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# Conformational Studies on Humulene by Means of Empirical Force Field Calculations. Role of Stable Conformers of Humulene in Biosynthetic and Chemical Reactions

**Haruhisa Shirahama,* Eiji Ōsawa, and Takeshi Matsumoto**

*Contribution from the Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, 060, Japan.* *Received September 17, 1979*

**Abstract:** The conformational behavior of humulene, an 11-membered, carbocyclic, biosynthetically important sesquiterpene, was studied by empirical force field calculations. Estimation of heats of formation of four strain-minimum conformers revealed, in addition to the known conformer CT, the possible presence of another comparably stable conformer, CC. The ring inversion barrier between the CT enantiomers was estimated at $\Delta H^{\ddagger} = 14.17$ kcal/mol. We suggest that the newly recognized CC conformer is responsible for the biosynthesis of hirsutanoid and bicyclohumulenone and a transannular cyclization reaction to yield bicyclohumuladiol.

Humulene is one of the fundamental compounds in sesquiterpene biosynthesis. Farnesyl pyrophosphate undergoes head-to-tail intramolecular cyclization to produce humulenic and germacrenic cations and from both of them versatile cyclic sesquiterpene skeletons are derived[1] (Figure 1). In 1966, Allen and Rogers[2] found that a tricyclic bromohydrin,[3] derived from humulene by treatment with NBS in aqueous acetone, had a conformation quite similar to that of humulene–$AgNO_3$ complex, by means of X-ray crystallographic analysis[4] (Figure 2). Since then, the conformational similarity between a reactant and the product has been discussed in several papers[5] describing humulene, germacrene, and other medium-sized cycloolefin chemistry. In the course of studies on the biogenetic-like synthesis of illudoids,[6] we were interested in the relationship among humulene conformations, its transannular in vitro reactions, and biosyntheses of humulene-derived sesquiterpenes. Roberts and his co-workers studied the conformation of humulene by means of NMR spectroscopy and estimated the ring flipping barrier. They were, however, unable to obtain information about the actual shapes of the stable conformations.[7] In the absence of any experimental clue to determine the predominant conformations of this apparently flexible molecule, we resorted to molecular mechanics calculations[8] to assess the relative stabilities of its conformers. The ring inversion barrier was also calculated by the same method. Among the many empirical force fields being available,[10] the most popular program, Allinger's "MMI",[11] was used in this work.

## Results and Discussion

Inspection of the molecular model shows that, in the 11-membered ring containing three endocyclic trans double bonds, the planes of the latter should be almost perpendicular to the plane of the ring. Thus the number of stable conformers is limited to the number of combinations of the directions of the three double bonds. Four stable conformations, CT, CC, TT, and TC,[12] then can readily be envisaged (Figure 3). The CT form appears in the crystalline silver nitrate complex.[4] Noting the chirality of three double bonds, eight possible stable conformers are *RSR*-CT, *RRR*-CC, *RRS*-TC, *RSS*-TT,[13] and the four enantiomers. Each of them can be correlated with seven other conformers through single or multiple double bond plane rotation. The correlation diagram of the eight conformers is depicted in Figure 4.[14] Calculations of heats of formation for the conformers at the corners and barriers of 12 interconversion processes along each edge of this cube[15] will cover the energy surface for the conformational change of humulene.

**1. Stable Conformers.** Energy minimizations of the four principal conformers were successfully achieved to give their precise geometries and heats of formation. Table I summarizes heats of formation and dihedral angles of the fully relaxed basic conformers and their perspective stereodrawings are depicted

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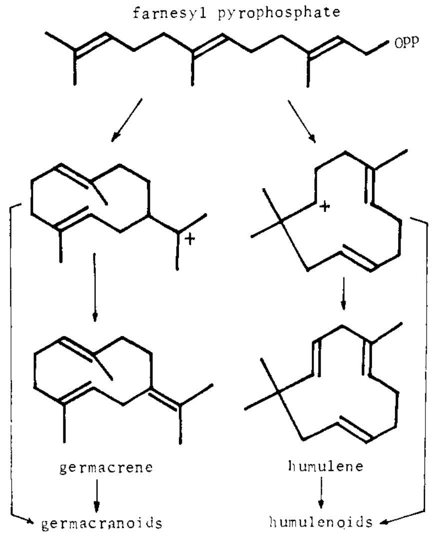


Figure 1.

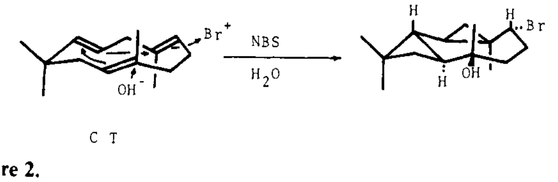


Figure 2.

in Figure 5. No other stable conformers appeared during the exhaustive examination of the double bond rotation processes. These results strongly suggest that, in addition to the known conformer CT, a new form CC should be equally stable. The importance of this finding will be discussed in section 3.

In the reactivities of the three double bonds of humulene, notable differences have been recognized. Epoxidation[16] and all the hitherto known intramolecular cyclization reactions[17] initiate at the 6,7 double bond. Sutherland and his co-workers explained[18] the reactivity difference by torsional strain. Mock states[19] that a twisted trans double bond has a larger lobe of the $\pi$ orbital on the convex face of the double bond than on the concave face, and the outside of such a double bond is susceptible to attack by reagents. The data obtained from X-ray analysis of the silver nitrate complex showed that the 6,7 double bond was certainly more twisted than the 2,3 bond.[20] Sutherland applied these X-ray data to his reaction in a solution though they were obtained from a solid complex.

While the present calculation gave a 6° smaller torsion for the 6,7 bond of the free CT molecule than for the same bond of silver complex (Figure 6), the torsional difference between 2,3 and 6,7 double bonds is large enough to invoke the observed reactivity difference. A small ground-state torsion about a double bond may produce a sizable effect in the relative reactivity.[19] The other stable conformer (CC) has less distorted double bonds than those of CT, so the CC form may not react even if both forms are present in comparable amounts in the reaction medium. Therefore, the large torsional strain of the double bonds may be responsible for the fact that only reaction products derived from the CT form have been found, in spite of sizable population of the CC conformers.[21]

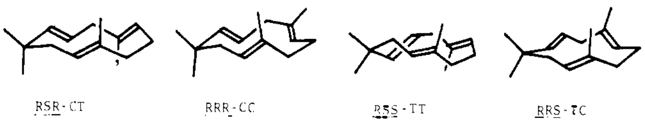


Figure 3. Four strain minimum conformers of humulene.

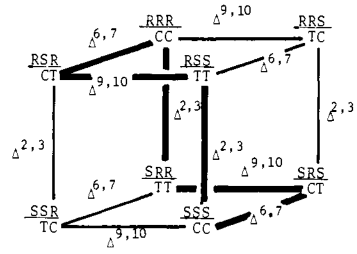


Figure 4. Correlation diagram among eight strain minimum conformations of humulene. Two conformers standing on both sides of the every edge of the above cube are interconvertible by a single rotation of a double bond indicated on the edge. Heavy lines show the lowest energy path for ring inversion (see Figure 8).

2. **Ring Inversion Barrier.** On the force-field estimation of ring inversion barriers in simple cyclic olefins, beautiful works[22] have been published by Anet and his co-workers. However, no studies on compounds like humulene, which have no symmetry element, have been attempted before the present work.[23] The rotation of a double-bond plane through the humulene ring proceeds in principle in either of two ways depending on which of the two substituents on the double bond passes through the inside of the carbocyclic ring during the rotation (Figure 7). Actually only one way is possible for the 2,3 and 6,7 double bond planes since a rotation placing a methyl group inside gives an extremely high strain to the molecule. Ring inversion, which is in the present case a process connecting any pair of enantiomers, can be completed by successive rotations of the three endocyclic double bond planes as shown in Figure 4. The actual path will go through the lowest energy path among the 12 possible routes,[24] and the highest barrier of the series of the three rotations on this path represents the activation energy of humulene ring inversion. The calculation procedure is given in the Appendix.

Table I

| dihedral angles | $AgNO_3$ complex[a] | CT | CC | TT | TC |
|---|---|---|---|---|---|
| 1—2═3—4[c] | −172.2[b] | −173.2 | −174.2 | −173.6 | −172.3 |
| 2═3—4—5 | 108.6 | 105.3 | 105.0 | 105.7 | 103.0 |
| 3—4—5—6 | −35.1 | −44.8 | −45.1 | −37.2 | −46.4 |
| 4—5—6═7 | −77.0 | −80.9 | 124.7 | −75.3 | 120.5 |
| 5—6═7—8 | 161.8 | 167.6 | −173.9 | 166.4 | −168.4 |
| 6═7—8—9 | −95.0 | −84.2 | 44.7 | −66.3 | 77.1 |
| 7—8—9═10 | 94.0 | 88.7 | 58.4 | −83.8 | −97.2 |
| 8—9═10—11 | −156.5 | −167.9 | −174.5 | 167.6 | 168.3 |
| 9═10—11—1 | 102.2 | 107.4 | 121.0 | −54.9 | −71.9 |
| 10—11—1—2 | −55.0 | −39.7 | −44.4 | −31.2 | −35.7 |
| 11—1—2═3 | 126.2 | 127.4 | 110.4 | 140.6 | 130.7 |
| heats of formation | 19.54 | 4.24 | 4.47 | 7.86 | 5.30[d] |

[a] Coordinates of carbons are taken from ref 4 and those of hydrogens are placed so that the conformation has least strain. [b] A positive dihedral angle is an assembly 1—2—3—4 denotes a clockwise rotation of plane 2, 3, 4 with respect to the reference plane 1, 2, 3 when viewing the assembly from 2 to 3. [c] The symbol ═ denotes a double bond. [d] In kcal/mol (25 °C, gas).

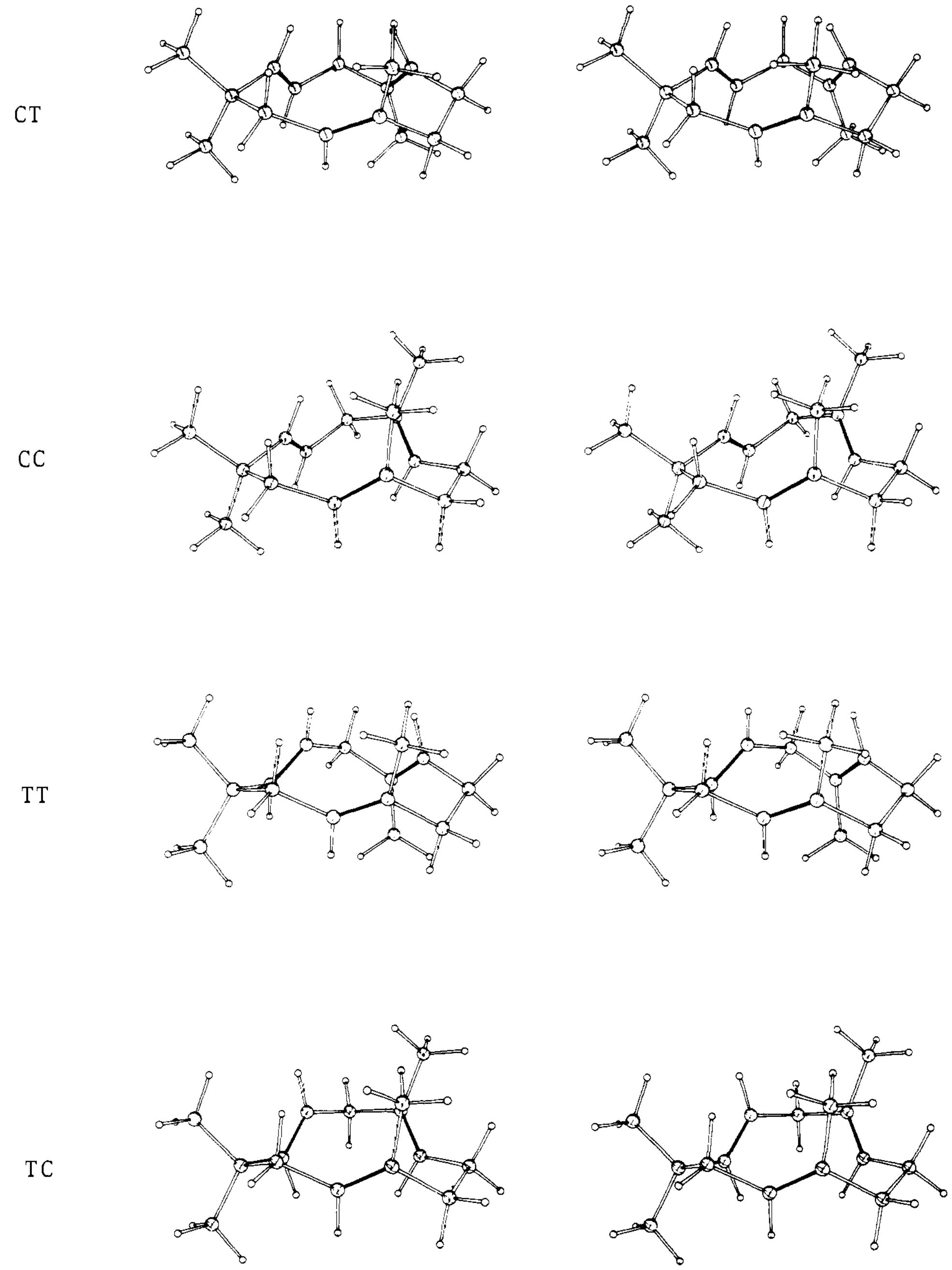


**Figure 5.** ORTEP stereodrawing of minimum energy structures of four basic humulene conformers.

**Table II.** Heats of Formation (kcal/mol) of All Transition-State Conformers[a]

| | | |
|---|---|---|
| $CT \xrightarrow{\Delta 6,7} CC$ | 14.87 | |
| $CT \xrightarrow{\Delta 2,3} TC$ | 21.11 | |
| | | rotation keeping |
| $CT \xrightarrow{\Delta 9,10} TT$ | 18.0 | C-9 outside of the humulene ring |
| | 25.7 | C-10 outside |
| $CC \xrightarrow{\Delta 2,3} TT$ | 18.64 | |
| $CC \xrightarrow{\Delta 9,10} TC$ | 16.36 | C-9 outside |
| | 24.7 | C-10 outside |
| $TT \xrightarrow{\Delta 6,7} TC$ | 17.75 | |

[a] The mode of conformational change from CT to CC is shown in Figure 11 and a profile of the energy change accompanied by the above conformational transformation in Figure 12.

Completion of the calculation for all the transformations represented by the correlation diagram demonstrated that the assumed correlations were correct and that any conversion of a conformer surely led to another one. The energies estimated for the transition states between two conformers are summarized in Table II. The lowest energy path along which the ring inversion should occur is indicated by heavy lines in the correlation diagram (Figure 4). The activation enthalpy for humulene ring inversion was thus estimated to be $\Delta H^{\ddagger} = 14.17$ kcal/mol (Figure 8), which is a reasonable value compared to the barriers $\Delta G^{\ddagger} = 10.6 \pm 0.3$ kcal/mol for humulene and $\Delta G^{\ddagger} = 15.8 \pm 0.3$ kcal/mol for zerumbone obtained by an NMR study.[7] The humulene ring inversion should be free at room temperature.

**3. Implication of the Results in the Biosyntheses of Illudoids and Hirsutanoids and Chemical Reactions of Humulene.** The implication of the relative stabilities of the four basic conformers with illudoid and hirsutanoid biosynthesis was already described.[23] We should like to point out the importance of the

**Table III.** Double Bonds ($\Delta^{6,7}$) Inversion Process in the Transformation from CT to CC Conformer[a]

| step I | | | | step II | | | | step III | | |
|---|---|---|---|---|---|---|---|---|---|---|
| rotation angles | dihedral angles, deg $\phi$(4-5-6-7) | dihedral angles, deg $\phi$(6-7-8-9) | $\Delta H_f^{\ddagger}$, kcal/mol | rotation angles | dihedral angles, deg $\phi$(4-5-6-7) | dihedral angles, deg $\phi$(6-7-8-9) | $\Delta H_f^{\ddagger}$, kcal/mol | dihedral angles, deg $\phi$(4-5-6-7) | dihedral angles, deg $\phi$(6-7-8-9) | $\Delta H_f^{\ddagger}$, kcal/mol |
| CT | −80.9 | −84.2 | 4.24 | −98 | 167.8 | −12.0 | 13.20 | 165.644 | −7.277 | 12.97 |
| −20 | −97.1 | −65.9 | 5.78 | −95 | 178.6 | −14.4 | 14.20 | 172.000 | −10.062 | 13.80 |
| −40 | −119.2 | −46.5 | 8.99 | −92 | −171.0 | −17.3 | 14.87 | −170.997 | −17.255 | 14.87 |
| −60 | −138.5 | −26.7 | 13.65 | −89 | −163.6 | −20.4 | 14.88 | −163.718 | −21.815 | 14.86 |
| −80 | −156.7 | −5.5 | 19.15 | −86 | −160.0 | −23.8 | 14.54 | −159.993 | −25.216 | 14.51 |
| −100 | 171.2 | 19.1 | 16.12 | −83 | −157.0 | −27.1 | 14.09 | −156.976 | −27.149 | 14.09 |
| CC | 124.7 | 44.7 | 4.47 | −80 | −154.2 | −30.3 | 13.58 | −154.195 | −30.310 | 13.58 |

Variation of All Dihedral Angles at Step I

| dihedral angles | CT | −20° | −40° | −60° | −80° | −100° | CC |
|---|---|---|---|---|---|---|---|
| 1—2═3—4 | −172.2 | −172.3 | −170.5 | −167.5 | −164.2 | −168.9 | −174.2 |
| 2═3—4—5 | 108.6 | 101.8 | 97.0 | 96.1 | 97.5 | 98.4 | 105.0 |
| 3—4—5—6 | −35,1 | −44.4 | −41.2 | −41.6 | −45.0 | −34.7 | −45.1 |
| 4—5—6═7 | −77,0 | −97.1 | −119.2 | −138.5 | −156.7 | 171.2 | 124.7 |
| 5—6═7—8 | 161.8 | 164.3 | 162.2 | 160.8 | 161.4 | 162.6 | −173.9 |
| 6═7—8—9 | −95.0 | −65.9 | −46.5 | −26.7 | −5.5 | 19.1 | 44.7 |
| 7—8—9═10 | 94.0 | 95.0 | 98.1 | 95.2 | 82.7 | 59.4 | 58.2 |
| 8—9═10—11 | −156.5 | −169.8 | −171.3 | −170.7 | −169.0 | −171.7 | −174.5 |
| 9═10—11—1 | −156.5 | 99.7 | 96.4 | 95.1 | 98.3 | 114.2 | 121.0 |
| 10—11—1—2 | −55.0 | −40.2 | −43.3 | −47.0 | −48.4 | −44.9 | −44.4 |
| 11—1—2═3 | 126.2 | 131.0 | 132.7 | 132.2 | 129.1 | 117.6 | 110.4 |
| $\Delta H^{\ddagger}$, kcal/mol | 4.24 | 5.78 | 8.99 | 13.65 | 19.15 | 16.12 | 4.47 |

[a] See Appendix.

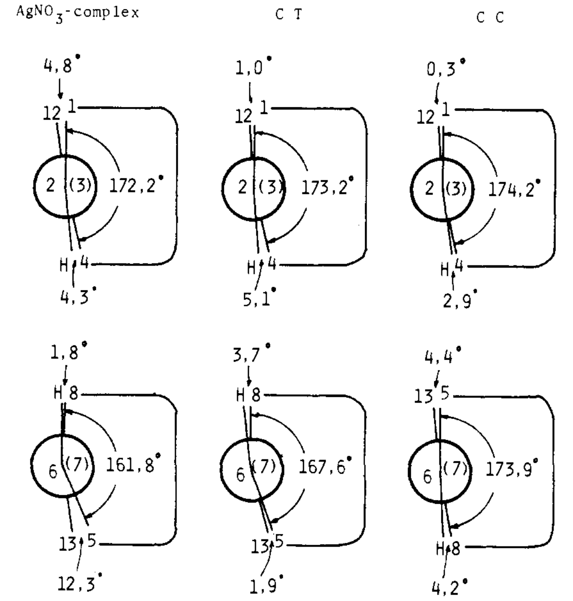


**Figure 6.** Torsional angles of six double bonds in the three conformers of humulene.

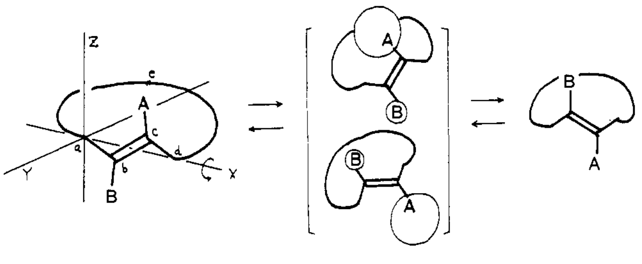


**Figure 7.** If both A and B are small enough to pass through the ring, two rotation modes are possible.

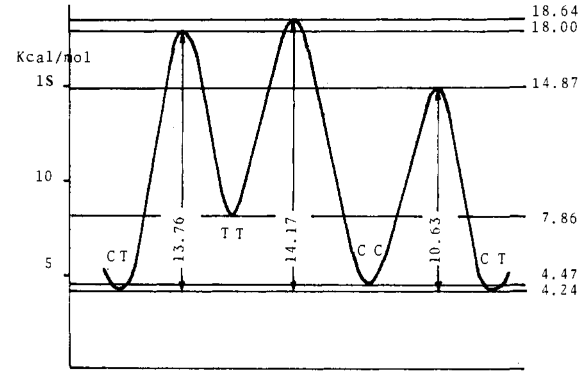
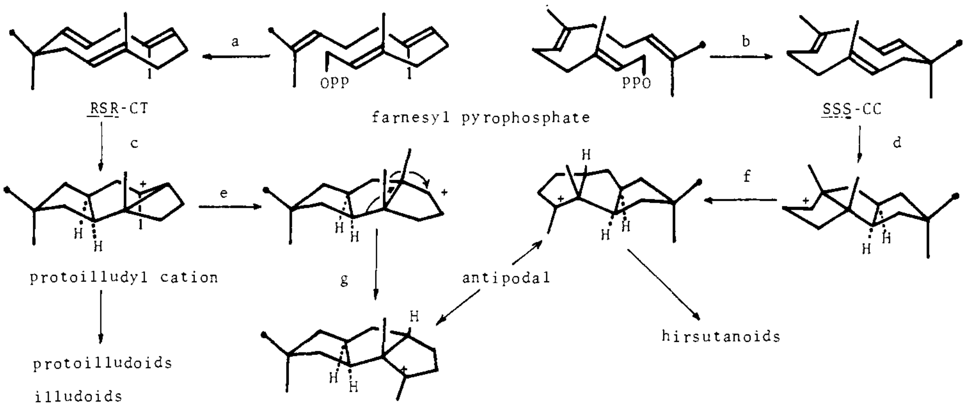


**Figure 8.** Lowest energy path for humulene ring inversion (the path shown by heavy lines in Figure 4).

new conformer CC in the transannular reactions of humulene. First, if the same conformation is kept almost unchanged throughout the reaction, the conformers CT and CC are well suited to the precursors of illudoids and hirsutanoids, respectively. Two separated biosynthetic paths [CT → protoilludoid (c) and CC hirsutanoid (d, f)] can be suggested [25] instead of assuming a single route [CT → protoilludane → hirsutane (c, e, g)][26] (Figure 9). Recently Cane and Nachbar demonstrated[27] that the labeled illudoid and hirsutanoid are to be biosynthesized through the paths represented by the abbreviated expression si, re, cis:cis, $R$[28] and re, si, cis:cis, $S$, respectively, noting the absolute stereochemistry of the cyclization reaction of farnesyl pyrophosphate. They successfully analyzed the stereochemistry of the formation of the dimethylcyclopentane moiety (namely, the formation of 3,6-seco-protoilludene), but ignored the mode of the second transannular cyclization reaction to give illudoid or hirsutanoid. Analysis of the structure and absolute configuration of the products suggests that the conformation designated *RSR*-CT-humulene is the precursor of illudoids and *SSS*-CC-humulene is that of the hirsutanoids in their biosynthetic transannular cyclization reactions.

Second, Hayashi and his co-workers recently reported[29] the isolation of a new natural product, bicyclohumulenone, which



• shows the labeled carbons which are derived from C-2 carbon of mevalonate.

Figure 9.

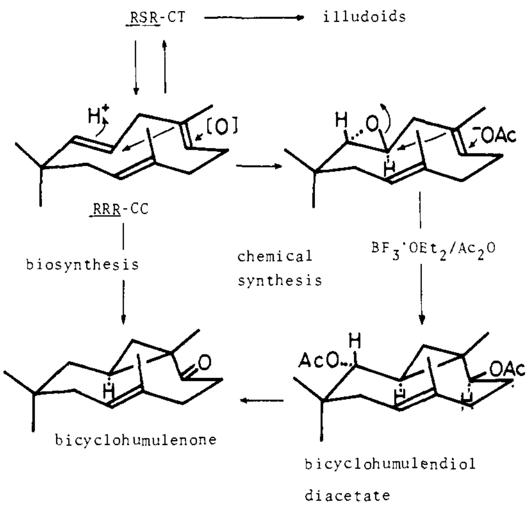


Figure 10.

can be derived from the conformer CC. Close examination of the absolute configuration of bicyclohumulenone reveals that the compound should have arisen from protonation at C-10 of the *RRR*-CC form. Thus, one explanation is that the two conformers of humulene, CT and CC, are separately trapped by two different enzymes so as to yield illudoid on one hand and bicyclohumulenone on the other hand (Figure 10).

Third, the CC conformer was furnished as the reactant also to a chemical reaction. Humulene yielded bicyclohumuladiol diacetate through treatment of 9,10-epoxyhumulene[16,30] with $BF_3 \cdot OEt_2-Ac_2O$ and the product was converted to (±)-bicyclohumulenone.[31] That is to say, not only the CT but also the CC form actually plays a role in the chemical reaction and the biosynthesis.

The estimated ring inversion barrier is not high enough to allow the separation of humulene enantiomers at room temperature. However, transannular distances between juxtaposed double bond carbons are so short [C2-C9, 3.2468 (CT), 3.4900 (CC); C3-C6, 2.8197 (CT), 2.7994 Å (CT)] referring to the distance between the two aromatic rings of quinhydrone (3.2 Å)[32] that an interaction among the three $\pi$ orbitals can be expected in the ground state. The transannular reactions with acids indeed proceed rapidly at 0 °C, and the activation energies are probably comparable to the barrier of ring inversion.[33]

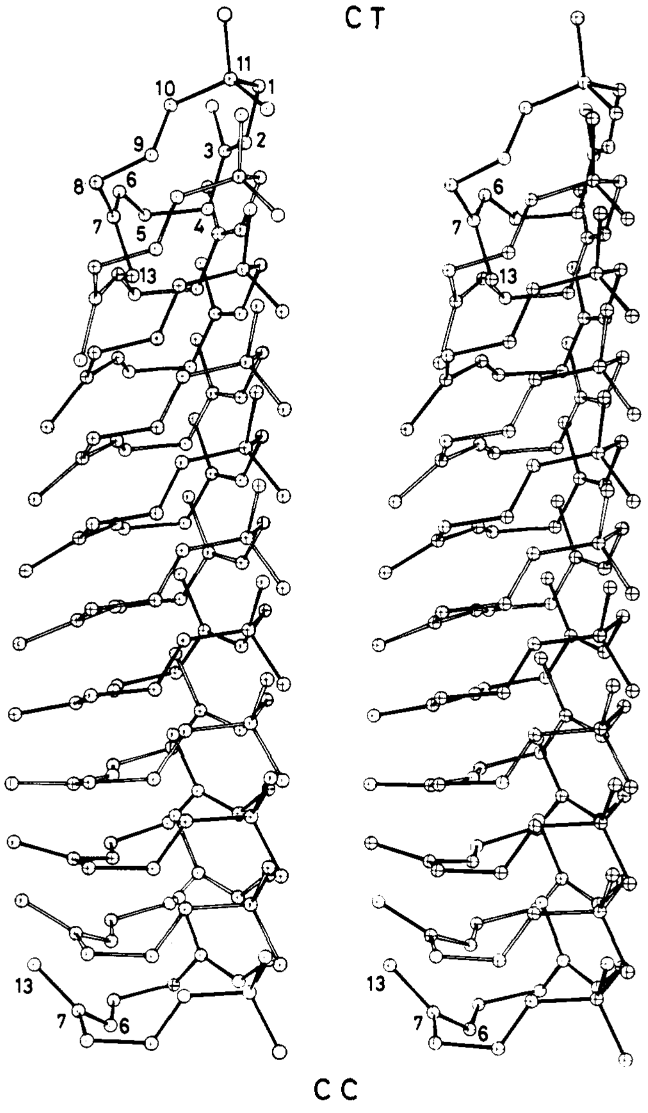


Figure 11.

## Conclusion

It is revealed that empirical force field calculations are effective in finding the stable conformers which are difficult to know experimentally. The two reacting conformers which account for the biosynthesis of humulenoids and the transannular chemical reactions turn out to be the two most stable ground-state conformers as well. The usefulness of the force-field calculations in estimating the detailed geometries and relative stabilities of conformers, and especially in disclosing the detailed ring inversion process, is demonstrated by using humulene as an example.

**Acknowledgments.** We are thankful to Hokkaido Takushoku Bank, Ltd., for providing computer facilities. A part of the

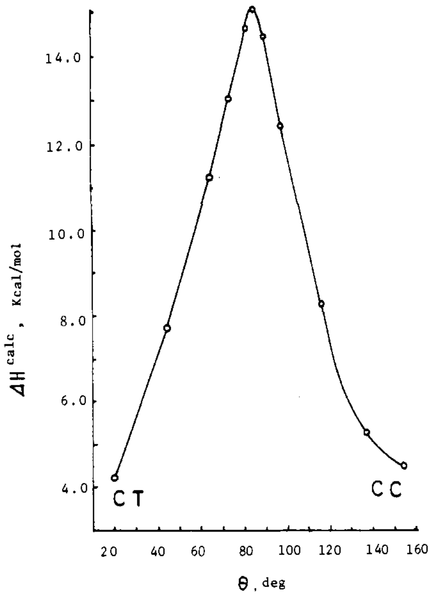


**Figure 12.** A profile of the energy change accompanied by conformational transformation (CT → CC). $\theta$ shows an angle made by two planes. One contains three carbons (C-2, C-6, and C-8) and the other C-6, C-7, and C-8.

calculations was performed at the Hokkaido University Computing Center. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Japan, No. 354184 (H.S.) and 447016 (E.Ō.).

## Appendix

The barrier to the conformational change was obtained as follows. One of the two allylic carbons on the double bond to be rotated is placed at the origin of the Cartesian coordinates, and the other along the $X$ axis (Figure 7). One of the ring carbons (e) farthest from the double bond was laid on the $XY$ plane. Heats of formation were calculated with conformers obtained by successive rotations of all atoms between the two allylic carbons (a, d) by about 20° keeping the five points fixed at $[a(x, y, z), b(z), c(z), d(y, z), e(z)]$, followed by short time relaxation until a maximum was observed (step I). The conformer with the highest heat of formation was fully relaxed under the above constraints and the same procedure as step I was carried out under positive and negative rotation with smaller degrees (step II). Full relaxation calculations were performed on the several conformers near the maximum point to obtain the real transition state conformer (step III). As an example of these three steps, the rotation procedure of the 6,7 double bond of the CT conformer is shown in Table III and the mode of transformation from the CT to CC form divided into ten stages is depicted in a stereodrawing (Figure 11). A profile of the energy change accompanied by conformational transformation (CT → CC) is reproduced in Figure 12.

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(24) *RSR*-CT → *SSR*-TC → *SSS*-CC (or *SRR*-TT) → *SRS*-CT, *RSR*-CT → *RRR*-CC → *RRS*-TC (or *SRR*-TT) → *SRS*-CT, *RSR*-CT → *RSS*-TT → *RRS*-TC (or *SSS*-CC) → *SRS*-CT. Two different ways of rotation of the 9,10 double bond plane (9H inside and 10H inside) are possible in each of the above six routes. Therefore, 12 paths are possible.

(25) We described this suggestion in the preliminary report.[23] Since then, Cane and his co-worker claimed the two different routes by clear evidence.[27] We had been suspicious of the single route, since the absolute configurations of dimethylcyclopentane moieties of the illudoids and the hirsutanoids are antipodal and co-occurrence of hirsutanoids and other illudoids has not been recognized.

(26) Biosynthesis of illudoid: ref 27. Peter, A.; Bradshaw, W.; Hanson, J. R.; Silverns, M. *J. Chem. Soc., Chem. Commun.* **1978**, 303. Hanson, J. R.; Marten, T.; Nyfeler, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 876. Cane, D. E.; Nachbar, R. B. *Tetrahedron Lett.* **1976**, 2097. Tanabe, M.; Suzuki, K. T.; Jankowski, W. C. *Ibid.* **1974**, 2271. Feline, T. C.; Mellows, G. *J. Chem. Soc., Chem. Commun.* **1974**, 63. Hanson, J. R.; Marten, T. *Ibid.* **1973**, 171. Anchel, M.; McMorris, T. C.; Singh, P. *Phytochemistry* **1970**, *9*, 2339. Turner, W. B. "Fungal Metabolites"; Academic Press: New York, 1971; p 228, and references cited therein (reports before 1970).

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(30) It was shown that the stable conformations of epoxides resembled those of original olefins, e.g., humulene–$AgNO_3$ complex/humulene diepoxide: Cradwick, M. E.; Cradwick, P. D.; Sim, G. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 404.

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