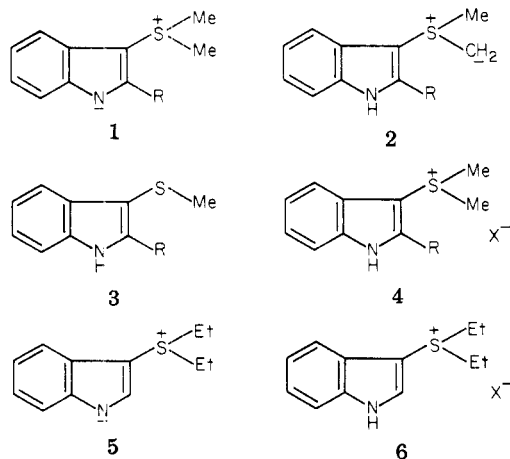
a, R = H; b, R = Me; c, R = Ph

a stable, crystalline sulfonium ylide, (a) is unusually basic

(the pK_a of the conjugate acid, sulfonium salt **4a**, is >11) and (b) incorporates deuterium into the *S*-methyl groups when dissolved in deuteriochloroform or deuteriomethanol (requiring the intermediacy of methylidene ylide **2**).[1] More recently, we have made a detailed study of ¹³C and ¹H NMR spectra of **1a**, its 2-methyl (**1b**) and 2-phenyl (**1c**) analogues, precursor 3-(methylthio)-1*H*-indoles (**3**), and dimethyl(1*H*-indol-3-yl)sulfonium salts (**4**) in aprotic solvents.[2] In the present report, we describe the preparation of these compounds and of the related 3-(diethylsulfonio)indolide (**5**) and corresponding sulfonium salt **6** and studies of various aspects of their chemical and physical properties including acid–base titration phenomena, ultraviolet spectroscopy in protic and aprotic solutions, ¹H NMR spectra in protic solvents, and electron ionization and field desorption mass spectrometry.

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