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An Application of Molecular Mechanics Calculations on Thermal Reactions of Ten-membered Ring Sesquiterpenes

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Molecular mechanics calculations were successfully carried out to evaluate relative stabilities of each conformation of germacrenes in their ground states and transition states. In the calculation of such a transition state model as shown in Scheme 1, the parameters for partial bonds were taken as mean values of those for a reactant and a product. Thus, the calculation results on each transition state model indicate that the elemenes are formed from the corresponding germacrenes through the most stable transition state (CC), regardless of the most stable conformers in ground state. Calculations were also carried out on ground and transition states of acoragermacrone and isoacoragermacrone, both of which have an α,β-unsaturated carbonyl system. The calculation results on each transition state model indicate that shyobunone (**5**) and epishyobunone (**6**) both are formed from acoragermacrone through the corresponding transition states [**5** from CC; **6** from C′C′ and C′T] in relative ratio (**5**/**6**=87/13) which is in good agreement with that of the experimental result (**5**/**6**=84/16). In the case of isoacoragermacrone, molecular mechanics calculations indicate that the preisocalamendiol-type transition state model is more favorable than the models corresponding to the Cope rearrangement products.

Conformation of ten-membered ring sesquiterpenes has been studied extensively, in connection with biosyntheses of many other types of sesquiterpene. Frequently, the ground state conformation of ten-membered ring sesquiterpenes was discussed in relation to the structure of their reaction products,[1] while it was also pointed out that the crown-like transition state is most favorable and determines the configuration of products.[2]

From the pioneering work by Hammond, a number of theoretical consideration to deduce the transition state structure have been made.[3] Moreover recently, semi-empirical[4] and non-empirical[5] molecular orbital methods have also been used to predict the transition states and reaction processes. At present, however, these theoretical methods can be applied to relatively small molecules and simple reactions.

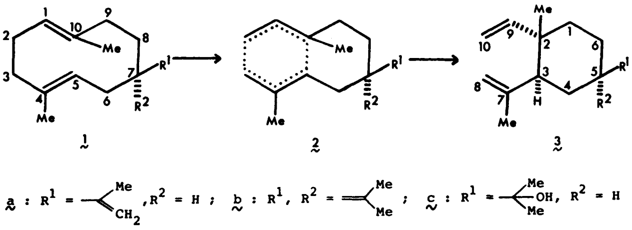
On the other hand, the frontier orbitals method[6] and the Woodward-Hoffmann rule,[7] both are extremely convenient and effective for deducing the structure of reaction product, but these methods are inefficient if the reaction conformer differs from the most stable conformer in the ground state.

The molecular mechanics calculations can be carried out easily and inexpensively, even on relatively large organic molecules, therefore, this calculation method has been widely used. Essentially, however, this method can only be used to such a molecule which consists of atomic groups with experimentally determined parameters. On this condition, there have been made some efforts to apply the molecular mechanics method on treatment of the transition states of oxidation reactions.[8] In the present paper, independently of these attempts, we wish to describe a successful application of the molecular mechanics calculations to a transition state model in thermal reactions of ten-membered ring sesquiterpenes. In this calculation method the transition state model was represented by a plausible structure with partial bonds, the parameters for which were taken as mean values of those for a reactant and a product.

Method of Calculation

Inspection of molecular models shows that each plane of the endocyclic double bond must be placed approximately perpendicular to the average plane of the ten-membered ring. Consequently, several stable conformers are possible for individual sesquiterpene. Steric energies of these conformers in ground state were calculated by means of the program COORD[9] with bond lengths, bond angles, and torsional angles obtainable from Dreiding molecular models, and then iterative calculations were made to minimize the steric energy of each conformer by means of the program MMI and MMPI.[10] Relative populations of these conformers at given temperature were calculated with energy values so far obtained, assuming they are in an equilibrium.

Transition State Model of Cope Rearrangement. In the reaction process of Cope rearrangement from germacrenes (**1**) to elemenes (**3**), we have proposed such a transition state model (**2**)[11] as shown in Scheme 1, and have applied molecular mechanics calculations to this model.[12]



Scheme 1. Thermal isomerizations of germacrenes.

Several modifications were required for application of program MMI to such a transition state model. Thus, in the energy minimize calculations of the transition state model (**2**), iterative calculations were made starting from the co-ordinate set corresponding to the each stable conformer in ground state, except for the co-ordinates of C_{10}. The position of C_{10} in **2** was located

TABLE 1. STERIC ENERGY AND RELATIVE POPULATION OF GERMACRENES IN EACH GROUND AND TRANSITION STATE

		Ground state		Transition state	
		Steric energy kcal mol^{-1}	Relative population % at 25 °C	Steric energy kcal mol^{-1}	Relative population[a)] %
Germacrene-A	CC	22.91	62.3	33.47	at 25 °C 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	CC	23.13	34.7	35.85	at 120 °C 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	CC	25.57	28.8	37.56	at 400 °C 95.8
	C′T	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

a) Experimentally, each thermal isomerization has been carried out at thecited temperature.

on a line between C_5 and C_{10} in **1**, assuming that the partially formed bond length ($C_5 \cdots C_{10}$) in **2** is equal to a mean value between the distance from C_5 to C_{10} in **1** and bond length C_2—C_3 in the product (**3**). The energy minimize calculations were executed fixing the positions of C_5 and C_{10} at the given positions and releasing all other part of molecule.

The parameters for the unusual bonds, which are characteristic of the transition state model (**2**) and not included originally in program MMI, were calculated by means of a simple arithmetical procedure. Accordingly, the parameters for the partial bonds were regarded as mean values of those of initial and final states: *e.g.* parameters for C···C in **2** were assumed to be mean values of C=C and C–C. Similarly, parameters for C···C were regarded as the half of C–C. The partially splitting bond length of $C_2 \cdots C_3$ was assumed to be 3.36 Å, which roughly corresponds to a mean value of the bond length C_2–C_3 in germacrenes and the average intramolecular distance between C_8 and C_{10} in elemenes.[13)]

We supposed, furthermore, the steric energy calculated for the transition state model, corresponds or is at least proportional to the height of the energy barrier of the Cope rearrangement, and the probability of the reaction can be substituted by the relative population of the transition state models in each conformation, under assumption of the Boltzmann's distribution.

Transition State Model for Preisocalamendiol-type Rearrangement. On thermal rearrangement of preisocalamendiol, such a transition state model (**A**) as shown in Scheme 4 was proposed,[14)] and application of molecular mechanics calculations to this type of transition state model revealed to be in good agreement with the experimental results.[15)] The co-ordinates of C_1 in **A** was calculated according to the same manner as that of the Cope rearrangement-type transition state. Each position of the remaining atoms except for C_1 and C_6 varied in the course of energy minimization.

Of the plausible conformers which arise from calculations of the ground state, some of them can adopt such a transition state as **A**, in which the carbonyl group and the methyl group on vinylic carbon C_{10} both are located on the same side of a plane of the ten-membered ring.

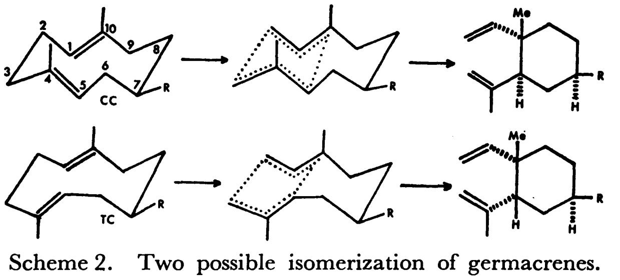
The partial bond lengths of O···H and $C_{15} \cdots H$ both are assumed approximately to be 1.7 Å, on the basis of the distance between O and C_{15} in the initial and final states of the reaction, as well as of an assumption in which this proton is nearly placed at the equidistant point from both O and C_{15} in the transition state model.

Parameters for the partial bonds were estimated according to the same procedure as described above.

Results and Discussion

*Germacrene-A (**1a**).* Germacrene-A (**1a**), a ten-membered ring sesquiterpene isolated from a sea fan, is an unstable compound and spontaneously converted into the corresponding elemene (**3a**),[16)] as shown in Scheme 1. Molecular mechanics calculations on the four conformers of **1a** were carried out to deduce the main conformations with energy minima and their results were summarized in Table 1.

Further calculations were also made on the transition state models corresponding to the conformers in each ground state, as shown in Scheme 2. The resulting structures of CC and TC in their transition states are shown in Fig. 1 and their steric energies and relative populations are also summarized in Table 1.



Scheme 2. Two possible isomerization of germacrenes.

From these data, it is evident that the most stable conformation of **1a** in a ground state is directly related to the corresponding elemene (**3a**) through the most stable transition state CC.

*Germacrene-B (**1b**).* Molecular mechanics calculations were carried out on germacrene-B (**1b**) which

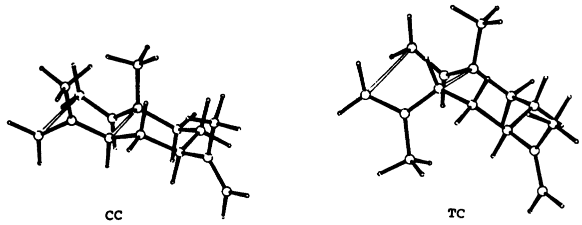


Fig. 1. Calculated minimum energy structures of two conformations of germacrene-A (**1a**) in transition states. The hollow bonds depict the partial bonds $C_5 \cdots C_{10}$ and $C_2 \cdots C_3$.[17]

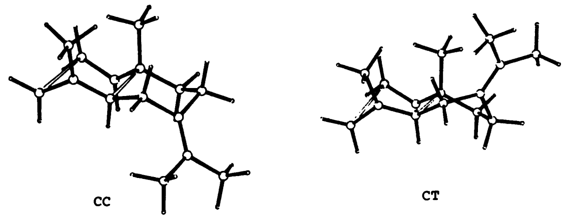


Fig. 2. Calculated minimum energy structures of two stable conformations of germacrene-B (**1b**) in transition states.

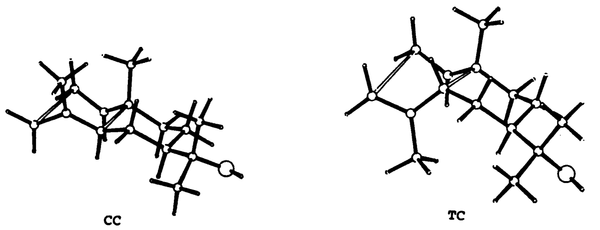


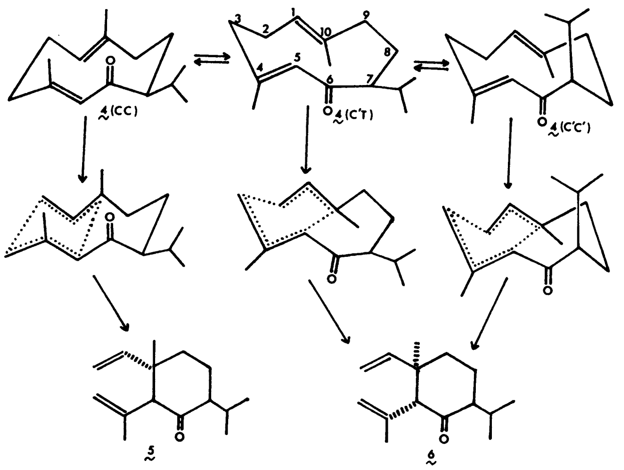
Fig. 3. Calculated minimum energy structures of two conformations of hedycaryol (**1c**) in transition states.

was also known to be thermally converted into the corresponding elemene (**3b**),[2b] indicating that the conformation CT is most stable,[18] although an X-ray crystallographic analysis revealed that a 1 : 1 silver nitrate adduct of **1b** adopts the conformation CC in a crystal state.[19] Of the two transition state models CC and CT (see Fig. 2), it is noteworthy that the former is more stable than CT,[20] as shown in Table 1. However, the same elemene must be derived from both CC and CT.

*Hedycaryol (**1c**).* In the case of hedycaryol (**1c**), its molecular mechanics calculations revealed that the favorable conformation in a ground state does not correspond to the structure of elemene (**3c**).[21] 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 in Fig. 3 and their steric energies and relative populations are also shown in Table 1. The conformation CC in the ground state is less stable than another conformation TC by 0.46 kcal/mol.[21] In their transition states, however, the conformation CC is more stable than the latter TC by 6.9 kcal/mol.

*Acoragermacrone (**4**).* Acoragermacrone (**4**) and isoacoragermacrone (**7**) both have an α,β-unsaturated carbonyl group. From a biogenetic point of view, acoragermacrone (**4**), an attractant of fruit-fly species,[22] is regarded as an important precursor of many sesquiterpenes which have been isolated from the plant *Acorus calamus* L.[11,23] In fact, Cope rearrangement of **4** affords shyobunone (**5**) and epishyobunone (**6**), both of which co-occur in the same plant, as shown in Scheme 3.[11,23]

Molecular mechanics calculations on the plausible conformers of **4** were carried out using program MMPI to deduce the main conformations with energy minima



Scheme 3. Thermal isomerization of acoragermacrone (**4**).

Table 2. Relative population of each conformation of **4** in both ground and transition states

Conformer	Ground state: Steric energy[a] kcal mol^{-1}	Ground state: Relative population % at 25 °C	Transition state: Steric energy kcal mol^{-1}	Transition state: Relative population % at 110 °C	Product
CC	25.17(−39.22)	80.8	36.40	87.0	Shyobunone (**5**)
C′C′	26.11(−38.29)	16.6	38.14	10.4	Epishyobunone (**6**)
C′T	27.25(−37.14)	2.4	39.11	2.5	
C′T′	30.76(−33.63)	0.0	50.21	0.0	
TT′	29.35(−35.04)	0.1	44.91	0.0	
T′C′	29.33(−35.06)	0.1	42.35	0.0	
T′C	30.67(−33.72)	0.0	51.39	0.0	

a) Heat of formation is also shown in parenthesis.

TABLE 3. HEATS OF FORMATION (kcal mol^{-1}) OF PLAUSIBLE CONFORMATIONS OF **7** IN TWO DIFFERENT TRANSITION STATES

Conformer	Ground state$^{a)}$	Transition state	
		Preisocalamendiol-type	Cope rearrangement type
TC	−43.09(74.6)	−8.99	−0.21
C′T	−42.09(13.8)		−7.36
CT	−41.82(8.7)		−6.05
T′T′	−41.15(2.8)	−6.53	2.60
T′C′	−37.77(0.0)	−3.34	2.48

a) Relative population(%) at 25 °C is also shown in parenthesis.

and their results were summarized in Table 2. Further calculations were also made on the transition state models corresponding to the conformers in each ground state (see Table 2). Thus, of seven transition state models, the most stable one is CC (see Fig. 4), from which shyobunone (**5**) must be produced. On the other hand, it is noted that epishyobunone (**6**) can be formed mainly from C′C′ (see Fig. 4) and slightly from C′T, as seen in Table 2. Furthermore, the relative ratio (**5**/**6**=87/13) is in good agreement with that of the experimental result (**5**/**6**=84/16).

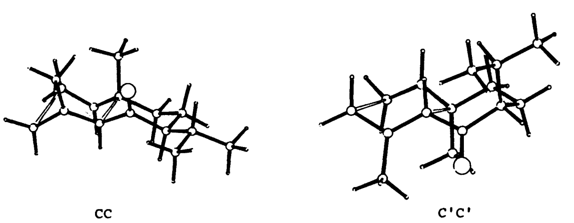
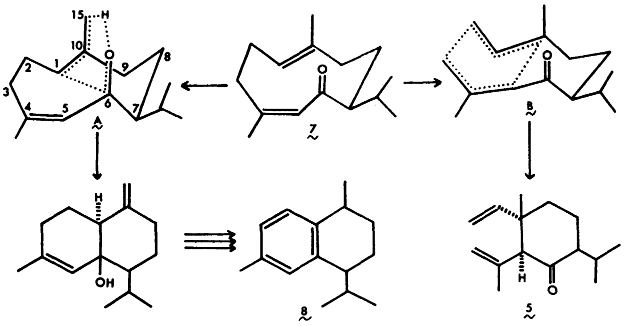


Fig. 4. Calculated minimum energy structures of two conformations of acoragermacrone (**4**) in transition states.



Scheme 4. Thermal isomerization of isoacoragermacrone (**7**).

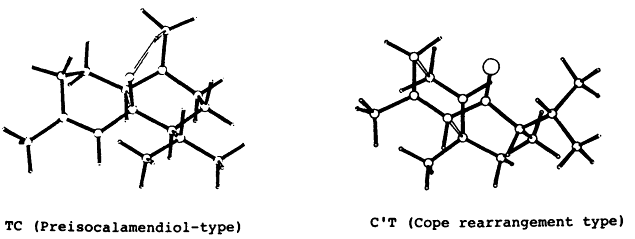


Fig. 5. Calculated minimum energy structures of most stable conformers in each different transition state model of **7**.

Isoacoragermacrone (7). We further applied molecular mechanics calculations to the possible conformers of isoacoragermacrone (**7**), in each ground state, and these results were summarized in Table 3. As expected from the base-catalyzed reactions of **7**,[11] clearly, isoacoragermacrone (**7**) is more stable than acoragermacrone (**4**) (see Tables 2 and 3). In the case of **7**, furthermore, two possible transition state models were considered as follows.

One of them is a presiocalamendiol-type transition state model (**A**)[15] leading to the formation of cadinene (**8**), as shown in Scheme 4. The remaining one is such a model as shown in Scheme 3, leading to the formation of Cope rearrangement products (see Scheme 4). Thus, molecular mechanics calculations were made on these two different models, and their results were summarized in Table 3. In addition, the most stable conformers in each different transition state model are shown in Fig. 5. As judged from these calculation data, clearly, the preisocalamendiol-type transition state model is more favorable than the models corresponding to each Cope rearrangement product.[24] This is compatible with the experimental results of thermal reaction of isoacoragermacrone (**7**).[25]

Conclusion

Although, germacrenes having an (*E*,*E*)-1,5-cyclodecadiene system are known to prefer the crossed conformation,[1a,2c,26] it has been proved that the stability of this system is affected by the substituent at C_7. Moreover, all sesquiterpenes calculated in this report exist in more than two conformers.[1a,21,27]

In the case of Cope rearrangement, however, the elemenes are formed from the corresponding germacrenes through the most stable transition state, regardless of the stable conformers in each ground state.[28] Moreover, the most favorable transition state of (*E*,*E*)-cyclodecadiene system is always CC, as pointed out before.[2] When the 1,5-cyclodecadiene system has carbonyl group at C_6 and one of the double bonds is *Z*-type or exocyclic,[15] the preisocalamendiol-type transition state is preferred rather than the Cope rearrangement type one. But, in the case of (*E*,*E*)-1,5-cyclodecadiene, large strain energy to form the $C_1 \cdots C_6$ partial bond prevents the preisocalamendiol-type transition state, resulting mainly in the formation of Cope rearrangement products.

Finally, our procedure, to which the ordinarily used programs are applied taking modified parameters calculated by means of simple arithmetic way for partial bonds, has been proved to be quite useful in order to estimate the stereochemistry and the reaction product's ratio in thermal reactions of germacrenes and germacrones.

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28) The energy barrier of the interchange between the conformational isomers in the ground state is much lower than the activation energy of the rearrangement. Therefore, it can be thought that the relative stabilities of conformers in the ground state are not so important for the consideration of the subsequent reaction process.