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MODEL STUDY FOR STEROIDAL D/C RING CLOSURE IN OLEFINIC CYCLIZATION REACTIONS; A MINDO/3 STUDY

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Abstract—MINDO/3 molecular orbital calculations are performed for the ring closure of (Z)- and (E)-alkenes as a model for the D/C ring closure to steroids. It is shown that a lower activation energy is needed for cyclizations in the chair configuration, than for cyclizations in the boat configuration. An analogous picture is found by comparison of (E)- and (Z)-alkenes. Cyclization of the (E)-alkene in the chair or boat configuration is energetically favoured over the ring closure of (Z)-alkenes. These results are in agreement with the Stork-Eschenmoser hypothesis.

In the last two decades much progress has been made in the field of steroid synthesis. The elucidation of the mechanism of the biosynthesis of lanosterol from 2,3-epoxysqualene strongly accelerated the development of model compounds.[1] In rapid succession, theories were formulated concerning the olefinic cyclization process. Independently, Stork[2] and Eschenmoser[3] developed a stereo-electronic theory explaining and predicting the course and stereoselectivity of polyene cyclizations. They postulated that the concerted formation of a cyclohexane ring in cationic cyclization reactions of open chain polyenes must proceed *via* an *anti*-parallel mechanism. Extension of this postulate would always result in a polycyclic product having the *trans, anti, trans, anti, trans* geometry. This postulate, however, can only account for the *in vitro* cyclization reactions. Under *in vivo* conditions many exceptions are observed, of which protolanosterol is the best known. This feature is believed to be caused by specific substrate-enzyme interactions. Recently, van Tamelen *et al*[4] claimed the formation of some tetracyclic compounds *via* a tricyclization, featuring 9, 10 *cis* stereochemistry to simulate the biosynthetic conversion of 2,3-epoxysqualene to the presterol. This implies a boat conformation of the six-membered ring during the nonbiological cyclization process. On the other hand, we observed a striking difference between (E)- and (Z)-alkene precursors[5] in cyclization experiments: the (E)-alkenes cyclized to tetracyclic structures in contrast to the (Z)-alkenes which, even under the most widely divergent reaction conditions, failed to cyclize.

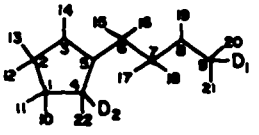
This difference is most probably due to kinetic and conformational aspects of the olefinic ring closure. These observations and the work of van Tamelen[4] stimulated us to obtain quantitative information on cyclization reactions of (Z)- and (E)-alkenes *via* a boat or chair transition state. To this end Molecular Orbital calculations were carried out on the cyclization of the monocyclic cations 1a–c to the bicyclic cations 2a–c. This ring closure reaction was chosen as a model, for it is found in the synthesis of several presteroids.[1a,5,6,7]

COMPUTATIONAL ASPECTS

To obtain more insight into the course of the cyclization, we have studied the potential energy surface of the reactions. To this end we optimized the geometry of the compounds under study. The semi-empirical MINDO/3 program as developed by Dewar and co-workers,[8] is used which is the best choice to perform semi-empirical calculations on carbocation systems and which includes an efficient geometry optimization procedure.[9,10] Since the $C_9H_{13}^+$ system contains sixty degrees of freedom, it becomes necessary to make simplifying assumptions concerning the geometry parameters of the system. The reaction coordinate method is used to locate the transition state on the energy surface.

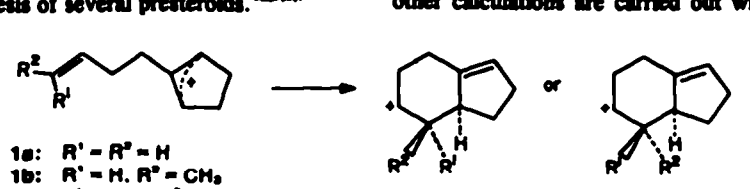
RESULTS

The course of the reaction may be characterized by several parameters. It is found out that the distance C(4)–C(9) was the most representative parameter (*vide infra*).



First we studied the course of the reaction for the parent system 1a→2a. To calculate the geometry of 1a and 2a the following assumptions have been made. The five-membered rings were optimized separately imposing C_{2v} symmetry and using four parameters. The atoms C(6)–C(9) in 1a are situated in a plane perpendicular to the ring. The cyclohexane skeleton in 2a is optimized separately in the 4-methylene cyclohexyl cation, with the six-membered ring in C_{2h} symmetry for the chair configuration and in C_{2v} symmetry for the boat configuration.

In order to keep the number of parameters to be optimized as low as possible during the reaction path, all other calculations are carried out with an intermediate



1a: R' = R² = H
1b: R' = H, R² = CH_3
1c: R' = CH_3, R² = H

2a–c, chair 2a–c, boat

geometry of the five-membered ring, acquired from the average parameters of the cyclopentene ring in 1a and 2a. This will be a good approach for the geometry of the transition state. In Table 1 this geometry is given. For most other parameters, standard values have been used (e.g. $C(sp^3)$–$C(sp^3)$ = 1.54 Å; $C(sp^3)$–$C(sp^2)$ = 1.50 Å; $C(sp^2)$–$C(sp^2)$ = 1.34 Å; C–H = 1.08 Å; angle $C(sp^3)$ = 109.5°; angle $C(sp^2)$ = 120°).

The distance C(4)–C(9) has been chosen as the reaction coordinate. For all intermediate structures the following ten parameters have been optimized: the distance C(7)–C(8); the angles (6,7,8), (5,6,7), (5,4,9), (22,4,D_2) and (8,9,D_1); the rotations around the axis C(5)–C(6), C(6)–C(7), rotation of D_1 around the C(8)–C(9) bond and rotation of C(9) around the C(4)–C(5) bond. (D_1 and D_2 are dummy atoms on the bisectrice of the angles (20,9,21) and (1,4,5), respectively). In Fig. 1 the heat of formation (ΔH_f°) is plotted *versus* the C(4)–C(9) distance for the ring opening of 2a *via* the chair (▲) and boat (×) conformation. For the boat ring opening (×) the parameters given above were optimized, which resulted in an activation energy of 22 kcal/mol; in the case of the chair ring opening the same parameters were optimized except the angle (5,6,7) and the rotation around the C(5)–C(6) axis. When this rotation was also taken into account, the activation energy dropped from 21 to 19 kcal/mol.

During the cyclization some main characteristics underwent a considerable change. The flow of positive charge is shown in Fig. 2. The charge density on the allylic positions C(3) and C(4) drops, while at the same time the charge on C(8) builds up when the ring closure reaction proceeds. A carbonium ion at C(8) is generated, implying a change in the C(8)–C(9) distance, which changes from a $C(sp^2)$–$C(sp^2)$ bond (1.33 Å) to a $C(sp^2)$–$C(sp^3)$ bond (1.48 Å). Another characteristic phenomenon is the position of H(22), which rotates out of the plane of the five-membered ring. The description of the reaction path as a combination of the two most important dihedral parameters (the rotations around the C(6)–C(7) and around the C(7)–C(8) bond) showed to be very tortuous. Stereochemical aspects arise when a hydrogen in 1a is replaced by a methyl group, giving 1b and 1c, respectively. The energy of both reactants is obtained by performing one SCF calculation. It is assumed that the transition state for the cyclization of 1b,c is reached at 2.25 Å for the boat and at 2.30 Å for the chair ring closure reaction, as was found for 1a. The transition states (TS) of the reactions 1b,c→2b,c were calculated by optimizing the afore mentioned ten parameters. In Table 2 the energies and main charge densities of the various species are gathered.

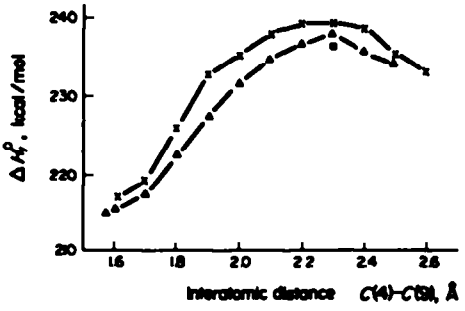


Fig. 1. The energy profiles for chair (▲) and boat (×) ring opening of 2a.

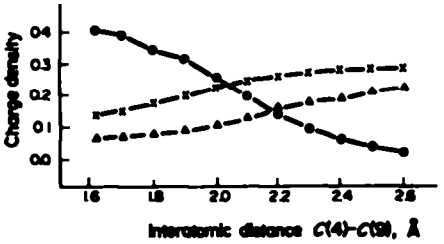


Fig. 2. Change of the positive charge on C(3) (▲), C(4) (×) and C(8) (●) during the boat ring opening of 2a.

Table 2. Heats of formation and charge densities

compound	ΔH_f° (kcal/mol)	charge density on C(3)	C(4)	C(8)
1a	217.5	0.235	0.283	-0.032
2a, chair	215.1	0.066	0.122	0.423
2a, boat	217.3	0.065	0.137	0.409
1a→2a, TS, chair	236.7	0.185	0.273	0.079
1a→2a, TS, boat	239.3	0.165	0.265	0.115
1b	208.2	0.234	0.282	-0.063
1c	211.7	0.235	0.282	-0.059
2b, chair	216.4	0.062	0.114	0.419
2c, chair	217.7	0.064	0.112	0.414
2b, boat	221.9	0.057	0.119	0.413
2c, boat	217.4	0.053	0.094	0.435
1b→2b, TS, chair	228.3	0.183	0.284	0.032
1c→2c, TS, chair	234.7	0.149	0.242	0.084
1b→2b, TS, boat	233.4	0.156	0.259	0.083
1c→2c, TS, boat	238.6	0.129	0.252	0.094

Note that the cyclization of an (E)-compound *via* a chair conformation leads to the *anti* configuration and *via* the boat conformation to the *syn* configuration. A similar argumentation for (Z)-alkenes leads to *syn* products from a chair cyclization and an *anti* product from the boat conformation. In Table 3 the activation energies are given for the several ring closure reactions.

DISCUSSION

The activation energies for the different cyclization processes put the Stork-Eschenmoser hypothesis in quite

Table 1. Geometry parameters of the five-membered ring

	System 1	System 2	Intermediate geometry
Distance C(2)–C(3) in Å	1.493	1.507	1.501
Distance C(3)–C(5) in Å	1.419	1.351	1.388
Angle (5,4,1)	116.86°	105.01°	109.94°
Angle (4,5,3)	103.71°	111.82°	107.50°

Table 3. Activitation energies for the chair and boat cyclization of the $C_9H_{13}^+$ and $C_{10}H_{15}^+$ cations

reaction	chair conformation	boat conformation
1a-2a	19	22
1b-2b	20	25
1c-2c	23	27

a new perspective. The hypothesis states that concerted cyclizations of (E)-alkenes yield *trans*-substituted products, while (Z)-alkenes afford *cis*-substituted compounds. This implies, as is confirmed by the calculations and shown in Table III, that *in vitro* synthesis will take place preferentially *via* the chair conformation (the thermodynamically favoured route) of the generated cyclohexenyl cation.

In the second postulate of their hypothesis, Stork and Eschenmoser pointed at the role of the enzyme during *vivo* cyclizations. It is known that before cyclization of 2,3-epoxysqualene takes place, the molecule is folded by the enzyme in a chair-boat-chair conformation which promotes the formation of protolanosterol. Thus, the B-ring formation then proceeds in an energetically unfavoured way (if the enzyme-substrate interaction is not taken into account), for now an (E)-alkene (*e.g.* 2,3-epoxysqualene) is cyclized in a boat conformation. These calculations substantiate once more the important role of the enzyme-substrate interaction. It should be borne in mind, however, that all calculations were performed with total neglect of solvation energy.

This approach is reasonable, realizing that hardly any activation energy should be involved when cation 1 is formed from the cyclopent-2-enol derivative upon treatment with a proton acid or a Lewis acid. The initial step of the cyclization process is the attack of the cation on the double bond. Thus, these calculated results are of at least qualitative accuracy in understanding the ring closure mechanism.

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