Nuclear Magnetic Resonance Spectroscopy. The Conformational Mobility of Humulene and Zerumbone[1a]

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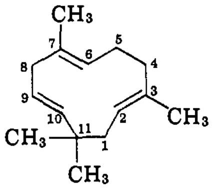
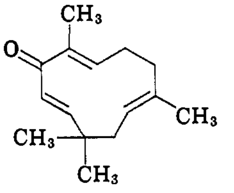
Abstract: The nmr spectra of humulene, zerumbone, and the product VII are temperature dependent. These changes are reported and discussed in the light of the possible conformational changes of these compounds. The potential energy barriers to these changes are measured.

The sesquiterpenes humulene and zerumbone have recently been shown to have the structures I and II, respectively.[2,3] X-Ray analysis of the silver nitrate adduct of humulene has shown[2] that the hydrogen on carbon atom 6 and the methyl group on carbon atom 3 are on the same side of the molecule, while the hydrogens on carbon atoms 2 and 10 are on the opposite side as represented in III or IIIa. The two methyl groups on carbon 11 in III are therefore expected to be chemically different as are the pairs of hydrogen atoms on carbons 1, 4, 5, and 8.



I

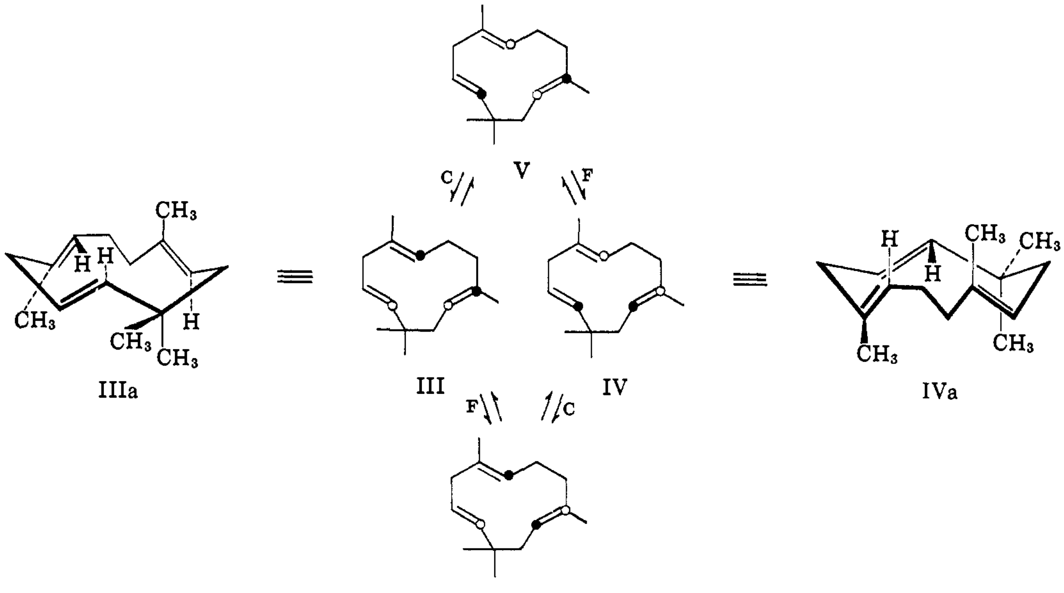


II

Flipping of the *trans*-2,3 double bond through the ring (process F) and crossing over of the hydrogen atoms on carbon atoms 6 and 10 (process C) lead to conformation IVa or IV, which is the mirror image of III. In this change, the two methyl groups on carbon atom 11 have changed places relative to III, as have the pairs of hydrogens on carbon atoms 1, 4, 5, and 8. Thus, interconversion of the mirror-image conformations III and IV renders the substituents on each of the saturated ring carbons identical.

In solution, the conformation of humulene may not be as in the crystal,[4] and the conformations represented as V and VI could well be preferred. V and VI are obtained from III and IV either by flipping the 2,3 double bond (process F) *or* by crossing over the hydrogen atoms on carbons 6 and 10 (process C).

There are reasons to expect that these conformational processes will be slow on the nmr time scale. Thus, rotation of the *trans*-alkene group in *trans*-cyclodecene has an activation energy of 10.7 kcal/mol,[5] and while the activation energy of this process in *trans*-cycloundecene is expected to be smaller,[6] interactions of the



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(2) A. T. McPhail, R. I. Reed, and G. A. Sim, *Chem. Ind.* (London), 976 (1964); J. A. Hartsuck and I. C. Paul, *ibid.*, 977 (1964).

(3) N. P. Damodaran and S. Dev, *Tetrahedron Letters*, 1977 (1965).

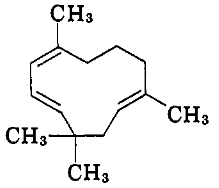
(4) See, for example, C. E. McEachan, A. T. McPhail, and G. A. Sim, *Chem. Commun.*, 276 (1965).

(5) G. Binsch and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 5157 (1965).

(6) The barriers to flipping of the double bond through the ring in the *trans*-cycloalkenes are 35.6, 19.1, and 10.7 kcal/mol for eight-membered,[7] nine-membered,[8] and ten-membered[5] rings, respectively.

inward-directed hydrogens and methyl group on atoms 2, 6, 10, and 3 during inversion, should raise the barrier in humulene.

To obtain information on this point, nmr spectra of humulene (I), zerumbone (II), and compound VII were examined at several temperatures. The spectrum of zerumbone shows the most remarkable changes and will be discussed first.



VII

At about 37°, the C-11 *gem*-methyl group of zerumbone appears as a broad singlet ($W_{1/2}$ = 3.3 Hz). At 75°, this signal is a sharp singlet ($W_{1/2}$ = 0.5 Hz). Below about 28°, the *gem*-methyl signal appears as a 1:1 doublet, with a relative chemical shift about 10 Hz at −10°. Overlapping broad peaks in the spectrum at 75°, assigned to the methylene groups in the molecule, are more complex at −10°. The vinylic hydrogens appear at 75° as a closely bunched overlapping group of lines assigned to the hydrogens 10, 9, and 6, and a slightly broadened triplet assigned to hydrogen 2. The triplet splitting is 8.5 Hz because of coupling with the two identical hydrogens on carbon 1. At −10°, the overlapping vinylic signals have modified somewhat while the triplet has become a doublet of doublets, with splittings 13.0 and 4.0 Hz, due presumably to coupling with the two hydrogens on carbon atom 1 which are no longer equivalent.

The free energy of activation for inversion in perdeuterioacetone is 15.8 ± 0.3 kcal/mol. The entropy of activation is 8.7 ± 2.7 eu, and the enthalpy of activation is 18.4 ± 0.8 kcal/mol. The free energy of activation is slightly solvent dependent as can be seen from the data in Table I. Addition of base or strong acid to aqueous methanolic solutions of zerumbone causes irreversible chemical changes.[8]

Table I. Free Energy of Activation (ΔF^*) for Conformational Inversion of Zerumbone

Solvent	Temp, °C	ΔF^*_T, kcal/mol
Perdeuterioacetone	28.5	15.9
Perdeuterioacetone	38.5	15.7
Deuteriochloroform	28.5	15.9
Perdeuteriomethanol	32.0	16.0
2:1 methanol-deuterium oxide	35.0	16.2
2:1 methanol-dilute acid	36.5	16.4

The spectrum of humulene in perdeuterioacetone at ambient temperature shows no sign of a slow conformational process, the *gem*-methyl group appearing as a sharp singlet. Below −81°, the *gem*-methyl signal splits to a narrowly spaced symmetrical doublet (δ 1.6 Hz at −87°). Because of solubility problems it was not possible to go much lower in temperature, so that while broadening of other signals was observed, these changes were not clear or complete by the lowest temperature reached. The free energy of activation for the process observed in humulene is 10.6 ± 0.3 kcal/mol at −81°. The slight solubility of humulene at low temperatures in the solvents used for zerumbone to determine solvent effects on the rate of inversion precluded any comparative study of solvent influences.

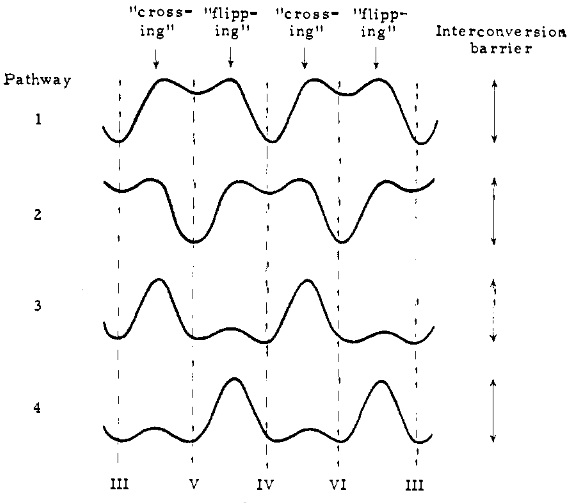


Figure 1. Possible potential-energy diagrams (qualitative) for the conformational process of humulene. In pathways 1 and 2 the crossing and flipping processes are shown as having equal energies although this is not necessary. The same is true for conformations III, IV, V, and VI in pathways 3 and 4.

The compound VII shows a sharp singlet for the *gem*-methyl group at ambient temperature which splits to a symmetrical doublet below −53° (δ 2.9 Hz at −75°). Again the peaks arising from the methylene groups in the molecule overlap at room temperature, but their appearance changes as the temperature is lowered to −75°. The spectra of the vinylic hydrogens 8, 9, and 10 are unaffected by temperature. The coupling of the vinylic hydrogen 2 does change but this is obscured by other signals. The free energy of activation for the process observed is 11.9 kcal/mol at −53°.

In each of the molecules studied, a conformational process is being observed, but it is difficult to be sure what processes or conformations are involved. It may equally well be (1) that III and IV are more stable relative to V and VI, (2) that V and VI are particularly stable relative to III and IV, (3) that all forms are of similar energy but the barrier to "crossing" is high, or (4) that all forms are of similar energy but the barrier to "flipping" is high. Potential-energy diagrams for these four situations are shown schematically in Figure 1. Each of the pathways represented could give rise to the observed spectra.

Some of these pathways seem less likely to be correct than others. Thus, because the barrier to double-bond flipping is expected to be high for reasons mentioned earlier, pathway 3 seems unlikely. Pathway 2 involves conformations which do not correspond to those found for the crystal and seems to be unlikely on this score.

For humulene, the barrier to inversion is similar to that for bond flipping in *trans*-cyclodecene, so for this compound, crossing of the inward-directed hydrogens

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(7) A. C. Cope and B. A. Pauson, *J. Amer. Chem. Soc.*, **87**, 3649 (1965).

(8) A. C. Cope, K. Banholzer, H. Keller, B. A. Pauson, J. J. Whang, and H. J. S. Winkler, *ibid.*, **87**, 3644 (1965).

in the 6 and 10 positions probably contributes little to the barrier, and the conformational changes seem best represented by pathway 4.

In the case of zerumbone, the barrier observed is much larger than would be expected for double-bond flipping, and much larger than is found for humulene itself. The effect of the keto group and the resultant cross-conjugated dienone should be to produce a system which is much more rigid than the 1,4-diene system of humulene. The interaction energy of hydrogens 6 and 10 during the "crossing" process should be larger, so that a conformational route similar to pathway 1 seems likely.

In the case of compound VII, the same conformational considerations hold as for I and II, because the hydrogen atom on carbon 10 and one of those on carbon atom 6 are directed inwards, in the conformation (similar to III and V) which appears most likely from an examination of models. The fact that the barrier is nearer in magnitude to that found in humulene than to that of zerumbone suggests that flipping of the *trans* double bond through the ring is the rate-determining step for inversion.

Bond flipping and the crossing of the inward-directed hydrogens are taken here to be two separate processes. Examination of models suggests that this may not necessarily be the case, for as the 2,3 bond flips through the ring, it comes very close to the hydrogens 6 and 10, which may rearrange themselves almost simultaneously to suit the bond flipping, and thus effectively give a one-step inversion. Bond flipping can proceed in two ways, with either the C-2 hydrogen or the C-3 methyl group passing inside the ring, with presumably the first possibility being much more likely.

The effect of solvents on the barrier to inversion of zerumbone is small, but it appears that the barrier is higher in more polar solvents. It can be postulated that in these solvents, for inversion to take place, some desolvation must occur and that this requires a small additional activation energy.

Experimental Section

Humulene,[3] zerumbone,[3] and VII[9] were available from previous studies. Nmr spectra were obtained using a Varian Associates A56/60A spectrometer equipped with a V6040 variable-temperature unit and C-1024 computer of average transients. The temperatures were calibrated with the hydroxyl chemical shifts of methanol and ethylene glycol samples. Spectra were taken of solutions about 0.5 *M* in solute with tetramethylsilane as internal reference. Solvents were commercially available and used without purification.

Free energies of activation were obtained in the usual way[10] from the coalescence of the signal of the *gem*-methyl group. In the case of II in perdeuterioacetone where a series of spectra over a wide temperature range was obtained, a computer-calculated line fit of the signals was made to obtain values for the rate constants as a function of temperatures. For this, a program written by G. M. Whitesides and F. J. Weigert based on the equations of Sack[11] was used. The enthalpy and entropy of activation for the process were obtained from the data in the usual way. Values of ΔF^* are estimated to be accurate to ±0.3 kcal/mol, and the errors quoted for ΔH^* and ΔS^* are from a root-mean-square treatment of the data at several temperatures.

The spectral parameters observed for the compounds I, II, and VII at the high-temperature limit in perdeuterioacetone solution follow.

I: δ 1.06 (6 H, s), $(CH_3)_2$ at C-11; 1.43 (3 H, m), 1.63 (3 H, m), CH_3 at C-3 and CH_3 at C-7; 1.82–2.23 (6 H, complex), H at C-1, C-4, and C-5; 2.48 (2 H, doublet, J = 7 Hz), H at C-8; 4.92 (1 H, broad triplet, J = 7.8 Hz), H at C-2; 5.18 (1 H, doublet, J = 16.8 Hz), H at C-10; 5.64 (1 H, doublet of triplets, J = 7.2, 16.8 Hz), H at C-9.

II: δ 1.17 (6 H, s), $(CH_3)_2$ at C-11; 1.58 (3 H, m) and 1.76 (3 H, m) CH_3 at C-3 and CH_3 at C-7; 2.03–2.50 (6 H, complex), H at C-1, C-4, and C-5; 5.36 (1 H, broad triplet, J = 8.5 Hz), H at C-2; 5.9–6.25 (3 H, complex), H at C-6, C-9, and C-10.

VII: δ 1.11 (6 H, s), $(CH_3)_2$ at C-11; 1.27 (3 H, m), and 1.76 (3 H, m), CH_3 at C-3 and CH_3 at C-7; 1.78–2.33 (8 H, complex), H at C-1, C-4, C-5, and C-6; 5.06 (1 H, doublet, J = 16.8 Hz), H at C-10; 5.69 (1 H, doublet, J = 9.25 Hz), H at C-8; 6.14 (1 H, doublet of doublets, J = 9.25, 16.8 Hz), H at C-9.

The spectrum of the protons 8, 9, and 10 of VII was not first order, and was analyzed with the aid of the LAOCOON program.[12]

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[9] S. Dev, to be published.

[10] L. W. Reeves, *Advan. Phys. Org. Chem.*, 3, 187 (1965).

[11] R. A. Sack, *Mol. Phys.*, 1, 163 (1958).

[12] S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 41, 3863 (1965).