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SYSTEMATIC CONFORMATIONAL ANALYSIS. A MICROCOMPUTER METHOD FOR THE SEMIQUANTITATIVE EVALUATION OF POLYCYCLIC SYSTEMS CONTAINING FIVE-, SIX- AND SEVEN-MEMBERED RINGS. 1. PROGRAM CHARACTERISTICS.

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Abstract - A computer program for the semiquantitative conformational evaluation of polycyclic systems, with focus on five-, six- and seven-membered carbocycles, is described. Starting from two-dimensional structural information of the product as input, the progam deduces the preferred geometry of the molecule, including conformer population distributions when the product is a conformational mixture. Relative enthalpy, entropy and relative free energy terms are also computed for the analyzed product. The SCA program is written in BASIC and has been designed for operation on microcomputer systems.

The knowledge of the preferred geometry of a molecule and of its corresponding energy is of fundamental interest. From this information one may gain insight into the relation between structure and activity, understand the course of kinetic controlled reactions (cf. product stereochemistry in steric-approach controlled reactions) and predict equilibria compositions. These are problems the organic chemist, especially when active in the field of natural and related products, is very often confronted with. Although impressive achievements have been recorded in recent years in the field of computerized molecular modeling[1], the synthetic chemist more often than not still prefers to have recourse to his favorite tool, the mechanical molecular model. In general such models help to visualize the spatial arrangement of atoms within a conformation with sufficient precision for his purposes[2]. In contrast with computer systems, models are inexpensive, readily usable in day-to-day working environment and yield results at the user's pace. The mere manipulation of a model, however, does not reveal the energy content of the various considered conformations. Implications thereof are not always fully realized. In particular, it is now a common practice to rationalize stereochemical results on the basis of "an inspection of models". In general, however, no mention is made of how the inspection is performed. Questions such as "Which conformations have actually been considered ?", "Do these conformations represent potential energy minima ?" and "Have all possible conformations been envisioned ?", often remain unanswered. This, in turn, raises questions not only about the reproducibility of a model inspection, but also about the correctness of the drawn conclusion, which often depends on the weight that a user will intuitively allocate to various interactions.

This paper describes a program for the systematic conformational analysis (SCA) of polycyclic systems with focus on five-, six- and seven-membered carbocycles. The program performs a "model inspection" in a systematic and semi-quantitative way. It operates on inexpensive microcomputer configurations. No prior knowledge is requested that is not directly apparent from the two-dimen-

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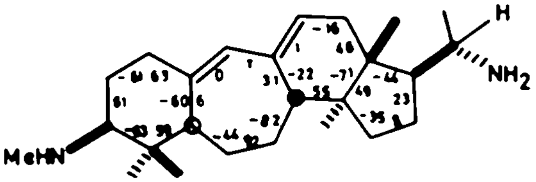
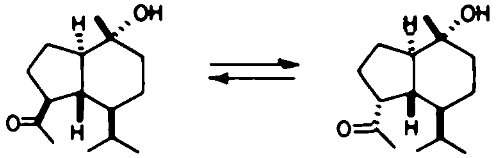
sional structural diagram of the molecule. All input information is introduced on an interactive basis, results are presented in a way appropriate to the needs of the user. The time requested for a complete analysis, including input, ranges from a few to several minutes (on the average, 2-3 min/cycle in the full molecule).

The main aim of the program is threefold. (1) The prediction of the preferred geometry of a molecule - or of its conformer population distribution when it is a conformational mixture - in the reassuring confidence that all reasonable conformations were envisioned and with an accuracy sufficient for most synthetic purposes. As a representative example the result of the analysis of 1 is schematically given. Diagram 1a shows the endocyclic torsion angles of the compound as found by X-ray diffraction[3]. Diagram 1b represents the preferred geometry as deduced by the program; other populated forms merely imply small differences in the five-membered D-ring geometry due to restricted pseudorotation (vide infra). Other reasonable geometries, but which are not populated, can be shown upon request together with their calculated conformational energies. From the above information (cf. 1b) one may attempt to predict the stereochemical outcome of steric controlled reactions. (2) The calculation of appropriate free energy terms, which are necessary for the prediction of the composition of isomerization equilibria. Next to a relative enthalpy term, the program also calculates an often neglected entropy term necessary for determining free energy differences. As representative results, the acetyl side chain in oplapanone[4] (2) is predicted to be thermodynamically stable (eq. 1), i.e., $\Delta G° = 9$ kJ/mol at 25°C, and the trans-fused hydrindanone to be preferred in the isomerization represented in eq. 2, i.e., $\Delta G° = -3$ kJ/mol at 25°C (1 cal = 4.186 Joule). Obviously, this information can be crucial when planning a synthesis[5].



1a



(1)

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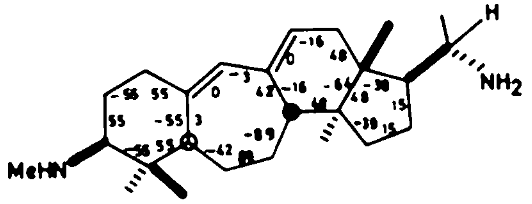
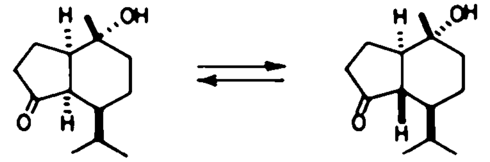


1b



(2)

(3) The generation of all reasonable starting geometries for eventual Westheimer strain energy minimization[6]. In contrast with other computer systems the SCA program does not include a minimization routine, where a planar or crude three-dimensional structure is refined toward the closest minimum energy conformation[7,8]. It does provide, however, for all possible candidates for further energy minimization whenever refined geometries and energies are requested[9].

The first part of the paper describes the principle of the method. The different programs that are part of SCA are then discussed in some detail with the focus on the requested input information and obtained result (output).

PRINCIPLE OF THE METHOD

The full analysis of a polycyclic molecule occurs in three distinct stages : the torsion constraint evaluation of each cycle in the molecule, the deduction and evaluation of possible conformations for each cycle separately and, finally, the deduction and evaluation of possible combinations among the above deduced conformations[10,11]. These functions are performed by six different programs, which work independently of each other, but use a common temporary file (TORSFILE) for storage and retrieval of relevant data (scheme 1). (1) During the user's input the program

Scheme 1. Program Structure

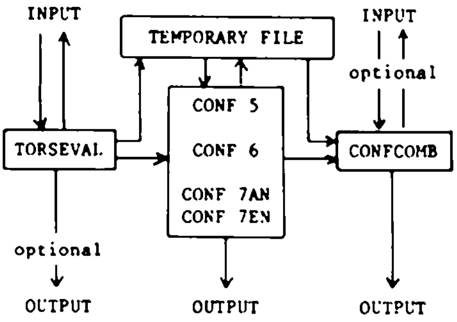


Table 1. Progam characteristics

Program	Instruction lines	Memory requirements[a] at storage	Memory requirements[a] at run-time[b]
TORSEVAL	369	11	11-12[c]
TORSFILE	-	-	2-4[c]
CONF 5	352	11	14
CONF 6	416	14	18
CONF 7AN	305	10	13
CONF 7EN	314	12	15
CONFCOMB	191	7	8-28[d]

[a] In Kbytes; [b] For 28 Kb free RAM; [c] Depending on the number of rings (maximum 8); [d] Depending on the number of combinations to be examined; in case of memory shortage this number is automatically reduced.

performs an evaluation of the torsional constraint in each cycle of the molecule : at each endocyclic bond the program calculates the smallest and the largest dihedral angle value (algebraic) that the ring can afford with respect to its intrinsic structural features (in particular the size of the ring) and to the torsion constraining structural features that are present at that bond (ring fusions, bridging, anchoring substituents)[11]. This crucial part of the analysis is performed by the program TORSEVAL for each cycle in turn. (2) For five-, six- and seven-membered rings the program then deduces all geometrically possible conformations ranked in increasing order of energy. The deduction is realized by matching the result of the torsion constraint evaluation against the set of standard forms that the program regards as allowed. This matching process has been discussed in detail for manual operation[10]. It involves the use of linear conformational notations which allow for very rapid deduction and guarantee that every possible form has been envisioned. For each deduced form a conformational energy value is calculated by summing up different energy contributions. Depending on the ringsize, this part of the analysis is performed by the program CONF5, CONF6, CONF7AN (saturated) and CONF7EN (unsaturated). (3) Finally, the program CONFCOMB determines which conformations, among those derived for each ring, are compatible with regard to the structure of the full molecule (cf. type of fusions and bridgings). During that process an energy term is involved which reflects how precisely the conformations of the different rings fit together. All allowed combinations are then generated ranked in increasing order of energy. Relative populations for the different combinations are calculated in a range of 10 kJ/mol, together with relative enthalpy, entropy (entropy-of-mixing) and free energy terms for the full molecule.

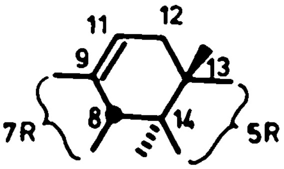
The way SCA is structurized allows for a minimal use of internal memory. In this laboratory the program is run on a Z-2D Cromenco System (Z-80 microprocessor, 64KB RAM, two 5-inch quad-capacity disk drives). The six programs which are part of SCA are written in BASIC (16K Extended Cromenco version). More detailed program characteristics are given in table 1. The present version of the program is available from the author.

INPUT

When running SCA the program TORSEVAL is first entered. This program is entirely in charge of the following steps. The user is only expected to provide information upon the program's request. Input information is either self-explaining (e.g., number of cycles in the system, ringsizes, atomnumbering) or presented as a menu where the user choses one of the options. In all cases is the input numeric; in this way all requested information is introduced in a convenient and rapid way.

In order to perform the torsion constraint evaluation, the program will request the following information for each cycle of the polycyclic system in turn. (1) The clockwise numbering of the ringatoms. The choice of numbering is entirely up to the user; in this way original numbering systems as in steroids can be maintained, which may facilitate the interpretation of the results. (2) Constrained bond information, for each endocyclic bond in turn. The program distinguishes four types of constraint : Z-bond, F-bond, B-bond and Imposed constraint. Z-bond refers to an endocyclic double bond (Z-geometry). Fusion- and Bridged-bonds are joined to a second ring. Distinction between both types is trivial; note, however, that only bonds which are adjacent to one of the bridgehead centers are identified as B-bonds[11]. If desired a constraint can be arbitrarily imposed at a bond; in this case the minimum and maximum torsion angle values are entered. When an F- or B-type constraint has been identified the program will further request information regarding the ringsize of the constraining cycle, and the hybridization and configuration of the atoms at the constrained bond. Assignments of hybridization and configuration are made upon clockwise consideration of the involved ringatoms. Configurational assignments are made relative to the planar ring using the familiar β(b), α(a) stereodesignation (cf. wedged and hashed stereobonds for an orientation above and under the plane, respectively). Next to sp^3(3)- and sp^2(2)-hybridization states the program considers "intermediate (i)" states when three-membered rings are involved. A sample input for the six-membered C-ring of 1 is shown in chart 1.

Chart 1. Input for the C-ring of product 1[a]



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Clockwise numbering : ? 8? 9? 11? 12? 13? 14

Is the following bond constrained (yes = 1, no = 0) :
 8/ 9 ? 1
        one or two constraints (1,2) : ? 1
        Z-bond(1), F-bond(2), B-bond(3), Imposed(4) : ? 2
             ringsize of fused cycle : ? 7
             hybridization : 33(1), 32(2), 23(3), 22(4), intermediate(5) : ? 2
             configuration : a(1), b(2) : ? 1
 9/11 ? 1
        one or two constraints (1,2) : ? 1
        Z-bond(1), F-bond(2), B-bond(3), Imposed(4) : ? 1
11/12 ? 0
12/13 ? 0
13/14 ? 1
        one or two constraints (1,2) : ? 1
        Z-bond(1), F-bond(2), B-bond(3), Imposed(4) : ? 2
             ringsize of fused cycle : ? 5
             hybridization : 33(1), 32(2), 23(3), 22(4), intermediate (5) : ? 1
             configuration : aa(1), bb(2), ab(3), ba(4) : ? 3
14/ 8 ? 0

Anchoring substituents off the ring (yes = 1, no = 0) ? 0

Enter numbering (0 to end) of :
        - exocyclic sp2-ringatoms : ? 0
        - ringatoms with beta-quaternary carbon : ? 0
        - ringatoms with beta-carbon : ? 13? 14? 0
        - ringatoms with beta-oxygen : ? 0
        - ringatoms with alpha-quaternary carbon : ? 0
        - ringatoms with alpha-carbon : ? 13? 14? 8? 0
        - ringatoms with alpha-oxygen : ? 0

Want to compare with experimental values (yes = 1, no = 0) ? 1
Enter clockwise experimental torsion angles starting from 8/9 :
? -22? 1? -16? 46? -71? 55
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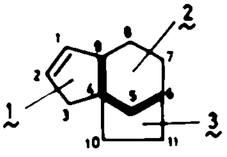
[a] Bold type numeric information is introduced by the user.

Using the foregoing assignments one may readily deduce the allowed torsion angle values at constrained bonds[11,12]. Note that two constraints may be present at the same bond. Consider product 3 : at bond 9,4 in cycle 1 are fused a six-membered ring and a seven-membered ring, while bond 4,9 in the six-membered ring 2 is both a F-bond (fusion with the five-membered ring 1) and a B-bond (bridging with the seven-membered ring). In practice the two inputs shown in scheme 2 are valid. In the first example one considers only the constraints that are directly related to one of the three analyzed cycles. The second way of input is clearly more time consuming and only strictly necessary when the deduced conformations are not to be combined. In general, when dealing with bridged systems (three cycles can be distinguished), one should only consider the two smaller rings for analysis (cf. cycles 2 and 3 in 3). (3) Anchoring substituent information. The identification of a substituent as an anchoring substituent (e.g., tert-butyl group) results

Scheme 2[a]

Cycle	Bond	Input (a)	Input (b)
1	2,1	Z	Z
	9,4	F(6)	F(6)
			F(7)
2	4,9	F(5)	F(5)
			B(7)
	7,6	-	B(7)
	6,5	B(5)	B(5)
	5,4	B(5)	B(5)
3	4,5	B(6)	B(6)
	5,6	B(6)	B(6)
	6,11	-	B(7)
	10,4	-	B(7)

[a] Numbers between parentheses refer to the ring-size of the constraining cycle.



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in effectively constraining the adjacent bonds. In practice the program will only allow a truly equatorial site in the puckered region of the generated conformations, so as to avoid any syn-diaxial interaction while minimizing possible gauche interactions. The specific algorithm imposes torsion angles of opposite sign at the adjacent bonds - with particular sign depending on the orientation of the anchoring substituent - and with magnitudes larger than 10° (absolute value)[12]. In the present treatment a number of geometrically possible but energetically improbable conformations are excluded. An alternative way of dealing with encumbering substituents is given below. (4) Substituent information. This relates to exocyclic sp^2-hybridized ringatoms (cf. ketones and exocyclic double bonds), and to ringatoms bearing α- and β-oriented substituents. In the latter case distinction is made depending on whether the connecting atom of the substituent is quaternary (e.g., *tert*-butyl), carbon or oxygen. Fused rings and bridgings are also regarded as substituents; atoms in a three-membered ring, however, are not. The program further uses this substituent information in determining semi-quantitative conformational energies for the generated conformations. (5) Experimental torsion angle values. Whenever the conformation of a ring is known (cf. X-ray data) the program will compare the geometries of the deduced conformations with the experimentally known via calculation of the corresponding standard deviations.

There is no practical limitation to the number of rings that can be analyzed by the program : up to eight rings, which can be part or not of the same molecule, can be dealt with in the same run. Every ringsize can in principle be examined by the TORSEVAL program. The deduction of conformations, however, is restricted at the present time to five-, six- and seven-membered rings. The result of the torsion constraint evaluation is shown upon request : for each endocyclic bond the minimum and maximum allowed torsion angles are given.

A number of structural features cannot be dealt with by the program : E-double bonds, trans-fusions with three-membered rings and bridgings involving sp^2-hybridized bridgehead centers. One should also keep in mind that the geometrical relationships, that are at the origin of the torsion constraint evaluation, are derived assuming standard valency angles[11,12]. Consequently, the procedure should not be applied to exceptionally strained systems where bond angles depart considerably from their ideal values. Such systems include e.g. bicyclo|1.1.1 pentanes, bicyclo|2.1.1|hexanes and *trans*-bicyclo |3.2.0|heptanes. Wherever a torsion angle value is "forced" to adopt a value larger than the ringsize limit, a fake value (i.e., 370°) is assigned as minimum and maximum allowable angle value. For five-, six- and seven-membered rings the program also considers the algebraic sum of angle values at every two adjacent bonds; if this sum is forced to be larger than the maximum allowable value for that ringsize then the program will consider the ring as geometrically non viable[11]. In our model these cases merely imply that the rejected ring cannot be built by means of a framework model with standard bond distances and valency angles. Whenever a ring is found too constrained by the TORSEVAL program, the program is interrupted and the user informed. When dealing with spirocyclic systems one should keep in mind that the program will not consider possible combinations of the deduced conformations of the rings since the combination procedure operates via the chaining of cycles through common bonds.

OUTPUT

After the input no interaction by the user is allowed until the final result of the analysis has been obtained. For each cycle of the system in turn, a CONF program will perform the deduction and evaluation of the geometrically possible conformations; at the end of the analysis of each cycle the deduced conformations are shown, ranked in increasing order of energy. A sample output for the six-membered C-ring is shown in chart 2. Each conformation is identified by a qualitative and a quantitative description. The qualitative description via a symbolic notation, e.g., 13+/HC for a half-chair conformation with atom 13 at the above top, allows for the direct reproduction of the conformation on a model. The quantitative description includes both the individual endocyclic torsion angles at each cyclic bond (internal coordinate) and a conformational parameter, the phase angle (puckering coordinate), that allows for the mapping of conformations on a model surface. The number of axial β- and α-oriented substituents is also given (Xb and Xa, respectively). When experimentally known torsion angle values have been input, the corresponding standard deviations are shown. This type of output is provided after the examination of each cycle in turn. Finally, the program CONFCOMB examines the combination of the conformations that were deduced for each cycle. In the case of product 1, where twenty forms were deduced for the six-membered A-ring, four for the sevenmembered B-ring, three for the C-ring (chart 2) and ten for the five-membered D-ring, a total of 2,400 possible combinations are considered.

Chart 2. Output for the C-ring of product 1[a]

```
Nr   Ph'A[b]  Conform   kJ/mol   Xb Xa    8/ 9   9/11   11/12   12/13   13/14   14/8

1    (-60)    13+/HC    15       (1 1)    -16    0      -16     48      -64     48
2    (-30)    13+/E     26       (1 1)     0     0      -29     58      -58     29
3    (-90)    14-/E     26       (1 1)    -29    0       0      29      -58     58

              experimental values :       -22    1      -16     46      -71     55
standard deviations : (1: 5), (2: 18), (3: 12)
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[a] For the used atomnumbering, see chart 1; [b] Phase angle; [c] Number of axial β(Xb)- and α(Xa)-oriented substituents.

Chart 3. Final output of the analysis of product 1[a]

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Allowed combinations in the 10 kJ/mol range :
Nr       Energy       Population       Cy 1       Cy 2       Cy 3       Cy 4

1        76           66               1          4          1          1
2        79           20               1          4          1          2
3        82           6                2          4          1          1
4        84           3                1          4          1          4
5        85           2                2          4          1          2
6        85           2                1          4          1          5
7        86           1                5          4          1          1
Relative enthalpy : 78 kJ/mol
Entropy of mixing : 15 J/mol.K
Entropy of symmetry : 0 J/mol.K
Relative free energy (298 Kelvin) : 73 kJ/mol
```

[a] Cycles 1, 2, 3 and 4 refer to the A, B, C and D rings of the steroid-like product 1, respectively.

For each possibility the actual torsion angles at both sides of constrained bonds (cf. fusions and bridgings) are compared with regard to the particular geometrical relationship that has been defined during the torsion constraint evaluation[11,12]. Whenever deviations occur from the ideal case (cf. bond angle bending) an energy term is included which is proportional to the deviation (vide infra). Combinations where deviations are encountered that correspond to differences in ideal torsion angle values larger than 30° are discarded. The remaining combinations are ranked in increasing order of energy; their conformational energies are obtained by summing the energy of the considered conformation of each cycle in the molecule and the above deduced "angle deviation" energy term. In the first instance only those geometries for the full molecule are shown that are effectively populated. The final result of the analysis of product 1 is shown in chart 3. The preferred geometry of the molecule (combination Nr. 1; 66 % populated) corresponds to a chair conformation for ring A, a sofa conformation for ring B (the fourth deduced form for that cycle), a half-chair form for ring C (vide supra) and a twist form for ring D. The corresponding full geometry is represented in 1b.

The structural diagrams of the different basic geometries that are considered by the program for each ringsize are given in the appendix. Conformations are unambiguously identified via a symbolic notation : one or more letters for the basic geometry involved, and an atomnumber followed by a + or - sign, for further defining the conformation within the basic geometry. In the case of a five-membered ring up to 100 different conformations can be considered by the program. The various basic geometries considered for six-membered rings represent 110 different conformations. Indeed, a basic geometry of type $\underline{C}_2$ or $\underline{C}_s$ represents a number of conformations equal to two times the ringsize. In practice the number of deduced conformations is reduced by search strategies that are implemented in the CONF programs[12]. It is interesting to note here that the torsion angle values that are shown in the output are not the values used in the matching procedure for deduction of allowed conformations - which are rounded values - but are calculated according to eq 3 (N = 5,7) and eq 4 (N = 6) :

$$\phi_j = \sum_{m=2}^{(N-1)/2} q_m \cos(\psi_m + 2\pi m(j-1)/N) \qquad (3)$$

$$\phi_j = \sum_{m=2}^{N/2-1} q_m \cos(\psi_m + 2\pi m(j-1)/N) + (q_{N/2}/\sqrt{2}) \cos(\pi(j-1)) \qquad (4)$$

N is the ringsize, q_m and ψ_m represent puckering coordinates (amplitude and phase angle, respectively). For j = 1,...N the N torsion angles $\phi_1,\ldots\phi_N$ of a particular conformation are obtained. The phase angle deduced by the program for five-, six- and sevenmembered rings is directly related to ψ_2. Puckering coordinates corresponding to the different basic conformations are available as supplementary material[12]. The origin and implications of eq 3 and 4 will be discussed elsewhere[13].

It is adequate to define here more precisely the energy values that are computed by the program. In principle the enthalpy of a molecule in a stable conformation is given by the bond energy to which is added its steric energy. The latter represents the total remaining molecular energy, the result of stretching, bending, torsion and van der Waals destabilizing interactions. The computed energy E_D for a conformation of a ring represents the difference between its steric energy and that of the lowest energy form in the series (cf. cycloalkane, cycloalkene and cycloalkanone type). The program considers a number of additive effects which contribute to yield this excess steric energy E_D[12]. (1) The conformational energy of the unsubstituted conformation. (2) The steric energy contribution of substituents. Three types of substituents are distinguished by the program, depending on the nature of the linking substituent atom : quaternary carbon (e.g., tert-butyl), carbon (e.g., methyl) and oxygen (e.g., hydroxyl, acetate). They are allocated a weight factor of 3, 1 and 0.5, respectively (cf. A-values)[14]. Substituent energy contributions depend on the specific location of the substituent and are taken relative to the lowest strain position. Note that equatorial (e.g. in 5-membered ring forms) and isoclinal substituents are not necessarily strain free. An axial substituent is recognized (cf. chart 2) when the energy contribution related to its specific position (weight factor 1) exceeds a certain value.
(3) The energy of a conformation may also depend on the location of an exocyclic double bond. The values used by the program were calculated for cycloalkanones. (4) Interactions between vicinal substituents contribute a destabilizing energy term, the magnitude of which is computed via $E_{vic} = 4W_1W_2E_\theta$, where W_1 and W_2 are the weights of the two substituents and E_θ is a function of the dihedral angle between both substituents in the considered form; E_θ equals 4, 3, 2 and 1 kJ/mol for angle values between 0°-20°, 20°-30°, 30°-40°, and 40°-70°, respectively. Following this equation the gauche interaction between two equatorial methyl groups in chair cyclohexane contributes 4 kJ/mole in destabilizing energy[15]. An angle of 0° between the same substituents would yield 16 kJ/mol, in accord with the lower estimate for the higher barrier in n-butane[16].
(5) Whenever a ring is connected to another ring via a fusion or bridging an energy term is involved with regard to how precisely the torsion angles in the considered conformations obey

$\tau = \Phi + \delta$, with δ an angle parameter whose value depends on the type of fusion or bridging, Φ the torsion angle value at the constrained bond in the considered conformation, and τ the corresponding angle value in the connected cycle when no angle bending is allowed (cf. trigonal symmetry in Newman projections)[11]. Upon examination of the combinations with the various conformations of the connecting cycle, the difference $\Delta\tau$ (absolute value) between the actual and ideal values of τ is considered. For differences between 0° and 15° an energy term is added equal to $\Delta\tau/4$, and for differences between 15° and 30° a term equal to $\Delta\tau/2$. One should note here that atoms which are part of a fused or bridging ring are considered as substituents with regard to steric energy contribution. No interaction, however, is counted between vicinal atoms which are part of the same fused ring.

When a molecule is a conformational mixture the conformations must be mixed according to a Boltzmann type distribution; therefrom the molar enthalpy and entropy can be calculated[17a]. Mole fractions are obtained from eq 5, where ΔS is most often zero; the enthalpy of a molecule with N stable (or discrete) conformations is given by eq 6, with N_i the mole fraction of the ith conformation and H_i its calculated enthalpy. The entropy is computed from the entropy-of-mixing formula (eq 7)[17a].

$$\ln(N_i/N_j) = -(H_i-H_j)/RT + \Delta S/R \quad (5) \qquad H = \sum_{i=1}^{N} N_i H_i \quad (6) \qquad S = -R \sum_{i=1}^{N} N_i \ln N_i \quad (7)$$

For our purpose the enthalpy of a conformation is $H_i = H_i^o + E_{Di}$, where H_i^o is the sum of the bond energy and the steric energy of the reference form and where E_{Di}, the computed conformational energy, is the excess steric energy relative to the reference form. In practice the program calculates a relative enthalpy term $\Sigma N_i E_{Di}$, with molar fractions obtained from $\ln(N_i/N_j) = -(E_{Di}-E_{Dj})/RT$, an entropy-of-mixing term $-R(\Sigma N_i \ln N_i + (k-1)\ln 2)$, and an entropy-of-symmetry term $-R\ln\sigma$. Thus, in systems which refer to the same H_i^o the calculated conformer population distributions and entropy terms should be meaningful. Computed enthalpy values, however, have no meaning in the absolute sense. In the first instance the above entropy terms are calculated with $k = 0$ and σ, the symmetrynumber[17b], $= 1$. Subsequently, corrected values for k and σ can be introduced; a few examples will be discussed in the following paper. To treat isomerization equilibria free energy differences need to be considered. The prediction of equilibrium compositions can only be meaningful for configurational isomers whose conformational energies were calculated relative to the same reference conformations.

DISCUSSION

The described method is to be regarded as an objective Dreiding model building system; bond distances and, in the first instance, bond angles are held at fixed characteristic values, and the various shapes that a cyclic molecule may adopt are defined by changes in the torsion angles. The very broad set of ring conformations that are considered by the program somehow guarantees that the real geometry of a molecule - or at least a good approximation - will be included in the deduced set. This, however, does not imply that this particular geometry will turn out to be the preferred conformation as predicted by the program : this, in turn, will depend on the computed conformational energies.

Basic geometries and energy terms that are used by the program are mostly taken from the literature and were originally obtained via molecular mechanics calculation[12,18-35]. Obviously, any shortcomings in the force fields used may seriously affect these values. Worse is that, with regard to the energetics of some systems, e.g., substituted six-membered boat conformations and substituted unsaturated seven-membered ring systems, little or no systematic work has yet been done. Here the program uses values that were intuitively assigned either by comparison with related systems or by mere qualitative inspection of models. A major advantage of the method resides in the simultaneous consideration of a variety of conformational effects that are difficult to evaluate during a model inspection. Such effects are merely considered additive; although this treatment is often used successfully[36], there is still no proof for its validity.

The way some interactions are delt with by the program is certainly not beyond criticism. Especially the introduction of a destabilizing energy term as being proportional to a difference in torsion angle values, while examining the combination of conformations of different cycles, cannot be regarded as an accurate quantitative treatment, but rather as a qualitatively reasonable one. Vicinal interactions involving substituents located on double bonds (cf. $A^{1,2}$- and $A^{1,3}$-strain)[37] are not considered here. No special treatment is presently reserved for evaluating syndiaxial interactions. The simple addition of the individual axial contributions is considered here sufficiently destabilizing. Other interactions, such as hydrogen-bonding and electrostatic interactions, are not considered altogether. The most important limitation of the method is its unability to recognize nonbonded interactions between substituents that are not located on the same ring; severe interactions of this type can take place within the concavity of *cis*-fused systems. Fortunately, however, this is the kind of interaction that is most easily identified during an inspection of models. In view of these limitations the method should be used in conjunction with molecular models.

Since the program is designed to run on microcomputers the present method represents a facile and inexpensive way for obtaining semiquantitative information about the geometry and energy of a wide variety of cyclic products. As will be shown in a following paper[38] useful results are obtained in various fields. It may help the synthetic chemist in predicting both the composition of certain equilibria and the stereochemical outcome of steric controlled reactions. It provides the conformational analist with starting geometries for further energy minimization[9]. And finally it may also serve educational purposes.

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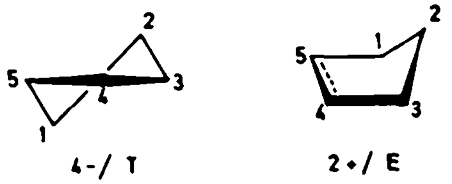
APPENDIX

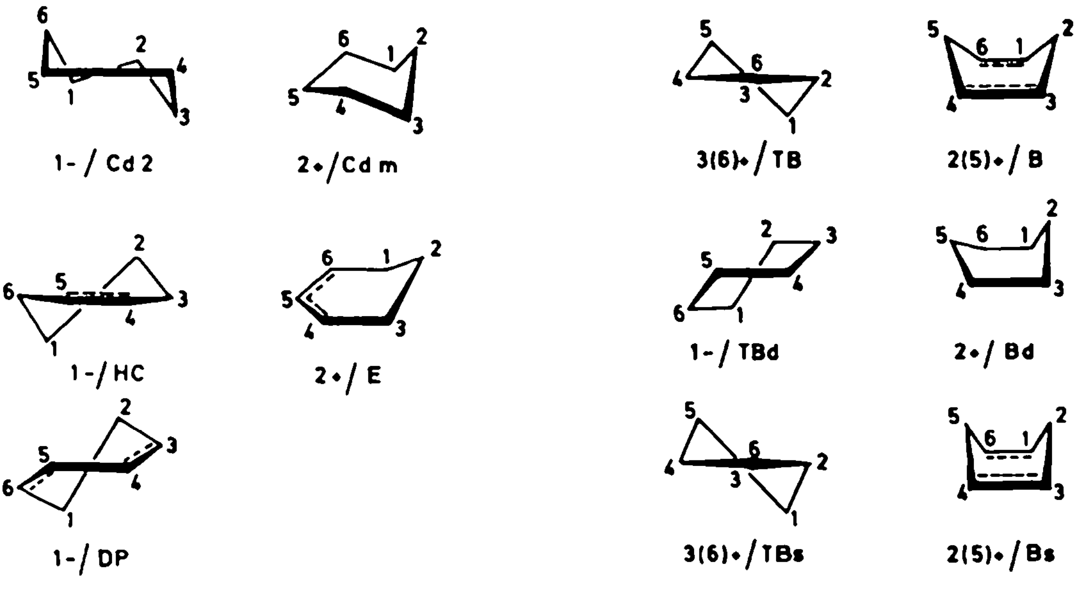
The considered basic geometries for five-, six- and seven-membered rings are shown in schemes I, II and III, respectively. Dotted bonds indicate the possible position of a double bond. Except a few high symmetric forms in the six-membered ring case, the basic forms are either C_2 forms (left columns) or C_s forms (right columns). All forms are viewed from above. C_s forms possess a symmetry plane; the atom, sectioned by the plane, is indicated in the notation, followed by a + or - sign, depending on whether the atom is located above or underneath the mean plane of the ring, respectively. C_2 forms are identified via an "octant rule" type projection : the ring is disposed symmetrically in "positive" (indicated by +) or negative (indicated by -) octants. When the diad axis sections a atom, this atom is located at the intersection and its numbering indicated in the notation. Several forms in the six-membered ring series deserve comment (vide infra). Using this notation the direct reproduction of a conformation with framework molecular models is readily and unambiguously done.

Scheme I[a]



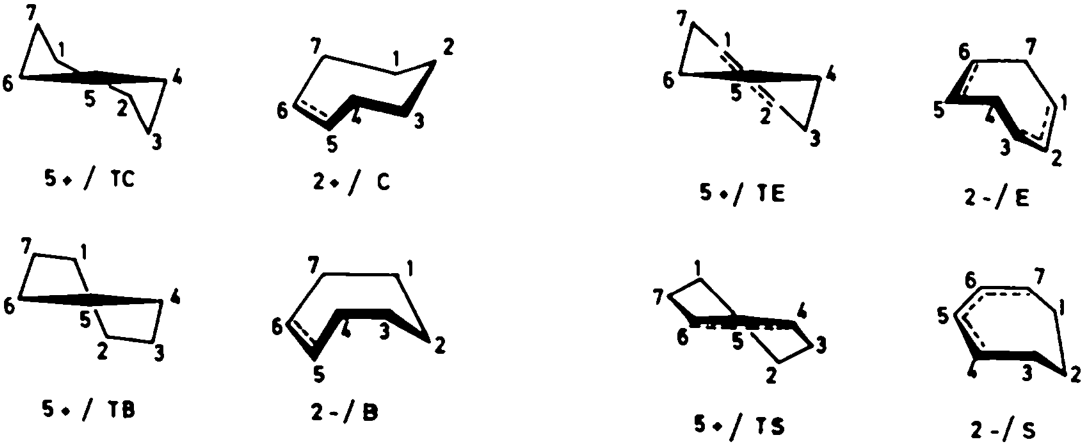
[a] Cyclopentane is characterized by pseudorotation. Symmetrical forms encountered during pseudorotation include the twist (T), envelope (E) conformations. Five different puckering amplitudes can be considered, i.e., q_2 = 18°, 28°, 38°, 48° and 58° (cf. equation 3), depending on the structure of the five-membered ring (cyclopentane, cyclopentene, cyclopentanone).

Scheme II[a]



[a] Three types of geometries are considered for cyclohexane : chairs, boats and intermediate forms. The latter are encountered during symmetrical chair-boat interconversions. Next to the regular chair (C) conformation the program also takes distorted chairs into consideration, i.e., the Cd2 ($\underline{C}_2$) and Cdm ($\underline{C}_s$) forms. They represent chair geometries in which one or more bonds are forced to adopt a large torsion angle value (max 80°) or a small torsion angle value (min 30°). The regular $\underline{D}_2$ and $\underline{C}_{2v}$ boat forms, designated as TB and B, respectively, are symmetrical forms part of a same pseudorotation circuit. Similarly, TBs and Bs are strained boats with a higher puckering amplitude. For the B and Bs forms, the symmetry plane considered for notation runs through the opposite atoms; for the TB and TBs, the diad axis runs through the opposite atoms. The program also considers distorted boat geometries, i.e., the symmetrical TBd ($\underline{C}_2$) and Bd ($\underline{C}_s$) forms. Finally, three intermediate conformations, i.e., the half-chair (HC), envelope (E) and diplanar (DP) forms are included in the saturated series so as to encompass the broadest possible range of geometries. The $\underline{C}_2$ forms where the diad axis bisects two opposite bonds (cf. Cd2, TBd, HC and DP), are disposed symmetrically with the flatter bond in front. The "octant sign" is then related to the disposition of the atoms of the opposite (puckered) bond : for +/forms the "above" atom is indicated, for -/forms the "down" atom. For cyclohexene, only HC, E, DP and undistorted boat forms (B, Bs) have to be considered.

Scheme III[a]



[a] Two families are considered for cycloheptane, both of which are characterized by pseudorotation. Symmetrical forms include the twist-chair (TC) and chair (C) conformations in one family, and the twist-boat (TB) and boat (B) forms in the other. For cycloheptene the program also considers, next to the classical chair and boat forms, the envelope (E) and twist-envelope (TE) forms, and the sofa (S) and twist-sofa (TS) conformations. Formal E-TE and S-TS pseudorotations are considered by the program. In both the E and S forms different conformations (cf. conformational energy)[12] result depending on the location of the double bond (5,6 versus 1,2 or 2,3 in E; 5,6 versus 4,5 or 6,7 in S).