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SYSTEMATIC CONFORMATIONAL ANALYSIS. A MICROCOMPUTER METHOD FOR THE SEMIQUANTITATIVE EVALUATION OF POLYCYCLIC SYSTEMS CONTAINING FIVE-, SIX- AND SEVEN-MEMBERED RINGS. 2. SCOPE AND LIMITATIONS.

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Abstract - Several applications of the previously described microcomputer program for systematic conformational analysis of polycyclic systems (five-, six- and seven-membered rings) are discussed. Examples are given in relation to the prediction of the stereochemical outcome of a steric approach controlled reaction, to the prediction of the composition of isomerization equilibria and to the qualitative evaluation of strain in particular pre-transitionstate geometries. Implications of the produced geometric and energetic (with focus on entropy) information are further discussed.

For the solution of a stereochemical problem, especially when cyclic compounds are involved, the organic chemist will turn, more often than not, to an inspection of molecular models. However, results drawn from such inspections are essentially of a qualitative nature and, moreover, often dependent on the examiner. Consequently, there is a need to perform model examinations in a systematic and quantitative way. With this goal in mind a computer program was developed for the systematic conformational analysis (SCA) of polycyclic systems containing five-, six- and seven-membered rings. Since many synthetic laboratories do not have routine access to large computer facilities, which are needed for the application of strain-energy minimization techniques, the program was designed for operation on inexpensive microcomputer configurations. In a preceding paper the principle of the method and the characteristics of the program were described[1]. Starting from structural information that is directly related to the two-dimensional diagram of the molecule the program yields the following information. (1) The set of all geometrically possible conformations of each cycle in the system. (2) The set of preferred full conformations of the molecule with the corresponding conformer population distribution. (3) Relative enthalpy, entropy and free energy terms for the product.

In the present paper the scope and limitations of the method are described. In the first part typical synthetic problems are dealt with. Next attention is paid to the geometrical information that is provided by the program. Finally the computed energy terms are discussed with special focus on the calculated entropy.

SYNTHETIC APPLICATIONS

First a typical example of how the SCA program can help to understand equilibria is discussed. In relation to a recent synthesis of 11-keto steroids a series of experimental observations were made which are illustrated in scheme 1[2,3]. (1) Enone 1 leads predominantly to either one of two Diels-Alder adducts depending on the reaction conditions : in methylene chloride at room tempera-

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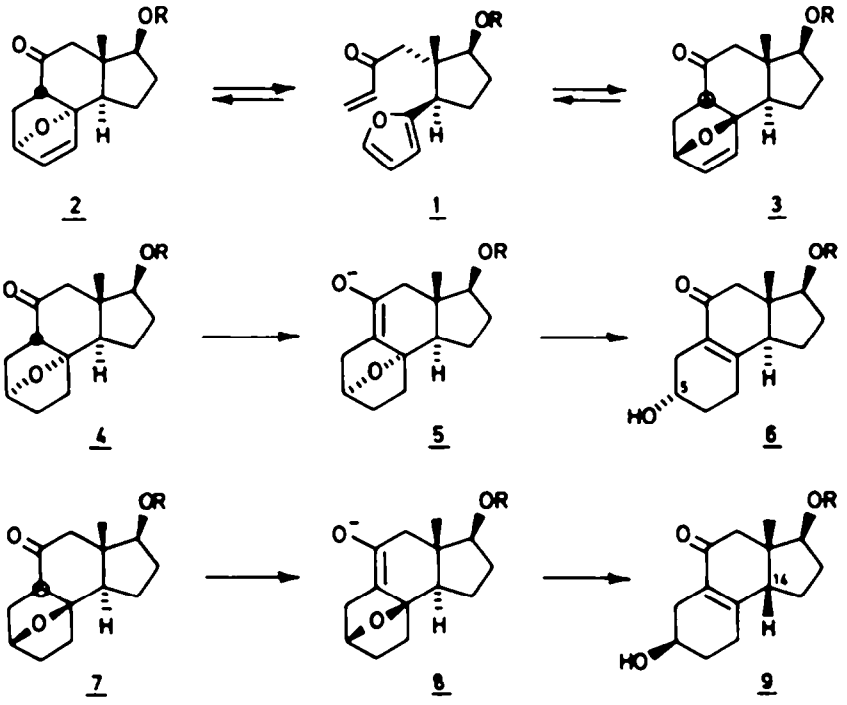
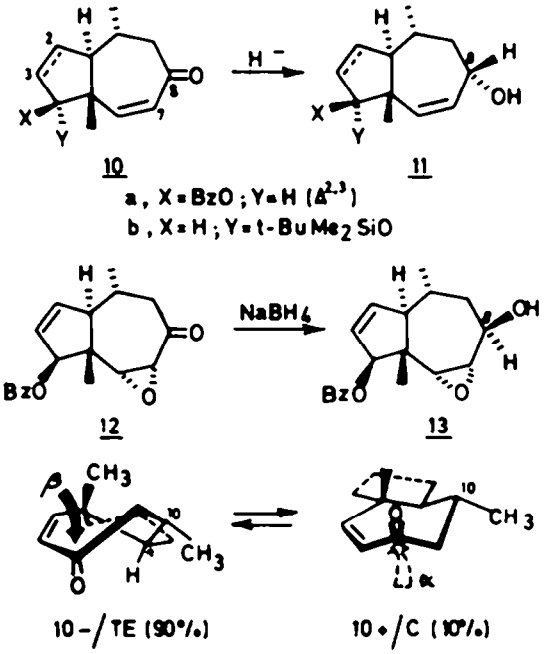
Scheme 1



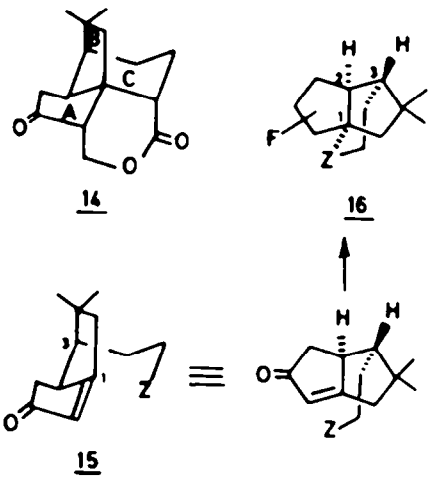
ture a 8:1 ratio of 2 and 3 is obtained (6 days; 61 % conversion), while in benzene at 80°C the same adducts are formed in a ratio of 1:9 (6 days; 50 % conversion), respectively. In the latter case a true equilibrium is involved since the same ratios are obtained when either pure 2 or 3 are subjected to the same conditions. (2) The oxygen bridge in the reduced adduct 4 is readily opened (sodium methoxide, room temperature, 2 h), leading to the expected enone 6. Isomer 7, however, is unaffected by the same basic conditions; reflux for 4 h is necessary to effect bridge opening. (3) Under these harsher conditions concomitant epimerization occurs at C-14 leading to enone 9 with a cis-fused CD-ring system[4]. A rationale for the above observations is readily provided by the program. (1) In line with the preferred formation of adduct 3 under thermodynamic conditions the program yields a ΔG° -13 kJ/mol for the equilibrium 2 ⇌ 3 (1 cal = 4.186 J). (2) Since the bridge openings in 4 and 7 must proceed via the corresponding enolate anions 5 and 8, it is essential to compare the relative energies of the latter in order to evaluate the activation energies of both endothermic processes. The program finds enolate 8 to have a conformational energy substantially larger (25 kJ/mol) than isomer 5. Accordingly, the process, which converts the more stable isomer 7 (compared to 4) to the less stable enolate anion 8 (compared to 5), is expected to have a high activation energy. (3) The obtention of C-14 isomerized product under the more drastic conditions (i.e., 7 → 9) is also not surprising in view of a calculated ΔG° -13 kJ/mol for the equilibrium 5-epi-6 ⇌ 9. The computed energy value is also quantitatively in accord with previous data for this type of isomerization[5].

The tentative prediction of the stereochemical outcome of steric approach controlled reactions is a common problem in synthetic chemistry. More often than not the organic chemist will approach this problem through an inspection of a molecular model. Unfortunately, however, the mere manipulation of a model will usually not reveal what he is looking for, namely the lowest-energy conformation of the product. This is especially true when dealing with flexible or conformationally unfamiliar cyclic systems. The following case exemplifies the potential use of the program in this type of problem. In connection with the total synthesis of helenanolides Grieco reported the exclusive formation of the α-riented alcohol 11a upon lithium aluminumhydride reduction of enone 10a[6]. A similar observation was independently made in this laboratory : diisobutylaluminumhydride reduction of 10b gives 11b with complete stereoselectivity (scheme 2)[7]. Surprisingly, the

Scheme 2



Scheme 3



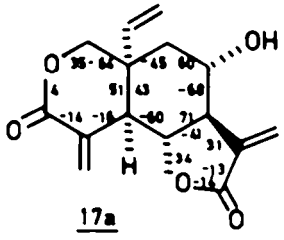
reduction of the corresponding epoxide 12 with sodium borohydride yields exclusively alcohol 13 with epimeric configuration at C-8[6]. The preferred geometry of 10 and 12 as derived by the program corresponds to a conformational mixture with the seven-membered ring in a twist-envelope (10-/TE; 90 % populated) and chair (10+/C; 10 % populated) conformation. Molecular model examination of both conformations clearly shows β-attack to be preferred on the TE form (steric hindrance by α-oriented H-1 and CH_3-10) and α-attack on the C form. From the individual endocyclic torsion angles of both conformations, which are shown in the program output, one may also deduce that some degree of conjugation in the α,β-unsaturated system of enones 10 is possible in the TE conformation, but not in the chair form : $\tau_{7,8}$ = 28° for 10-/TE and $\tau_{7,8}$ = -61° for 10+/C. Consequently, under steric control the reduction of enones 10 should yield the α-configuration of the alcohol at C-8. The opposite stereoselectivity found for the reduction of epoxide 12 could be due to a chelation effect involving the epoxide oxygen atom. The above observation has been rationalized by Toromanoff using the concept of dynamic stereochemistry[8]. Here it is assumed that hydride addition to unsaturated ketones takes place in the axial direction on the reactive conformation of the enone. This in turn implies that for enones 10 chair conformations are involved, and for epoxide 12 a twist-envelope form, in contrast with the steric approach rationale. Whatever the true explanation might be it should be emphasized that the program is ideally suited for generating the initial (reactive) conformations of a substrate which are needed for applying the dynamic analysis of conformational intermediates.

Although the program only provides information about the geometry and energy of ground state conformations it may help to evaluate the strain in cyclic systems which need to adopt a particular geometry for further reaction. Since its recent discovery quadrone (14) has been a favorite target for synthetic chemists[9]. An attractive but eventually unsuccessful approach has involved bond formation between C-1 and Z via intramolecular reaction (scheme 3). Depending on the proposed route Z represents a diene (Diels-Alder reaction)[9], an olefin (ene reaction)[10], an allene (photocycloaddition)[10] or a nucleophile (Michael reaction)[10]. In every case a bicyclo[3.2.1]octane system (BC, 16) must be formed at the convex side of the diquinane system. Therefore the side-chain at C-3 must adopt an orientation as shown in 15, resulting in a pseudo-bridged cyclic system with sp^2-hybridized C-1. It is now possible to evaluate qualitatively the torsion constraint in the five-membered ring B in this specific pre-transition-state geometry[11]. Therefore bond 1,2 is regarded as a fusion bond with the cyclopentenone ring A and bond 2,3 as a bridged

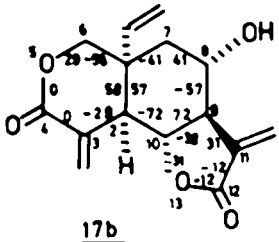
bond (part of six-membered C ring). Provided this input the program does not deduce any geometrically viable conformation for ring A. Note that the program may consider up to one hundred different five-membered ring conformations, including maximally puckered (and strained) forms. This result indicates a very strained geometrical situation that should be difficult to realize in practice. The synthetic chemist, therefore, should be prepared for failure, or at least serious trouble, when attempting the reaction.

GEOMETRIC AND ENERGETIC IMPLICATIONS

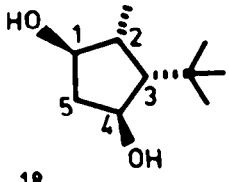
When a polycyclic molecule is analyzed, the program first deduces, for each ring separately, a set of geometrically possible conformations. For each form a conformational energy value is computed. With regard to the conformation of the full molecule, the program examines possible combinations among the deduced forms for each ring. Combinations which are less than 10 kJ/mol higher in energy than the preferred one are eventually shown; these represent the conformations which are likely to be populated. We will briefly discuss here the case of vernolepin (17). Diagram 17a shows the endocyclic torsion angles derived by X-ray diffraction[12]. Diagram 17b represents the preferred conformation as deduced by the program (41 % populated). Its geometry corresponds to an envelope conformation for the six-membered lactone ring A (1-/E), a distorted chair form for ring B (10+/Cdm) and a twist conformation for the five-membered ring C (12+/T).



17a



17b



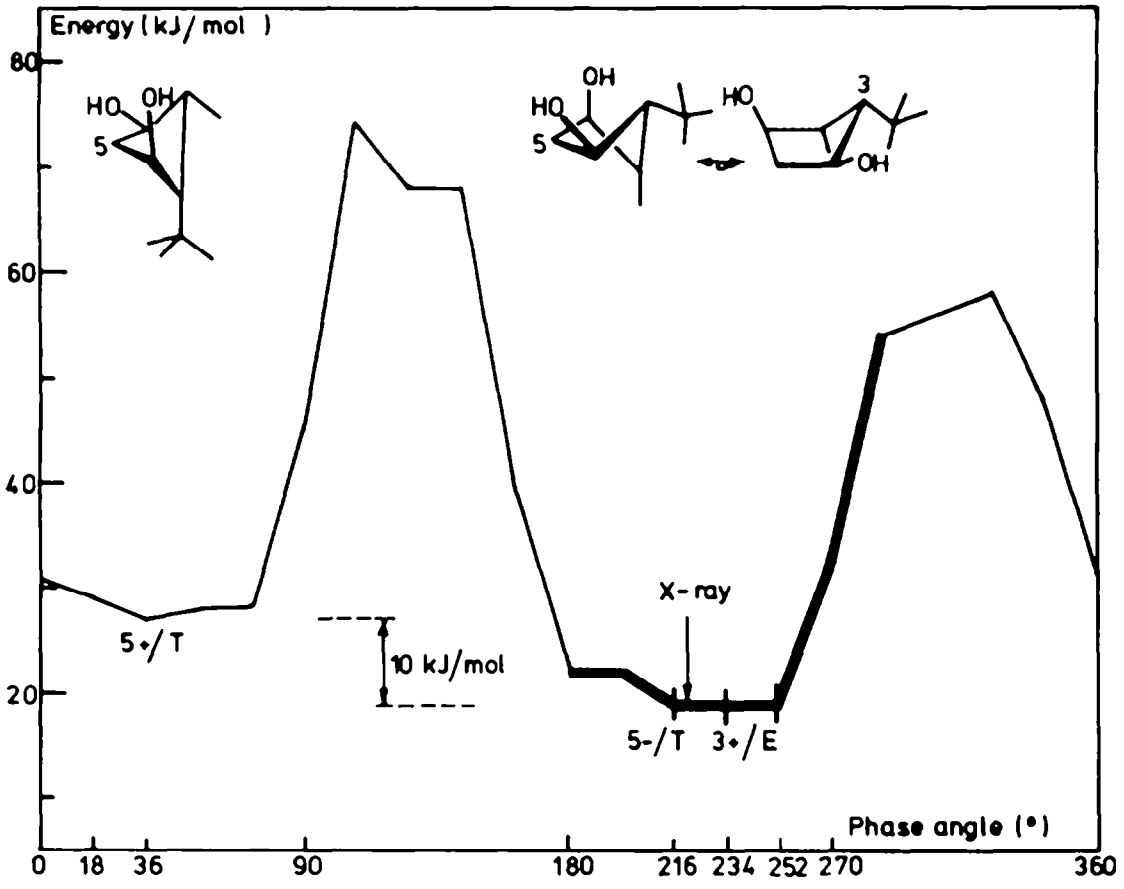
18

The calculated standard deviations for the three conformations with respect to the X-ray geometry are 10, 13 and 2, respectively. Other populated conformations represent seven combinations among half-chair (6+/HC, 1-/HC) and envelope (1-/E) forms for ring A, distorted chair conformations (10+/Cdm, 9-/Cdm) for ring B, and two twist conformations (12+/T) with a different puckering degree for ring C. Geometrically there is not much difference between the 6+/HC, 1-/E and 1-/HC forms, the 10+/Cdm and 9-/Cdm are also very similar. Although the program considers each combination to be an effective minimum energy conformation, the result should be rather interpreted as revealing a picture of the same minimum energy well (vide infra). It should be noted here that, although the program is designed for the analysis of carbocycles, some heterocyclic rings as lactones can also be examined. In the vernolepin case the bonds being part of the carboxyl group (4,5 and 12,13) and of the π-conjugated enone system (3,4 and 11,12) were imposed a torsion constraint[1] in order to account for electron delocalization ($\tau_{min} = -15°$, $\tau_{max} = +15°$).

Next to a symbolic qualitative description, the deduced conformations are further defined by the inclusion of an internal coordinate, i.e., the individual endocyclic torsion angles, and of a puckering coordinate for each cycle, i.e., the phase angle. The latter is a parameter which helps to understand the conformational behavior of a cycle. The case of cyclopentanediol 18 illustrates this aspect. Five-membered ring compounds do not necessarily occur in well-defined, single symmetric conformations but more often than not in a multitude of intermediate ones. Cyclopentane itself is characterized by full pseudorotation[13]. Following Altona the torsion angles of all conformers that are part of the same pseudorotation circuit (constant ϕ_m) are described by eq 1[14]. The different conformers - an infinite number for unsubstituted cyclopentane - are generated by varying ϕ, the phase angle of pseudorotation. The symmetrical C_2 (Twist) and C_s (Envelope) forms that are considered by the program, are generated for discrete values of ϕ, i.e., 0°, 36°, ... and 18°, 54°, ... respectively. So, for a given value of ϕ_m twenty symmetrical forms are obtained.

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

Figure 1. Energy profile for 18

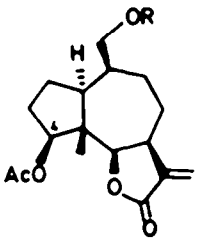


For substituted cyclopentane derivatives there is a barrier to pseudorotation. For each deduced conformation the program gives the corresponding phase angle and conformational energy content. From these data the energy profile for the pseudorotational circuit is readily drawn. This is shown for 18 in figure 1 (ϕ_m = 48°). The crystal geometry of the compound corresponds to ϕ_m = 44° and ψ = 219°[15]. The deduced result by the program suggests here that a portion of the pseudorotational circuit is preferentially populated (cf. $\psi \sim$ 180-270°). The bold line in the figure indicates the portion that is maintained when the tert-butyl group is considered as an anchoring substituent[1].

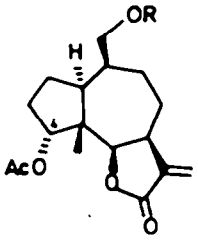
The shown individual torsion angles may also be directly correlated with ^{1}H NMR coupling constant values. An almost trivial example is related with hysterin (19a)[16], to which the C-4 epimeric structure 19b[17] was originally assigned (scheme 4). The great majority of cyclopentane geometries in the final set of conformations for both 19a and 19b show an endocyclic torsion angle value at bond 3,4 comprised between +15° and +39°. The corresponding dihedral angle values between the hydrogen atoms at C-3 and the hydrogen at C-4 are shown in the scheme. Natural hysterin exhibits a triplet pattern (J = 9.2 Hz) for H-4 located at 5.13 ppm, which is only compatible with a β-oriented acetoxygroup at C-4 (19a). With regard to the geometry of the seven-membered ring the preferred conformation (93 % populated) corresponds to the 6-/TC form (ψ = 231), whereas the X-ray geometry[18] is the 7+/TC form (ψ = 206). The latter conformation is predicted to be far less populated (6 %). The intermediate conformation in the seven-membered pseudorotation circuit, i.e., 10+/C (ψ = 219) is much higher in energy. The energy profile suggested by this result would thus show two distinct wells, with at each well a particular portion of the cyclopentane circuit being

preferentially populated.

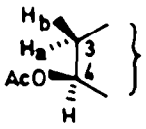
Scheme 4



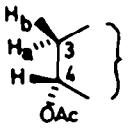
19a



19b



+(15°-39°) τ(H3a,H4) -(81°-105°)



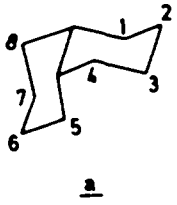
+(135°-159°) τ(H3b,H4) +(15°-39°)

For the calculation of free energy terms the program considers a relative enthalpy and entropy term. The former represents the excess steric energy relative to the lowest energy basic conformation in the series. Consequently, the shown steric energies have no absolute meaning; the therefrom calculated conformer population distributions, however, are meaningful since they refer to the minimum energy conformation of the deduced set. In interpreting the results one should keep in mind that for the calculation of conformational energies some interactions have not been taken into account. Nonbonded interactions between substituents which are not vicinally located are not considered more destabilizing than the mere additive effect of the substituent contributions taken individually. One may reasonably expect that this simplified treatment will not lead to erroneous results in flexible systems, since very often these can adopt conformations in which the substituents can take less sterically demanding positions. In non flexible systems, however, the computed conformational energy values can be seriously underestimated. We consider the conformational equilibrium between the methyl substituted a- and b-cis-decalins 20-23. In table 1 the results of this method are compared with those obtained by the molecular-mechanics method of Allinger[19] and by the semiquantitative method developed by Corey in connection with the LHASA program[20]. Agreement is poor for 22 and even worse for 20. This is not surprising since no destabilizing energy term is counted for the C-5/CH_3 interaction in 22a and for the C-5/CH_3 and C-7/CH_3 interactions in 20a. The above limitation is not considered a very important one.

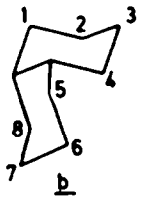
Table 1. Conformational energy differences[a] between the chair,chair-conformations a and b of the methyl-cis-decalins 20-23

cis-decalin		SCA	Allinger[b]	LHASA[c]
20	1α-Me	8	21	22
21	2β-Me	8	7	8
22	3α-Me	8	16	15
23	4β-Me	4	2	4

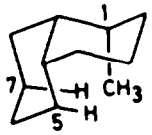
[a] In kJ/mol; [b] Ref. 19; [c] Ref. 20.



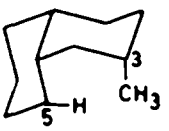
a



b



20a



22a

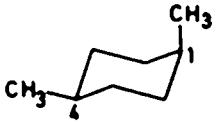
(1) The number of sterically demanding substituents (cf. axial orientation) at each face of the ring is included in the output for each deduced conformation (cf. Xb, Xa)[1], so as to draw the attention of the user whenever such nonbonded interaction should be taken extra into account (Xb or Xa > 1). (2) Interactions originating from substituents which are oriented within the concave side of a cyclic system are among those most easily recognized during a model inspection.

It is important to discuss here in some detail how the program deals with entropy. In the computation of the entropy the program considers the following terms. (1) The entropy-of-mixing-conformations term, $-R\Sigma N_i \ln N_i$ where N_i represents the mole fraction of each final deduced conformation that has a conformational energy less than 10 kJ/mol higher than the lowest energy form.

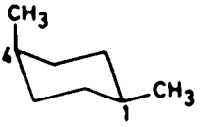
(2) An entropy-of-mixing-conformations term, Rln2, with regard to racemates (vide infra). (3) The entropy of symmetry, -Rlnσ, where σ is the symmetrynumber. (4) A correction term, -Rkln2, where k represents the number of negative entropy contributions (vide infra). The program has not the capability to recognize symmetry. In first instance it also treats a cyclic system as being one enantiomer of a chiral compound. This is inherently coupled to the α,β-stereodesignation which is used for the configurational assignments[11]. More often than not, in practical examples, the analyzed product is a racemate. Accordingly, the program always considers, next to the classical entropy-of-mixing term (1), an extra term Rln2 (2). Obviously, this is not warranted for optically active products or when the mirror-image forms are already comprised in the deduced set (cf. meso-type). In some special cases the program also deduces two conformations which are in fact identical and should therefore not be mixed. In practice the program first calculates the entropy according to terms (1) and (2) only (σ = 1, k = 0). Subsequently, the result can be corrected by introduction of the appropriate symmetrynumber σ and of the required number k of -Rln2 contributions whenever the entropy-of-mixing is overestimated. The case of dimethylcyclohexanes illustrates the point (table 2). For each of the isomers is shown the entropy-of-mixing that is first arrived at, and the corrections that need to be introduced; the latter are related to a symmetrynumber >1 and to redundant mixing of conformations (meso and identical forms). E.g., for cis-1,4-dimethylcyclohexane chair forms a and b are the deduced preferred conformations. The program does not recognize their identity nor the presence of a symmetry plane; consequently, two corrections need to be introduced (k = 2).

Table 2. Experimental and calculated entropies (J/K.mol) and enthalpy differences (kJ/mol) for cis(c)- and trans(t)-dimethylcyclohexanes

	Entropy-of mixing[a]	Entropy Corrections σ[b]	k[c]	Total SCA	d	ΔS Exp.[e]	ΔH Exp.[f]	SCA
c-1,2	11.5	1	(1,0)	5.8	5.8	3.0	7.8	8
t-1,2	5.8	2	(0,0)	0.0	0.5			
c-1,3	5.8	1	(1,0)	0.0	0.0	-5.2	-8.2	-8
t-1,3	11.5	1	(0,1)	5.8	5.8			
c-1,4	11.5	1	(1,1)	0.0	0.0	5.0	7.9	8
t-1,4	5.8	2	(1,0)	-5.8	-5.6			



a



b

[a] According to $-RLN_i \ln N_i$ + Rln2; [b] Symmetrynumber, to be used in -Rlnσ; [c] According to -Rkln2 : the first value refers to meso-type correction, the second value to the case of identical forms; [d] See ref. 21 (p. 56); [e] Ref. 22; [f] Ref. 21 (p. 53).

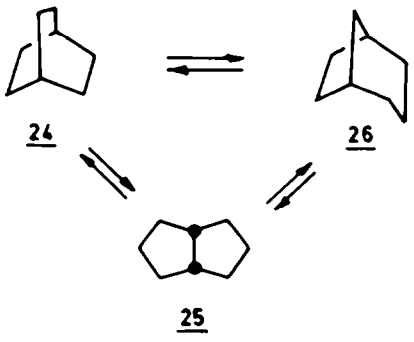
The total resulting entropy obviously rejoins the value obtained by classical conformational treatment[23], since the present method is only different with respect to the order in which the different entropic contributions are considered. In practice only entropy differences are relevant. And comparison between different species will only be meaningful when the other factors which contribute to the total entropy (vibration, translation, rotation) are equal. The calculated difference between cis- and trans-1,2-dimethylcyclohexane is for instance considerably larger than the experimental value because interference with methyl rotation is not accounted for. A fine agreement between calculated and experimental enthalpy differences is observed.

In the above example we have dealt with the entropy of simple six-membered ring systems where only one or two rigid chair conformations were populated. For flexible systems the situation is generally much more complex. In general the program deduces here a large set of probable conformations, which are considered potential energy minimum forms and yield upon mixing an important entropy term. There is some experimental evidence for the soundness of such a treatment. Fuchs has recently reported the thermodynamic parameters for the base catalyzed cis-trans equilibria of a series of dialkyl cyclopentane-1,3-dicarboxylates, and concluded that the found positive entropy differences for the equilibria cis $\rightleftharpoons$ trans (2-4 J/mol.K) apparently originate in a more variegated conformational population of the trans-isomers due to

less restricted pseudorotation[24]. The difference in entropy-of-mixing terms between cis- and trans-1,3-dimethylcyclopentane computed by the program is 2 J/mol.K in accord with the above interpretation. It should be noted that in this calculation no entropy of symmetry is considered for the C_2 symmetrical conformations in the trans-series (15 % populated; $\sigma = 2$); in the cis- series no correction is introduced : the deduced forms are of the meso-type but intermediate forms in the circuit are not (the meso-correction would involve -Rln2).

Table 3. Relative entropy calculations for the equilibrium between bicyclooctanes 24, 25 and 26[a]

	Entropy calculation correct.[c]				Entropy difference		
	Mix.[b]	σ	k	Total		SCA	Exp.[d]
24	6	6	1	-15	24 ⇄ 25	47 ± 3	46 ± 7
25	35	1-2	0-1	$^{35}_{29}$[e,f]	25 ⇄ 26	-21 ± 6	-21 ± 3
26	14	1	0-1	$^{14}_{8}$[e,f]	24 ⇄ 26	26 ± 3	23 ± 10



[a] In J/K.mol; [b] According to $-R\Sigma N_i \ln N_i$ + Rln2 with σ = 1, k = 0; [c] See text; [d] Ref. 25; [e] Maximum value; [f] Minimum value.

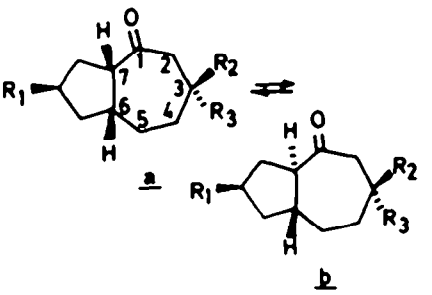
An impressive illustration of the entropy treatment is related to the Lewis acid catalyzed equilibrium between the bicyclooctanes 24, 25 and 26[25]. The experimentally found entropy differences (25°C) for the equilibria 24 ⇄ 25, 25 ⇄ 26 and 24 ⇄ 26 are shown in table 3, together with the calculated entropies for the three products. Only one conformation is deduced for 24 with both six-membered rings in a regular C_{2v} boat conformation (σ = 6, meso-form). Ninety four combinations are found populated for cis-fused 25 leading to a maximum entropy-of-mixing term of 34.9 J/mol.K. Several among these conformations, however, have a σ 2, and although the meso-type forms are not expected to contribute much in a decrease of entropy (vide supra), a minimum entropy-of-mixing term (34.9 - Rln2) is also considered. The three conformations found for 26 arise from small variations in the five-membered ring geometry. Since the preferred conformation (53 % populated) possesses a symmetry plane a maximum correction of -Rln2 is considered leading to an entropy value comprised between 14.2 and 8.4 J/mol.K. The therefrom calculated differences for the three corresponding equilibria compare remarkably well with the experimental values.

After discussing the relative enthalpies and entropies we will consider now the calculation of the free energy terms which are necessary for the prediction of equilibria compositions. The enthalpy term computed by the program being a relative steric energy value, one is only allowed to compare differences in free energy between cyclic compounds which possess identical reference basic conformations. This is the case for configurational isomers. We will consider now the equilibria between the cis- and trans-fused perhydroazulenes 27-30. The base catalyzed equilibrium compositions at 25°C (methanol-benzene solution) were determined by House and are shown in table 4[26,27]. House also defined the low-energy conformers for each of the isomeric perhydroazulenes via force field calculations using Allinger's MM2 program[28]. The computational procedure involved the assembly of Dreiding molecular models for all conformations suggested by our previously reported manual method for systematic conformational analysis[29]. Atom coordinates obtained from these models were entered as initial coordinates for energy minimization. In every case one or more conformations had calculated steric energies 10 kJ/mol lower than calculated energies for other reasonable conformations. The free energy differences that one may calculate from the reported steric energy values and from the corresponding entropy-of-mixing terms, however, indicate equilibria that would be in favor of the cis-fused derivatives, 2-3 kJ/mol, except in the case of 28a ⇄ 28b. This stands in contrast with the experiment which shows the trans-fused compounds to be thermodynamically favored in every case. For the same equilibria this program yielded the thermodynamic parameters shown in table 4. In every case is the trans-fused perhydroazulene predicted to be more stable (ΔG° negative). A quantitative

Table 4. Thermodynamic parameters (25°C) related to the equilibria between cis- and trans-fused perhydroazulenic ketones 27-30 (a ⇌ b)[a].

Equilibrium	SCA calculated ΔH°	ΔS°	ΔG°	Exp. ΔG°
27a ⇌ 27b	-5.1	5.9	-6.9	-4.7[c]
28a ⇌ 28b	-2.8	11.0	-6.0	-5.1[b]
29a ⇌ 29b	-5.6	2.5	-6.3	-9.0[c]
30a ⇌ 30b	-5.0	5.7	-6.7	-2.1[c]

[a] Enthalpies and free energies in kJ/mol, entropies in J/mol.K; [b] Ref. 26; [c] Ref. 27.



a b

27 R_1 = H ; R_2 = H ; R_3 = H

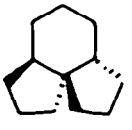
28 R_1 = t-Bu ; R_2 = H ; R_3 = H

29 R_1 = H ; R_2 = H ; R_3 = t-Bu

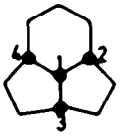
30 R_1 = H ; R_2 = t-Bu ; R_3 = H

comparison between the calculated and experimental values show that one should allow for deviations in energy of at least ± 5 kJ/mol. Finally, the fair agreement that is noted here between calculated and experimental values is also an indication that the conformational energy values used by the program for cycloheptanone are very reliable[30]. Crystal structures of appropriate crystalline derivatives of 27a, 27b, 28a, 28b and 29a have also been obtained[26,27]. In every case, except for 28a, does the deduced preferred conformation for the seven-membered ring - or a directly adjacent conformation in the pseudorotation circuit - correspond to the X-ray geometry. The observed 4+/TB conformation for the cycloheptanone in 28a was found by the program to be populated to a minor extent (2 %).

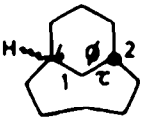
An important limitation of the program is related to the analysis of cyclic skeletons which can be represented by a closed graph. To obtain the graph individual cycles are represented by points, and points corresponding to cycles that have bonds in common are connected by lines. The threecyclic system 32 corresponds to a closed graph situation; 31, however, does not. Parenthetically, upon analysis of 31 the program will find the six-membered ring too constrained for further evaluation indicating a cyclic system that cannot be assembled by a molecular model.



31



32



33a β-H at 4

33b α-H at 4

The analysis of a cyclic system like 32 is thwarted because it is difficult to introduce unambiguously the correct torsion constraints in each individual cycle. If one only considers the three cis-fusions in 32 the program deduces a preferred set of mainly irrelevant conformations which cannot be assembled by a molecular model. This is not surprising in view of the constraints that were considered for the six-membered ring at bonds 1,2 and 1,4 (two separate cis-fusions with five-membered rings), whereas the real situation implies a fusion with a bicyclo[3.3.0]octane at two adjacent bonds. It is tempting to solve this problem by considering a second constraint at the six-membered ring bonds 1,2 and 1,4, i.e., a bridging with an eight-membered ring. However, when dealing with bridgings with large rings (> seven-membered) one also needs to consider the following pitfall. We consider the bicyclic system 33 where ϕ is the endocyclic torsion angle in the six-membered ring at bond 1,2 and τ the corresponding angle in the bridging cycle. The maximum attainable torsion angle in a six-membered ring is 80°; we will assume here for the bridging cycle a ϕ_{max} value of 160° (ϕ_{max} for an eight-membered cycle is 150°)[11]. Since here $\tau = \phi - 120°$, ϕ may adopt the following values : -80°, from -40° to 0°, and from 0° to +80°.

In this treatment, however, the configuration at C-4 is not taken into account. Inspection of a model shows that the 1,2-bond in the six-membered ring of 33a can adopt the values -40° to +80°, while only the values -80° and +80° are possible at the same bond in 33b. Consequently, such cases should be treated with extreme care. If one wishes to analyze such systems with the present program the following procedure should be used : (1) as first constraint is introduced the fusion; (2) the second constraint should consist of the minimum and maximum torsion angle values as deduced from a prior model inspection.

Notwithstanding some limitations the SCA program should be of considerable use with respect to suggesting rapid answers to a variety of problems in a ready and reliable way. Specifically, it should help in the prediction of the stereochemical outcome of steric approach controlled reactions, in the prediction of the composition of isomerization equilibria and in the qualitative evaluation of strain in some pre-transition state geometries. The results pertaining to the geometry and energy of conformations are shown in a way appropriate to the direct needs of the user. The inclusion of conformational parameters allows for the drawing of energy profiles, which leads to a better understanding of the conformational behavior of a cyclic system. The way the program deals with entropy may have important implications especially for flexible ring systems.

Obviously, this program does not intend to replace molecular models or energy minimization techniques. Rather it should be considered as a complementary tool to both methods. Finally, even within the present limits of the system, there is certainly room for improvement especially with regard to certain conformational energy terms and interactions that have hitherto not been accounted for.

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