Tetrahedron Letters No. 24, pp 2245 - 2246.
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0040-4039/79/0608-2245$02.00/0

# CONFORMATIONAL ASPECTS OF GERMACRENE B
## ARE THE GERMACRENES RESOLVABLE ?

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Summary — Molecular mechanics calculations revealed that germacrene B has two comparably stable conformations. The lowest barrier ($\Delta H^{\ddagger}$) to ring inversion of the most stable conformer to its mirror image is estimated to be 23 Kcal/mol.

Germacrene B is a typical ten-membered cyclic sesquiterpene and an important biosynthetic precursor from which various types of terpenoids are derived.1) Our current interest2) on humulene conformations and recently published contradictory results3) on the ring inversion barrier of germacrone (9-oxogermacrene B) prompted us to study conformational behavior of the title compound.

The work of Wharton et al4) on hedicaryol conformation implies that for germacrene B, four strain-minimum conformations (CT, CC, TC, TT)5) and their correlation diagram can be depicted as shown in Fig 1 and 2. In its crystalline complex with $AgNO_3$, the compound is shown to adopt the CC from by X-ray analysis.6) To assess the relaxed geometries and relative stabilities of the four principal conformers as well as energy barriers between them, molecular mechanics calculations were performed.7) Energy minimization of the conformers and estimation of the barriers to the rotations8) of 2,3 and 6,7 double bond planes through the ring and around the 9,10 single bond were successfully achieved. Heats of formation of the fully relaxed four basic conformers (CT, CC, TC, TT) are 4.08, 4.31, 5.35 and 5.14 Kcal/mol respectively. Conformation CT and CC are more stable than the other two.9) These results reminded us of very similar situation2) in humulene, an eleven-membered cyclic triene, in which two stable conformers were found by calculation and one of them had been actually discovered in the crystalline $AgNO_3$ complex. Fig 2 shows barriers to rotation of the $\Delta^{2,3}$, $\Delta^{6,7}$ bonds and around the 9,10 bond.10) Fig 3 displays energy

Fig 1

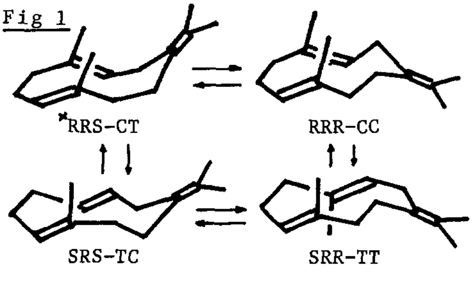
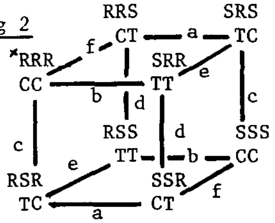


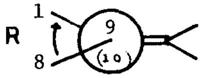
Fig 2



| | ΔH‡ Kcal/mol | operations |
|---|---|---|
| a | 26.79 | rotation of the 2,3 double bond |
| b | 29.44 | |
| c | 27.16 | rotation of the 6,7 double bond |
| d | 28.08 | |
| e | 12.56 | change of the sign of torsional angle of the assembly 8-9-10-1 |
| f | 16.56 | |

Each edge shows a single operation of double bond rotation or rotation around the single bond, 9-10. See ref. 8.

* The three letters represent successively the chirality associated with the 2,3 and 6,7 double bonds, and assembly 8-9-10-1.#

# 

profile of the lowest ring inversion path from the CT conformer to its mirror image. The estimated barrier, ΔH =23.08 Kcal/mol, implies that resolution[3b] of germacrene could be realized under certain strictly controlled conditions but that the resolved enantiomer should be susceptible to racemization.[11]

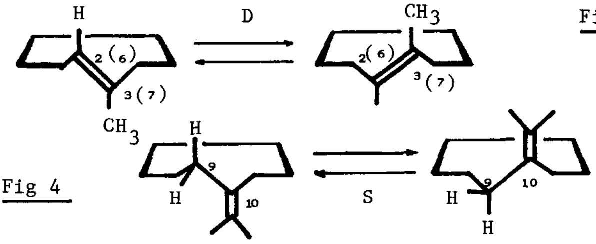


Fig 4

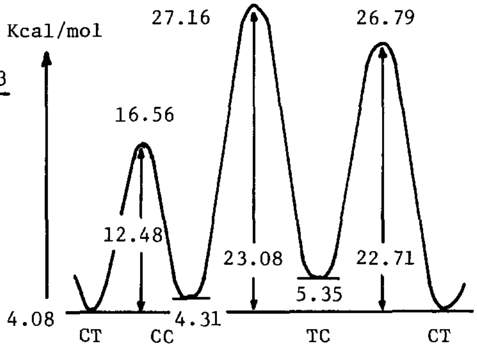


Fig 3

## References and Notes

1) W. Parker, J. R. Roberts, R. Ramage, Quart. Rev., 331 (1967). 2) H. Shirahama, E. Ōsawa, T. Matsumoto, Tetrahedron Lett., 1987 (1978). Two comparably stable conformers were found and based on this result, an independent biosynthetic route for each of illudoid and hirsutanoid biosynthesis was proposed. An experimental support for the above proposal appeared recently. D. E. Cane, R. B. Nachbar, J. Amer. Chem. Soc., 100, 3208 (1978). 3) Tori et al[a] described that ring inversion of germacrone was free at room temperature based on the nmr spectra, while Hill et al[b] reported optical resolution of the compound. a) I. Horibe, H. Shigemoto, K. Tori, Tetrahedron Lett., 2849 (1975). b) R. K. Hill, M. G. Fracheboud, S. Sawada, R. M. Carlson, S. J. Yan, ibid, 945 (1978). 4) P. S. Wharton, Y. C. Poon, H. C. Kluender, J. Org. Chem., 33, 735 (1973). 5) Notation: See ref. 2. 6) F. H. Allen and D. Rogers, J. Chem. Soc., (B) 257 (1971). 7) The program "MMI" (QCPE 318) was used. See N. L. Allinger, J. T. Sprague, T. Liljefors, J. Amer. Chem. Soc., 96, 5100 (1974); D. H. Wertz, N. L. Allinger, Tetrahedron 30, 1579 (1974). Calculations were performed at the Hokkaido University Computing Center and Hokkaido Takushoku Bank. Generous donation of computing time by the latter is gratefully acknowledged. 8) Rotations of double and single bonds are dipicted schematically as shown in Fig 4. Anet et al[10b] termed these rotations D and S processes respectively. 9) Nmr studies demonstrated that 8-acetoxygermacrene B existed in two conformations corresponding to CT and CC at 30°C.[a] Our calculations for this compound gave almost same heats of formation for the two conformers.[b] a) I. Horibe, K. Tori, K. Takeda, T. Ogino, Tetrahedron Lett., 735 (1973). b) unpublished results. 10) Detailed procedure will be described elsewhere. Reliability of the method was verified by calculations of an experimentally known ring inversion barrier: for trans, trans, trans-1,5,9-cyclododecatriene, ring inversion barriers ($\Delta G^{\ddagger}$), 9 Kcal/mol[a] and 8.6 ± 2 Kcal/mol,[b] were obtained from nmr data, while our calculations gave 10.8 Kcal/mol ($\Delta H^{\ddagger}$). a) J. Dale, Topics in Stereochem., 9, 199 (1976). b) F. A. L. Anet, T. N. Rawdah, J. Amer. Chem. Soc., 100, 5004 (1978). 11) By inference, this conclusion may be extended to germacrone. Two conformers of urospermal, a germacranolide, were isolated by chromatography as crystals, whereas in solution each of them racemized to a mixture of enantiomers at room temperature. R. K. Bentley, J. G. St. C. Buchanan. T. G. Halsall, V. Thaller, Chem. Comun., 435 (1970).

Received in Japan 23 February 1979)