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THE SCA PROGRAM : AN EASY WAY FOR THE CONFORMATIONAL EVALUATION OF POLYCYCLIC MOLECULES

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Abstract - The present version of the SCA (Systematic Conformational Analysis) program analyzes polycyclic derivatives containing five-, six- and sevenmembered rings and derives a restricted number of best candidates for further energy minimization. The program requires an IBM PC, XT, AT or compatible equipped with a mouse, an enhanced graphics adaptor and an EGA monitor. Molecules are entered as two-dimensional structural diagrams. The program will then select the most representative geometries among all possible basic conformations together with an approximate conformational energy. Conformations so obtained may be viewed three-dimensionally. Alternatively, input files may be created for direct further molecular mechanics treatment. The latter link makes it possible to perform energy minimizations on structurally complex and flexible molecules in the reassuring confidence that all best candidates were considered.

A few years ago one of us reported on a microcomputer method for the semiquantitative conformational evaluation of carbocyclic systems containing five-, six- and sevenmembered rings.[2] Essential features of the SCA (Systematic Conformational Analysis) program included : (1) its operation on inexpensive microcomputer configurations;[3] (2) a full semiquantitative conformational evaluation starting from the two-dimensional structure of the molecule. The latter feature is of prime importance since, to the best of our knowledge, available molecular modeling systems typically require the user to introduce, at the input stage, information that is already pertinent to the three-dimensional geometry of the molecule, such as cartesian coordinates (or some variant thereof), pre-designed cyclic conformations (e.g., chair cyclohexanes) or staggered alkane fragments.[4]

The aims of the previous program were 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. (2) The calculation of appropriate free energy terms (including an entropy-of-mixing-conformations term) for the prediction of the composition of isomerization equilibria. In practice the latter prediction is restricted to configurational isomers possessing the same bond energy since the computed conformational energies of the derived conformations are excess steric energies relative to a standard minimum energy from (e.g., chair cyclohexane, half-chair cyclohexene). (3) The generation of all reasonable starting three-dimensional geometries for eventual Westheimer strain energy minimization by other programs.[5]

This first version of SCA had important shortcomings (vide infra). The purpose of this paper is to describe the features of an enhanced full graphics version of SCA which offsets most previous deficiencies and which is primarily designed for the generation of high quality preliminary three-dimensional geometries that are suited for direct subsequent force field calculation, e.g., by Allinger's MMP2 program[6] or for further manipulation by the Macro Model

modeling system.[7] It now operates on IBM PC, XT, AT or compatibles equipped with a mouse, an enhanced graphics adaptor and an EGA monitor.[8] Input molecules are entered graphically by means of a mouse in exactly the same way as when they are drawn by the chemist, i.e., stereogenic centres are characterized by the familiar α,β-stereodesignation (cf. hashed and wedged stereobonds for an orientation under or above the plane). Although ring appendages are handled by the present program, the prime objective still resides in generating conformations for the (poly)cyclic part of the molecule, consisting of five-, six- and sevenmembered rings. The output consists of the cartesian coordinate set of all entered atoms for all deduced conformations, and input files may be created for direct further molecular mechanics treatment. Alternatively the possibility for direct graphic display of the obtained conformations makes the program an inexpensive stand-alone system for semiquantitative conformational evaluation.

Major limitations of the original SCA program were related to the input of the two-dimensional structures which were introduced in a nongraphical interactive way, to the output of conformations which were identified via symbolic notations for the separate rings of the polycyclic system rather than by cartesian coordinates, and to serious deficiencies in the energy calculation.[2a] How these different points were solved in the current version is described in the following sections. The main program SCA is in charge of directing the program flow and interacts with twelve subprograms as shown in figure 1.

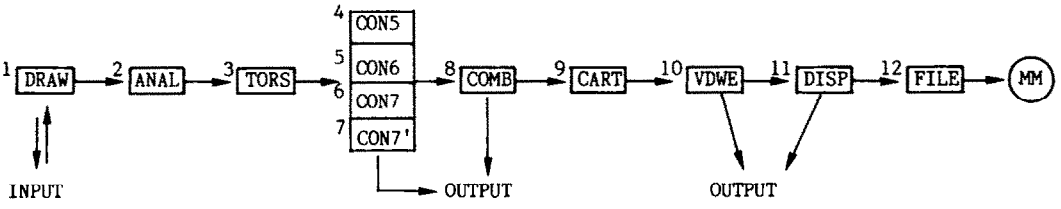
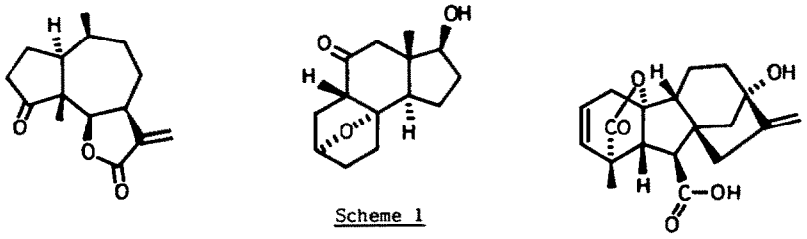


Figure 1. Program structure

As far as input is concerned, ultimately the chemist desires to introduce molecules in exactly the same manner as he is used to draw them two-dimensionally. In particular he wants to deal with stereochemistry via the familiar α,β-stereodesignation. This is the way input is now handled by the program DRAW. Scheme 1 shows a set of structures exactly as they are introduced graphically by means of a mouse, using the following four options : planar ring templates (3- to 7-membered); single, double or triple bond drawing; change carbon atom type to hydrogen, oxygen, nitrogen, sulfur and lone pair; α,β-stereodesignations via directional hashed and wedged bonds, respectively.

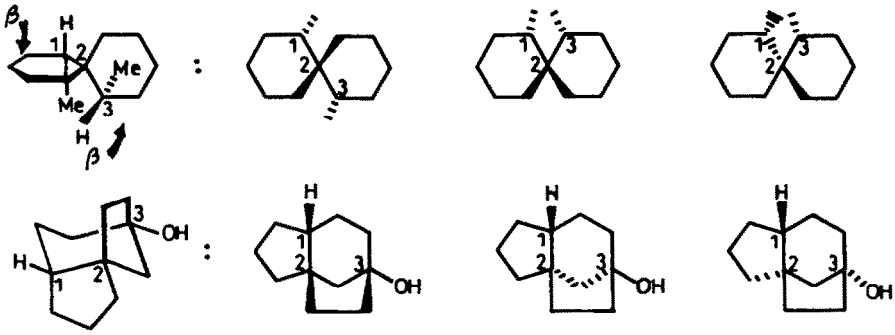


Scheme 1

Stereogenic ring atoms should be defined by at least one stereodesignation. Hydrogen atoms need not be drawn except if they are part of a functional group (e.g., hydroxyl) or if they must serve as a stereodesignator at fusion or bridgehead positions. The structure will automatically be supplied with all lacking hydrogen atoms and lone pairs.[9] Scheme 2 shows different but allowed ways of drawing a particular spirocyclic and bridged system. Note that in the case of the spirocycle two perpendicular β-directions must be distinguished and hence two stereodesignations be used at the spirocentre.

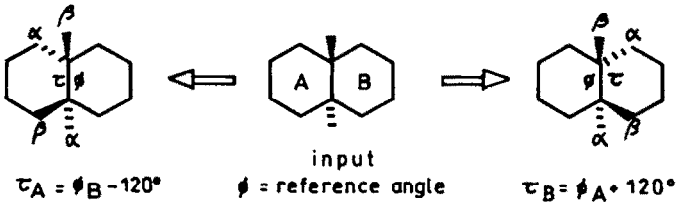
All specifically introduced atoms will be numbered by the program. The user is allowed to change the program numbering if desired. Stereogenicity in appendages (i.e., noncyclic atoms) is delt with in a separate way (vide infra). Stereodesignations are used by the program for two main

purposes : (1) to define the orientation (i.e., α or β) of substituents relative to a reference ring; for that purpose, every ring in the molecule in turn will serve as planar reference ring;



Scheme 2

(2) to define how the different rings are connected to each other for the purpose of deriving the relationships which exist between torsion angles at common cyclic bonds (i.e., fused and bridged bonds). This is exemplified in scheme 3 for a trans-fused decalin where rings A and B in turn serve as reference rings. This procedure is crucial for determining the allowed endocyclic torsion angle signs and magnitudes at both sides of the fusion[10].

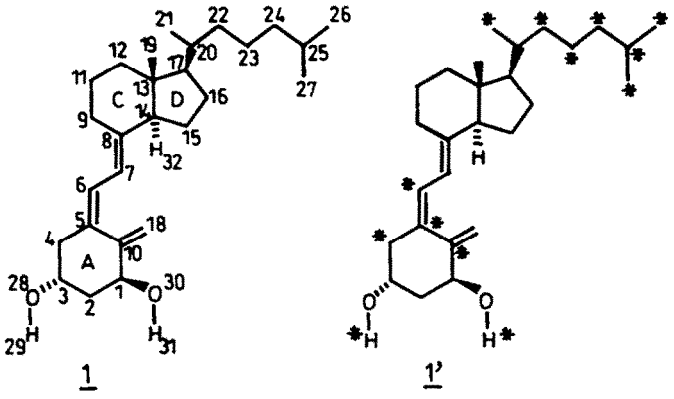


Scheme 3

It is necessary here to discuss in some detail how appendages are handled by the program. Appendages can be introduced in the DRAW program, but no conformational search is effected with regard to torsion angles that are not endocyclic. These residual torsion angles should be defined by the user at the input and define the appendage conformation that the program will further consider. Consequently, all non-hydrogen atoms (except if they were specifically drawn) that are separated from the ring skeleton by two bonds or more should be defined in space by means of a dihedral angle involving three known atoms. If the last of these three atoms is sp^3-hybridized the program expects dihedral angle values of +60°,-60° and 180°; in the case of sp^2-hybridization values of 0° and 180°. When the molecule possesses different cyclic systems that have no common atoms, e.g., the A-ring and the CD-ring systems in 1α-hydroxy vitamin-D_3 (1), the cyclic system which was drawn first in DRAW will have a higher priority implying that the orientation of the second system, relative to the first, needs to be defined by means of residual angles. This case is exemplified in scheme 4 for 1 where the CD-ring system has received the higher priority and where an extended conformation is defined for the chain at C-20. The starred atoms in 1' must all be defined by dihedral angle lists as shown in scheme 4.

As mentioned previously hydrogen atoms (except stereodesignators) need not be drawn : the program will automatically supply the required hydrogens on the skeleton. Four cases are shown in scheme 5 : diagrams 2-5 show the structures as they are drawn, diagrams 2'-5' how they are subsequently completed by the program at atoms 1, 2 and 3.

The analysis of the full structural diagram in terms of connectivity (atom and bond types, ring sizes, hybridization) and stereochemistry is performed by the program ANAL. The latter provides all structural information that is needed in the subsequent programs.

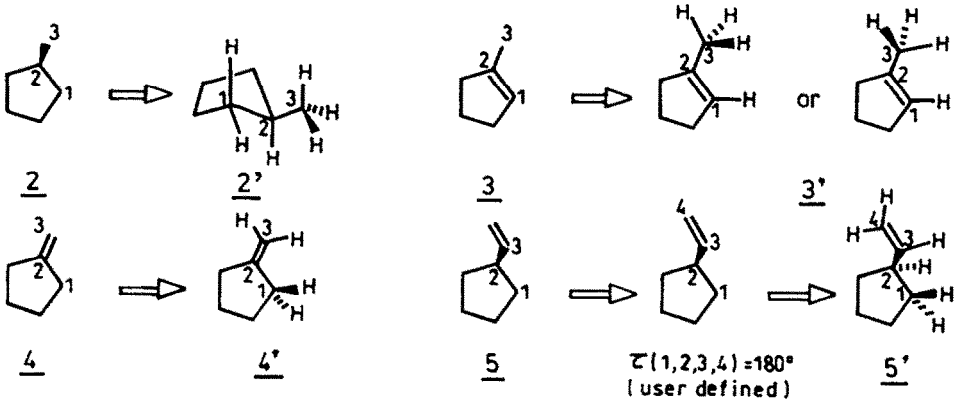


1 1'

Residual atoms and dihedral angle lists

6	9-8-7-6	:	0°
5	8-7-6-5	:	180°
4	7-6-5-4	:	180°
10	7-6-5-10	:	0°
29	2-3-28-29	:	60°
31	10-1-30-31	:	180°
21	16-17-20-21	:	180°
22	16-17-20-22	:	+60°
23	17-20-22-23	:	180°
24	20-22-23-24	:	180°
25	22-23-24-25	:	180°
26	23-24-25-26	:	180°
27	23-24-25-27	:	+60°

Scheme 4



2 2' 3 3' 4 4' 5 5'

Scheme 5

The further analysis first involves a torsion constraint evaluation of each individual cycle present in the polycyclic molecule. From the mere knowledge of the two-dimensional structure of the molecule, i.e., connectivity (ring sizes, hybridization) and stereochemistry (α,β-stereodesignations), the program TORS derives the allowed range of endocyclic torsion angles (sign and magnitude) that can be afforded at each cyclic bond.[2a]

The CON programs then match this result against a set of standard forms for cycloalkane (cycloalkanone) and cycloalkene five-, six- and sevenmembered rings (so-called templates) and deduce all geometrically allowed conformations.[2a] For each deduced form a preliminary conformational energy value is calculated by considering a number of additive terms which contribute to yield an excess steric energy. (1) The conformational energy of the unsubstituted form relative to the minimum energy form in each series; (2) The influence of the location of an exocyclic double bond (cycloalkanone versus cycloalkane); (3) A steric energy contribution of substituents, the magnitude of which depends both on the specific location in the considered form and on the substituent type. At this stage, three types of substituents are distinguished, depending on the nature of the linking substituent atom : carbon (e.g., methyl, ethyl, isopropyl), heteroatom (e.g., hydroxyl, acetate) and quaternary carbon (e.g., tert-butyl), which are allocated different weight factors; (4) Interactions between vicinal substituents (cf. gauche oriented or eclipsed substituents). This deduction and preliminary energy evaluation, which is performed by different CON programs depending on the ring size, yields a list of geometrically possible basic conformations for each individual cycle in the molecule. This list can be rather extensive.[11] E.g., for a six-membered ring up to 110 different conformations can be envisioned. In the previous SCA version 62 different conformations are deduced for the A-ring of 1 involving

regular and distorted chair conformations, various types of boat forms, half-chair and diplanar conformations.

For the purpose of eventually deriving only a restricted list of best candidates for further energy minimization, a further reduction in the above list of conformations for each individual cycle is performed. The followed procedure depends on the ring size and is briefly summarized below. (1) For five-membered rings the program analyzes the deduced conformations (in increasing order of energy) as a function of pseudorotation; only those conformations are maintained which are not adjacent to or next to adjacent to a lower energy form in the original list. Whereas for a cyclopentane derivative twenty different conformations (ten twist and ten envelope forms) were originally deduced, now this number is reduced to four to six forms (depending on the case), which are evenly distributed along the pseudorotation cycle. (2) For six-membered rings distinction is made between three families. Within the chair family (regular and distorted chairs) only one representative is maintained; the same is true for the inverted series. Indeed, in practice it turns out that within the same series (cf. chair inversion) all chair type conformations yield the same energy minimum upon minimization. Within the boat-family, which includes regular boat and twist-boat forms next to distorted ones, care is taken not to include forms which, within the pseudorotation cycle, are adjacent to a lower energy form. Also, distorted boat type conformations are only maintained if they are deemed sufficiently different in geometry from regular forms. An analogous procedure is followed to restrict the number of conformations in the intermediate family, involving half-chair, envelope and 1,3-diplanar forms. (3) Within each family of cycloheptane conformations (chair and boat type) only those conformations which are not adjacent in pseudorotation to a lower energy form are maintained in the original list. In this way only representative geometries are selected which offer the best chances of yielding different minima upon eventual energy minimization (vide infra).

The program COMB performs the combination of the separately deduced conformations for each ring so as to produce geometries for the cyclic molecule. The result consists of a list of allowed combinations ranked in increasing order of energy. At this stage the geometry of each combination is defined by the specific conformation of each constituent cycle, as indicated by an unambiguous symbolic notation.[2a]

A major shortcoming of the previous SCA version involved the computation of conformational energy terms related to nonbonded interactions. In particular, vicinal interactions involving substituents located on double bonds (cf. $A^{1,2}$- and $A^{1,3}$-strain) and syndiaxial type interactions were not evaluated. A crucial limitation also resided in its unability to recognize nonbonded interactions between substituents that are not located on the same ring; severe interactions of this type, however, can take place within the concavity of cis-fused systems. Table 1 shows the conformational energy differences between the chair,chair-conformations a and b of four methyl-cis-decalins (6-9) as computed by molecular mechanics (MM2), by the previous[2b] and the present version of SCA. Comparison of the results of the molecular mechanics calculation and the computed values of the previous SCA version clearly reveal these deficiencies.

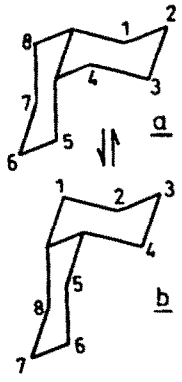


Table 1. Conformational energy differences[a] between the chair,chair-conformations a and b of the methyl-cis-decalins 6-9

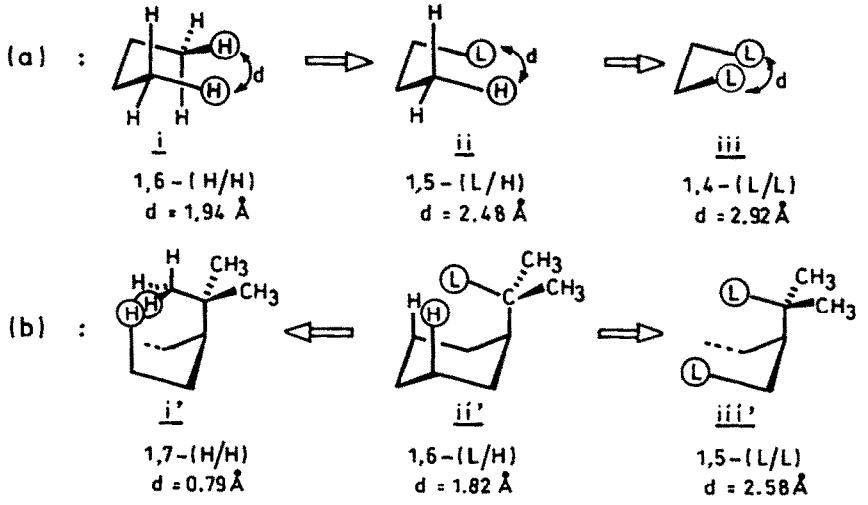
	cis-decalin	MM2	SCA[b]	SCA[c]
6	1α-Me	21	8	23
7	2β-Me	7	8	8
8	3α-Me	16	8	15
9	4β-Me	2	4	1

[a] In kJ/mol; [b] previous version; ref. 2; [c] present version (see text).

This problem has now been partly solved by including a destabilizing energy term that is concerned with all nonbonded interactions in each full conformation. Therefore, the program CART first generates the cartesian coordinates of all atoms in the conformations that were deduced by the program COMB. The computation of the nonbonded energy term is then performed by the program

VDWE. It is necessary here to remind the reader that the purpose of SCA is not to perform a true molecular mechanics calculation, but rather to provide a fast and reliable way of generating best candidates for further energy minimization. Accordingly, simplified potential functions for different interaction types are considered, which yield a repulsive nonbonded energy term as a function of the distance that separates the involved atoms. In particular only two atom types are considered, i.e., S (Small : hydrogen and lone pair) and L (Large : other than hydrogen), and three interaction types, i.e., S-S, S-L and L-L. The corresponding functions are given in equations 1-3 (E in kJoule/mole; d in Å) :

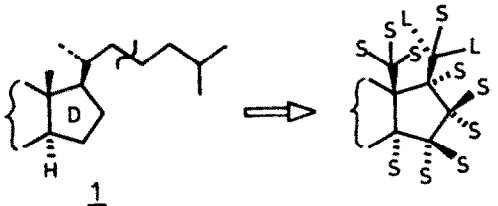
$$\text{S-S interaction : } E = -10.4\ d + 24.2 \quad \text{(eq 1)}$$
$$\text{S-L interaction : } E = -18.3\ d + 49.3 \quad \text{(eq 2)}$$
$$\text{L-L interaction : } E = -35.4\ d + 107.3 \quad \text{(eq 3)}$$



Scheme 6

The above linear functions were derived by using two reference points which were obtained as follows. Consider the gauche-butane interaction shown in scheme 6 (i) : the interaction is worth approximately 4 kJ/mol and formally involves two hydrogen atoms in a 1,6-relation at a distance of 1.94 Å.[12] If one methyl group is replaced by an undefined L substituent (ii), the same interaction energy is formally maintained and the distance between L and H, now in a 1,5-relation, is 2.48 Å. When both methyl groups in i are replaced by L substituents (iii), the distance L-L corresponding to the 4 kJ/mol interaction is 2.92 Å. On the other hand, an energy value of 16 kJ/mol is assigned to the interaction between a L and S substituent in a 1,6-relation (ii'). The latter value is deduced from the A-value of a tert-butyl group,[13] i.e., 24 kJ/mol, which corresponds to the formal difference between the axial (2 gauche-butane + 2 L-S 1,6-interactions) and the equatorial (4 gauche-butane interactions) orientation on cyclohexane. In much the same way as above, the same destabilizing energy of 16 kJ/mol is assigned to a S-S 1,7-interaction (i') and to a L-L 1,5-interaction (iii'). From the above reference points equations 1-3 are readily derived. That this treatment is reasonable, at least when involving H-H interactions, is shown by the result in table 1, which reveals a fine correspondence between the computed values by the new SCA version and the eventual molecular mechanics treatment. Obviously, this new energy term should not be added as such to the preliminary conformational energies as computed by the different CON programs. Only the original contributions relative to (1) the conformation type, and to (2) the influence of an exocyclic double bond (vide supra), are eventually maintained. The rules which are followed for the identification of S and L substituents are given below. Noncyclic atoms which are separated from a ring skeleton by three

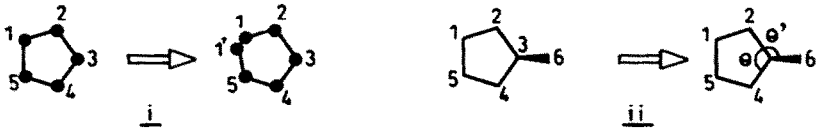
or more bonds are not considered. Noncyclic atoms separated by two bonds, and which are not equal to hydrogen (or a lone pair) are identified as L substituent. Remaining hydrogen atoms and lone pairs, including those which are directly situated on the cyclic skeleton, are identified as S substituents. This is exemplified for the D-ring of 1 in scheme 7.



1

Scheme 7

Interactions between geminal substituents are not considered. Otherwise, all L-L and L-S interactions are taken into account. Among S-S interactions only those involving hydrogens and/or lone pairs situated in different rings of the cyclic system are considered.
The above mentioned cut-off of ring appendages is a necessary simplification. Indeed, during the generation of the full cartesian coordinate set by the program CART small irregularities may occur, which are, however, exacerbated while moving further away from the ring skeleton. The effect is comparable to a small deviation, e.g., in a valency angle at one end of a rigid chain, which results in a much larger deviation at the other end of the chain. The above irregularities are related to the problem of formal ring closure and to the correct attachment of appendages and rings to the reference cyclic framework, while proceeding form the internal coordinate set to the eventual cartesian coordinate set. They originate from the program dealing in the first place only with (endocyclic) torsion angles and not with valency angles. The generation of a correct set of cartesian coordinates, however, implies the knowledge of bond distances and bond angles, next to torsion angles. The program uses the same bond distances (equilibrium values) as used in MM2. How the program deals with valency angles is illustrated for two cases in scheme 8.



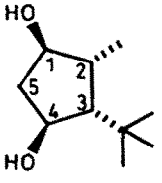
Scheme 8

Depending on the ring size average endocyclic valency angles are considered in the first instance : 95° for five-, 100° for six-, and 105° for sevenmembered rings. When dealing with a formal ring closure, as indicated for a cyclopentane in scheme 8 (i), the program uses five bond distances, four valency angles (corresponding to the above average angle) and three of the five known endocyclic torsion angles in order to derive the cartesian coordinates of atom 1' (the point of formal closure). By raising the magnitude of the average value of the three endocyclic bond angles, the distance between 1 and 1' is reduced until a minimal distance is found. Atom 1 is repositioned at half this distance; the bond distances 1,2 and 1,5, the internal valency angles at atoms 1,2 and 5 and the endocyclic torsion angles at all bonds, except bond 3,4, are recalculated. In general, the final value of the average valency angle found is very close to the real one. The main deficiency of this method resides in that somewhat different results are obtained depending on which atom is considered by the program for closure. The same is true when appending a substituent on a ring (ii; scheme 8). Defining the position of atom 6 relative to the five-membered ring implies the knowledge of the dihedral angle between atoms 1 and 6 at bond 2,3 and the bond angle θ' between atoms 2 and 6. The former value may be deduced from the endocyclic torsion angle at bond 2,3 since the orientation (α or β) of atom 6 relative to the ring is known (both dihedral angles are related via ± 120°).[10] The value of θ' is adapted following the equation $\theta' = 109.5 + (109.5-\theta)/2$. Again one should realize that defining the position of 6 relative to the fragment 3,4 instead of the fragment 2,3 as above may lead to a

somewhat different result. Obviously, this implies that the destabilizing energy term, that is calculated for each conformation in the program VDWE, may differ somewhat depending on the numbering of the atoms that is used by the program; this internal numbering is originally defined during the DRAW program.

The result of the program VDWE is a novel ranking of the conformations that were originally generated by the program COMB. The original listing of COMB is still shown to the user : since the generation of the cartesian coordinate set is the most time consuming part of the analysis (10 sec/form for 1), the user is still allowed to restrict the number of conformations that will be further manipulated by the CART and VDWE programs. Each final conformation is characterized by the geometry of its constituent cycles; for each of these is given : the symbolic notation which defines unambiguously the conformation of the individual cycle, the original ranknumber as deduced by the CON program (and hence the endocyclic torsion angles at each bond) and the phase angle which helps in identifying forms on a conformational surface.[2] The final conformations can also be displayed graphically in two modes (Dreiding model or ball-and-stick) with the possibility of rotation around x,y,z-axes.

A full analysis is performed very rapidly. In the case of product 1, after the molecule has been entered graphically and the residual torsion angle list defined, the generation of ten best candidates for further energy minimization requires $\sim$ 2 minutes. For the latter purpose files may be created very conveniently for input in MMP2[6] or for further manipulation by MacroModel.[7]



10

In practice we have found the combination SCA-MacroModel to be very powerful.[14] This is exemplified below for the cyclopentanediol derivative 10. Figure 2 shows energy profiles for 10 where conformational energies are plotted against the phase angle. The phase angle ψ defines a conformation in the pseudorotation circuit (constant ϕ_m), following the equation :

$$\phi_j = \phi_m \cos(\psi + 4\pi(j-1)/5;\ j = 1, 2, .. 5;\ 0° \leq \psi < 360° \quad \text{(eq. 4)}$$

where ϕj = (j = 1 to 5) represent the endocyclic torsion angles of the conformation.[16] Symmetrical C_2 (twist) and C_s (envelope) forms are generated for discrete values of ψ, i.e., 0°, 36°, ... and 18°, 54°, ..., respectively. The crystal geometry of the compound corresponds to $\phi_m = 44°$ and $\psi = 219°$.[15] The hashed line represents the twenty symmetrical forms deduced by the previous SCA program.[2] The bold line shows the same conformations (numbered 1-20) with the conformational energies as computed by the VDWE program. These twenty different SCA forms were all minimized via MacroModel.[14] Three local minima were so obtained.[17] Conformations 13-20 all yielded the lowest energy from A ($\psi \sim 216°$), which corresponds to a slightly distorted 5-/T form with a steric energy of 100.9 kJ/mol; forms 1-6 gave the minimum energy form B ($\psi = 342°$), corresponding to the 1-/E form (107.0 kJ/mol); form C ($\psi = 36°$), the 5+/T form (111.4 kJ/mol) resulted from the minimizations of conformations 7-11. The final result of the conformational evaluation of diol 10 by the present version of SCA is shown in Table 2. Instead of twenty conformations, six best candidates for further energy minimization are selected, i.e., forms 3,6,9,13,16 and 19 (figure 2). These eventually yield all minima of interest. The approximate time requested for minimization is also given in table 2, and somehow reflects how much (in phase angle) the selected form is separated from the local minimum.

In conclusion, the present version of SCA examines the full conformational space of a polycyclic molecule (with composite rings smaller than eight-membered) and deduces a restricted number of best candidates for finding all local minima upon energy minimization, in the reassuring confidence that no minima will be overlooked. It does so starting from a graphically introduced two-dimensional diagram of the molecule in a very cost effective way, especially with

regard to the time required. The authors will undertake the necessary steps to make the program available through QCPE.

Figure 2. Energy profile for 10

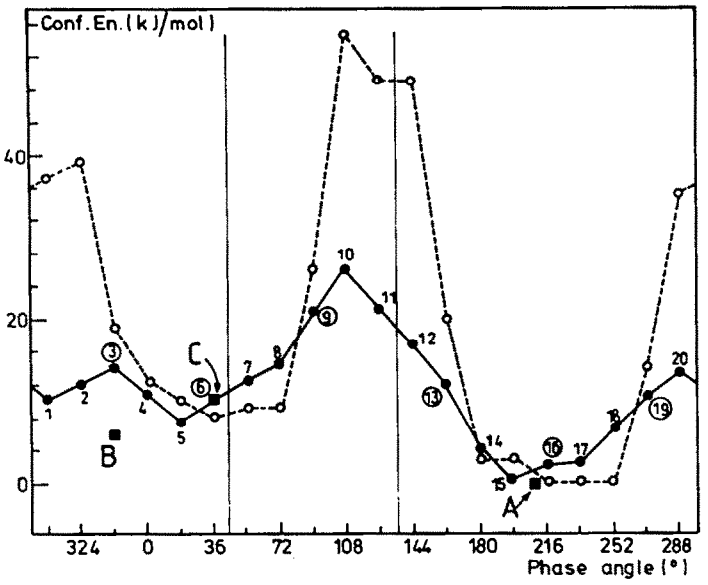


Table 2. Conformational evaluation of diol 10. Results of SCA and of eventual energy minimization

	SCA-output			Energy minimization		
Nr	Conf.En[a]	Form[b]	Phase[c] angle	Nr[d]	MM2[e]	CPU time[f]
1	36	5-/T	216	16	A	60
2	44	5+/T	36	6	(C→)B[d]	240
3	44	4-/E	270	19	A	240
4	46	1+/E	162	13	A	240
5	48	1-/E	342	3	B	120
6	55	4+/E	90	9	C	120

[a] In kJoule/mol; [b] following notation in ref. 2; [c] according to equation 4; phase angle ψ in degrees; [d] rank number as in figure 2; [e] eventual minimized conformation via MacroModel : A = 5-/T; B = 1-/E; C = 5+/T; [e] this conformation first leads to C during the minimization process (60 CPU sec), but eventually yields form B as local minimum; [f] approximate time (in CPU sec) required to reach the local minimum on a Microvax-II.

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References and notes

1. (a) Present address : Merrell Dow Research Institute, Strasbourg (France); (b) Senior Research Associate of the National Fund for Scientific Research (Belgium).
2. (a) P.J. De Clercq, Tetrahedron, 40, 3717 (1984); (b) P.J. De Clercq, Ibid., 3729.
3. This laboratory configuration included : Z-2D Cromenco System (Z-80 microprocessor, 64 KB RAM, two 5-inch quad-capacity disk drives); the program was written in BASIC.
4. For some exceptions, see : (a) W.C. Still and A.J. Lewis, Chem. Tech., 118 (1974); (b) E.J. Corey and N.F. Feiner, J. Org. Chem., 45, 757, 765 (1980); (c) N.C. Colin, P. Colin, and G. Lemoine, Tetrahedron, 37, 1711 (1981); (d) W.T. Wipke and M. Hahn, ACS Symposium Series, 306, 136 (1986); (e) D.P. Dolata, A.R. Leach, and K. Prout, J. Computer Aided Molecular Design, 1, 73 (1987).
5. For reviews, see : N.L. Allinger, Adv. Phys. Org. Chem., 13, 1 (1976); U. Burkert, N.L. Allinger, "Molecular Mechanics"; American Chemical Society; Washington, DC (1982).
6. From QCPE; N.L. Allinger and H.L. Flanagan, J. Comput. Chem., 4, 399 (1983).
7. MacroModel, version 1.5, kindly provided to us by Professor C. Still (Columbia University, New York).
8. In this laboratory the program now runs on a TULIP AT (80286 processor; MS-DOS 3.1) with 640 Kb of memory, one 1.2 Mb floppy disk drive, a 20 Mb hard disk drive, one serial port, one

mouse interface, a mouse (Genius, Microsoft Compatible), an enhanced graphics adapter and a Multisync monitor.
9. Lone pairs are, however, not added in the case of carbonyl groups (cf. reference 7).
10. P.J. De Clercq, Tetrahedron, 37, 4277 (1981).
11. See the appendix in reference 2a.
12. This is an overestimation of the 0.75-0.8 kcal/mol reported 1,2-diequatorial chair cyclohexane methyl-methyl interaction; H.R. Buys, E. Havinga, Tetrahedron Lett., 3759 (1968); M. Tichy, S. Vasickova, S.V. Arakelian, and J; Sicher, Collect. Czech. Chem. Commun., 35, 1522 (1970).
13. S. Winstein, N.J. Holness, J. Am. Chem. Soc., 77, 5562 (1955).
14. MacroModel runs on a MicroVax-II configuration, with Tektronix 4207 graphics terminal and Tektronix 4957 data tablet. The calculation of minimized steric energies uses Allinger's MM2 force field (Allinger's August 1985 parameter set) and block diagonal Newton Rahson minimization until RMS 0.1 or better is reached.
15. D. Van Haver, M. Samson, and M. Vandewalle, Tetrahedron, 33, 255 (1977).
16. C. Altona, H.J. Geise, and C. Romers, Tetrahedron, 24, 13 (1968).
17. The anti-periplanar orientation of the H-O-C(1)-C(2) and of the H-O-C(4)-C(3) bonds was considered in the input.