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STEREOSPECIFICITY IN THERMAL ISOMERIZATION OF PREISOCALAMENDIOL, A TEN-MEMBERED RING SESQUITERPENE AN APPLICATION OF MOLECULAR MECHANICS CALCULATIONS

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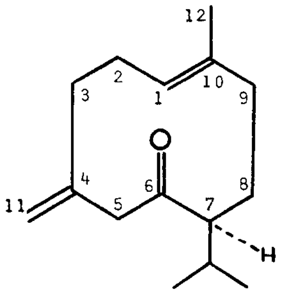
Summary Molecular mechanics calculations were carried out to explain stereospecificity in the cyclization reaction of preisocalamendiol (1), a ten-membered ring sesquiterpene, suggesting that this stereospecificity does not depend on relative stabilities of the conformational isomer of 1, but is due to those of the corresponding conformers in each transition state. Particularly, molecular mechanics calculations, which were made on the basis of such a transition state model as 3, can explain the experimental results much well.

In the course of our studies on biomimetic reactions of germacrene-type sesquiterpenes,[1] preisocalamendiol (1) was found to be converted into dehydroisocalamendiol (2) in 86% yield on thermal isomerization (180°, 90 min) which took place in highly regio- and stereospecific manner.[1c] It is interesting to know whether the stereochemistry of the reaction product (2) depends on the predominant conformation of the starting material (1), as demonstrated in the case of humulene.[2]

As shown in Figure 1,[3] preisocalamendiol (1) may adopt eight conformations, of which the conformer CC is directly related to the product (2). Thus, molecular mechanics calculations[4] were carried out to estimate relative stabilities of these conformers, as follows.

Approximate coordinates in the eight conformers of 1 were calculated by means of the program COORD[5] with bond lengths, bond angles and torsional angles obtainable from Dreiding molecular models. Then, iterative calculations were made to minimize the steric energy of each



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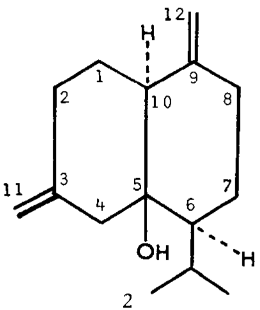

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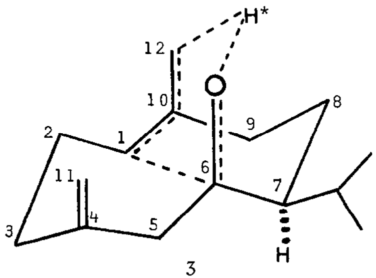


3

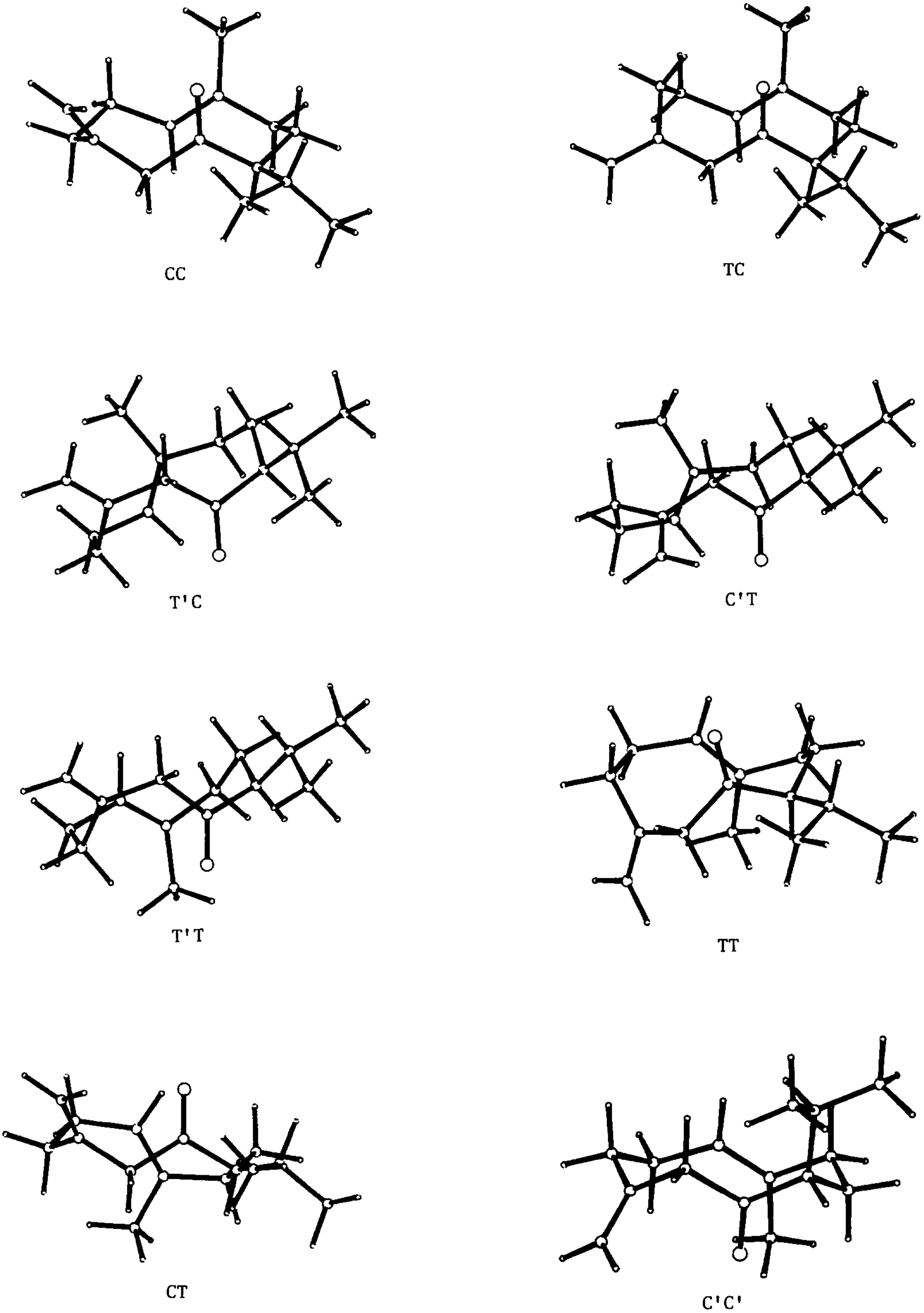
conformer at 25° and 180°, respectively. As summerized in Table 1, relative ratio of the most stable conformer CC is 62% at 25° and decreased to 46% at 180°, suggesting that the high stereospecificity in the thermal isomerization of **1** can not be explained by relative stability of each conformer of **1**.[6]

We further examined another possibility, in which the stereochemistry of the reaction product was attributable to the relative stability of each conformer in the corresponding transition state, by applicating molecular mechanics calculations to such a plausible model (**3**) as cited in the previous paper.[1c] In this case, several assumptions are required to employ the MMI program in order to calculate the steric energy of such a model as **3**, as follows. i) Steric energy of such a model as **3** corresponds or is at least proportional to the height of the energy barrier of the cyclization reaction. ii) The distance between C_1 and C_6 varies as the reaction proceeds. Therefore, the partially formed bond length ($C_1 \cdots C_6$) in **3** may be regarded as a mean value between the distance from C_1 to C_6 in **1** and the bond length $C_5—C_{10}$ in **2**. Each position of the remaining atoms except for C_1 and C_6 was changed in the course of energy minimization. iii) Of the eight conformers, the four ones [CC, TC, T'T, and C'C'] can adopt such a transition state as **3**, in which the CO group and the vinyl Me group both are located on the same side of a plane of the ten-membered ring. iv) The distance between O and C_{12} is about 3.2 Å in these four conformers of **1** and changes to 3.55 Å in **2**. Therefore, the distance [O—C_{12}] is assumed to be *ca.* 3.4 Å in **3**. In addition, the partial bond lengths of $O \cdots H$ and $C_{12} \cdots H$ both are approximately 1.7 Å, if the asterisk-proton (H*) is placed at the equidistant point from both O and C_{12}. Although this value is pretty large for O—H or C—H bond, the corresponding force constants are chosen so that this abnormal value does not cause large stretching energy. v) The program MMI has no force constants for such partial bonds as shown in **3**. However, they are regarded as mean values of those of the initial and final states, *e.g.* the force constants of $C \overset{\cdots}{-} O$ in **3** are assumed to be mean values of C=O and C—O.[7]

On the basis of these assumptions, molecular mechanics calculations were carried out to evaluate the energy values of the transition states derived from each conformer, and their relative populations at 180° were estimated as shown in Table 2. It is noteworthy that the transition state (**3**) derived from the conformer CC is predominant enough to explain the stereo-

Table 1 Relative populations of eight conformers of **1**

Conformer	Steric energy (kcal/mol)	Relative population 25° (%)	180° (%)
CC	19.14	62.0	45.9
TC	20.03	13.8	17.1
T'C	20.04	13.6	16.9
C'T	20.35	8.1	12.0
T'T	21.22	1.9	4.6
TT	22.11	0.4	1.7
CT	22.50	0.2	1.1
C'C'	22.90	0.1	0.7



CC

TC

T'C

C'T

T'T

TT

CT

C'C'

Figure 1 ORTEP^8 drawing of minimum energy structures of eight conformations of **1**.

Table 2 Relative populations of transition states derived from four conformers of 1

Conformer	Steric energy (kcal/mol)	Relative population at 180° (%)
CC	52 44	79 8
C'C'	53 73	18 9
TC	56 24	1 2
T'T	58 75	0 1

specificity in the thermal isomerization of 1

In conclusion, the above mentioned procedure which is in very good agreements with the experimental results has been proved to be quite useful in order to explain the stereospecificity in the thermal isomerization of 1, although another possibility is not necessarily ruled out, in which the stereospecificity is explained on the basis of relative stabilities of each conformer in their ground state

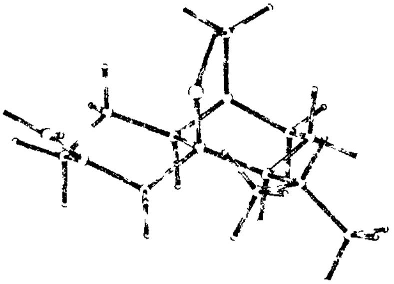


Figure 2 Calculated minimum energy structure corresponding to CC of 3

Molecular mechanics studies on conformational problems of sesquiterpenes are in progress

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2) a) H Shirahama, E Ōsawa, and T Matsumoto, Tetrahedron Letters, 1978, 1987, and references cited therein, b) N S Zefirov, Tetrahedron, 33, 2719 (1977)

3) Notation of the conformers J K Sutherland, Tetrahedron, 30, 1651 (1974)

4) Program MMI (QCPE 318), made by N L Allinger and converted by Dr E Ōsawa to fit FACOM 230-7 system, was used All calculations were performed at Nagoya University Computation Center

5) QCPE 226 (made by J Rhee) was used

6) The compound (2) must be derived from two conformers (CC and CT), whose combined population is 63% at 180° The calculated value (63%) is smaller than the experimental value (86%)

7) Similarly, the force constants for $C_1 - C_{10}$ and $C_{10} \overset{..}{-} C_{12}$ are assumed to be mean values of $C{=}C$ and $C{-}C$

8) ORTEP drawing was carried out using a program made by C K Johnson and revised by K Sasaki

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