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STEREOCHEMICAL STUDIES ON GERMACRENES: AN APPLICATION OF MOLECULAR MECHANICS CALCULATIONS

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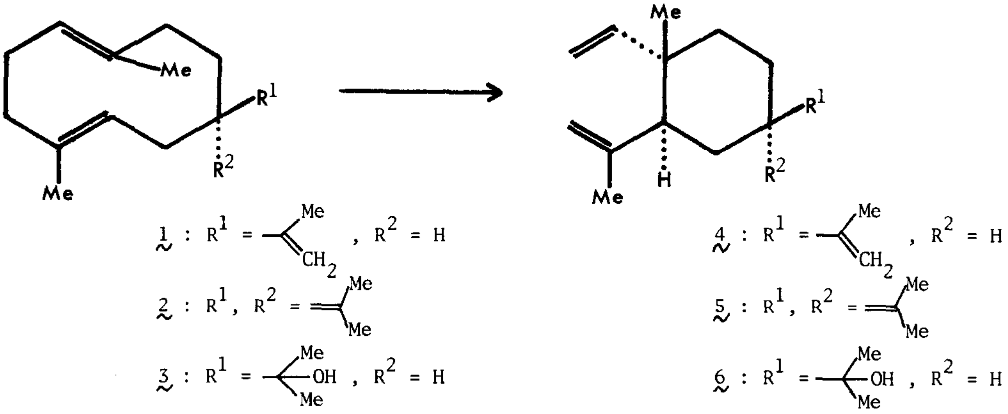
Summary: Molecular mechanics calculations were successfully carried out to evaluate relative stabilities of each conformation of germacrene-A (1), germacrene-B (2) and hedycaryol (3) in their ground states and transition states. Thus, the calculation results on each transition state model indicate that the elemenes are formed from the corresponding germacrenes through the most stable transition states (CC), regardless of the most stable conformers in each ground state.

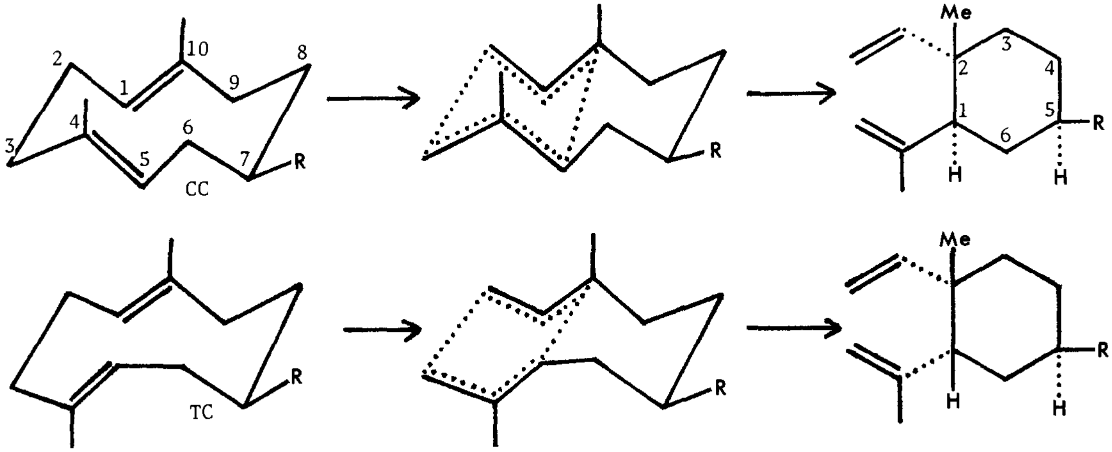
From a biogenetic point of view, many sesquiterpenes are considered to be derived from germacrenes or germacrones as an important precursor, and their conformations have been discussed in connection with their transannular reactions as well as with thermal isomerizations.[1] On the basis of molecular mechanics calculations, previously, we reported that the stereospecificity in the thermal isomerization of preisocalamendiol was due to relative stabilities of its conformational isomers in each transition state.[2] In the present paper, we wish to describe some quite interesting results concerning with conformational problems of ten-membered ring sesquiterpenes, as follows.

Germacrene-A (1) is an unstable compound and spontaneously converted to the corresponding elemene (4),[3] as shown in Scheme 1. Thus, molecular mechanics calculations on the four conformers of 1 were carried out using Program MMI[4] to deduce the main conformations with energy minima and their results were summarized in the Table. Further calculations were also made on the transition state models corresponding to the conformers in each ground state, as shown in Scheme 2. In these calculations, the distances between C_5 and C_{10} are taken as mean values between the dis-

Scheme 1. Thermal isomerizations of germacrenes.



Scheme 2. Two possible isomerizations of germacrenes.



tances from C_5 to C_{10} in the starting material and the bond length C_1-C_2 in the product. Furthermore, the force constants of C$\overset{\cdots}{-}$C are assumed to be mean values of C-C and C=C, as described in the previous paper.[2] The resulting structures of CC and TC in their transition states are shown in Figure 1 and their steric energies and relative populations are also summarized in the Table. From these data, it is evident that the most stable conformation of 1 in a ground state is directly related to the corresponding elemene (4) through the most stable transition state CC.

In the next step, molecular mechanics calculations were carried out on germacrene-B (2), which was also known to be thermally converted into the corresponding elemene (5),[6] indicating that the conformation CT is most stable, although an X-ray crystallographic analysis revealed that a 1 : 1 silver nitrate adduct of 2 adopts the conformation CC in a crystal state.[7] Of the two transition state models CC and CT (see Figure 2), it is noteworthy that the former is more stable than CT, as shown in the Table.[8]

In the case of hedycaryol (3), its molecular mechanics calculations revealed that the favorable conformation in a ground state does not correspond to the structure of the elemene (6).[9] Therefore, we also applied the molecular mechanics calculations to such transition state models as shown in Scheme 2. The resulting structures of CC and TC in their transition states are shown

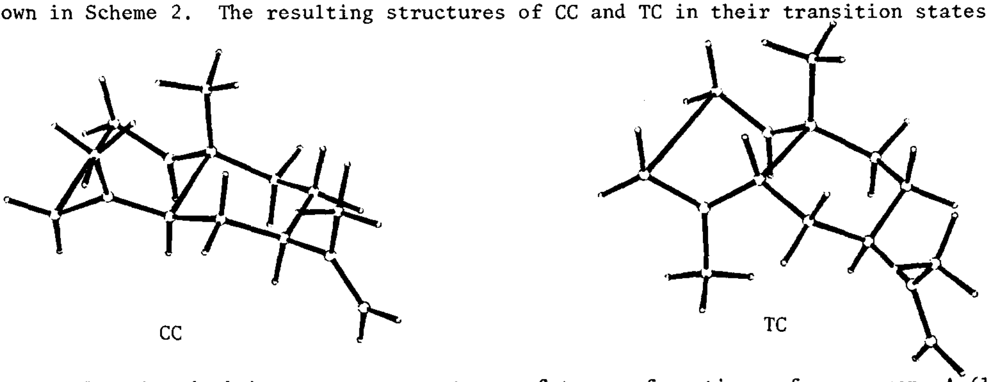

CC TC

Figure 1. Calculated minimum energy structures of two conformations of germacrene-A (1) in transition states.[5]

Table

	Ground state		Transition state	
Germacrene-A	Steric energy (kcal/mol)	Relative population at 25° (%)	Steric energy (kcal/mol)	Relative population at 25°* (%)
CC	22.91	62.3	33.47	100.0
TC	23.24	35.7	40.61	0.0
T'C	25.09	1.6	39.36	0.0
C'T	25.97	0.4	38.31	0.0
Germacrene-B	Steric energy (kcal/mol)	Relative population at 25° (%)	Steric energy (kcal/mol)	Relative population at 120°* (%)
CC	23.13	34.7	35.85	86.3
CT	22.91	50.5	37.29	13.6
TT'	23.94	8.8	41.57	0.1
TC'	24.17	6.0	41.66	0.1
Hedycaryol	Steric energy (kcal/mol)	Relative population at 25° (%)	Steric energy (kcal/mol)	Relative population at 400°* (%)
CC	25.57	28.8	37.56	95.8
CT	26.45	6.5	42.38	2.6
TC	25.11	62.0	44.44	0.6
T'C	26.98	2.6	43.64	1.0

* Experimentally, each thermal isomerization has been carried out at the cited temperature.

in Figure 3 and their steric energies and relative populations are also shown in the Table. The conformation CC in a ground state is less stable than another conformation TC by 0.46 kcal/mol.[9] In their transition states, however, the conformation CC is more stable than the latter TC by 6.9 kcal/mol.

In conclusion, the above mentioned procedures, which are in very good agreements with the experimental results, have been proved to be quite useful in order to explain the stereochemistry in Cope rearrangements of germacrenes depending on relative stabilities of the conformations in transition states.

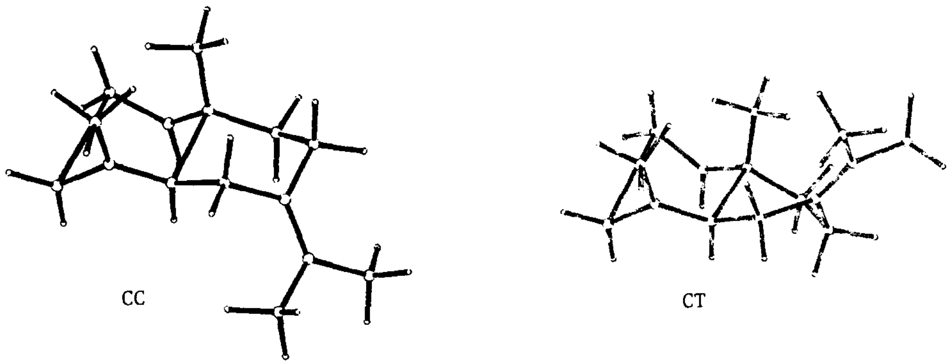


Figure 2. Calculated minimum energy structures of two stable conformations of germacrene-B (2) in transition states.

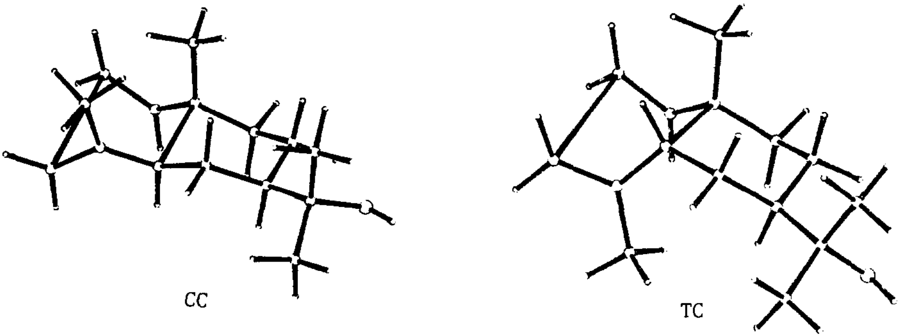


Figure 3. Calculated minimum energy structures of two conformations of hedycaryol (3) in transition states.

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References and Notes

1) K. Takeda, Tetrahedron, 30, 1525 (1974); J.K. Sutherland, ibid., 30, 1651 (1974).
2) Y. Terada and S. Yamamura, Tetrahedron Lett., 1979, 1623.
3) A.J. Weinheimer, W.W. Youngblood, P.H. Washecheck, T.K.B. Karns, and L.S. Ciereszko, Tetrahedron Lett., 1970, 497.
4) Program MMI (QCPE 318), made by N.L. Allinger and converted by E. Ōsawa to fit FACOM 230-75 system, was used. All calculations were performed at Nagoya University Computation Center.
5) ORTEP drawing was carried out using a program made by C.K. Johnson and revised by K. Sasaki.
6) E.D. Brown, T.W. Sam, J.K. Sutherland, and A. Torre, J. Chem. Soc. Perkin I, 1975, 2326.
7) F.H. Allen and D. Rogers, J. Chem. Soc. (B), 1971, 257.
8) The same elemene must be derived from both CC and CT.
9) Private communication from Prof. E. Ōsawa; E. Ōsawa, K. Shimada, M. Kodama, and S. Ito, Tetrahedron Lett., 1979, in press.

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