position of the product after conversion to hydrocarbons was largely **14a** (60%) with smaller amounts of **1c** (20%) and **2** (10%); the remainder was a complex mixture of low molecular weight hydrocarbons.

Lithium Aluminum Hydride Reduction of Perhydroamphotericin B. Isolation of 3,5-Dimethyldocosane (14b). Perhydroamphotericin B (1 g) was refluxed 24 hr with lithium aluminum hydride (2 g) in THF (160 ml). The excess lithium aluminum hydride was destroyed by slow addition of water (20 ml) diluted with THF (50 ml). The mixture was filtered and the filter cake was dissolved in 5% sulfuric acid (250 ml) at − 5° while 1-butanol (250 ml) was added simultaneously. The layers were separated and the aqueous layer was extracted as rapidly as possible with two 250-ml portions of cold 1-butanol. The combined butanol extracts were washed with sodium bicarbonate solution until neutral and then with water, and evaporated to dryness. A solution of the resulting polyol (1.3 g) in methanol (75 ml) was treated with a solution of periodic acid (1.95 g) in water (26 ml) and allowed to stand for 5 min before work-up as described previously (part B of periodic acid oxidations) and conversion to hydrocarbons. The major product (60%) was identified as 3,5-dimethyldocosane (**14b**) on the basis of its mass spectrum (Figure 5b); a minor product (20%) was **14a**. A small amount of the C_{41} hydrocarbon **1c** was also present.

Alkaline Treatment of Perhydroamphotericin B. A solution of perhydroamphotericin B (1 g) in methanol (20 ml) and water (40 ml) containing 600 mg of sodium hydroxide was heated on a steam bath for 15 min. It was cooled, diluted with water (100 ml), and extracted with two 250-ml portions of 1-butanol. The butanol extracts were washed with water until the washings were neutral and then evaporated to dryness. The residue was reduced with lithium aluminum hydride and converted to hydrocarbons as described previously. Vpc analysis revealed a complex mixture of more than 20 products. Two were clearly predominant, constituting roughly one-quarter of the total and present in a relative ratio 2:1. The major hydrocarbon was **14b**, identical with the major product of lithium aluminum hydride reduction of perhydroamphotericin followed by periodate cleavage described above, and the other on the basis of its mass spectrum was **14c**.

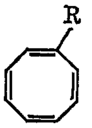
Nuclear Magnetic Resonance Spectroscopy. Ring Inversion in 3,5,7-Cyclooctatrienone[1a]

Camille Ganter, Sanford M. Pokras,[1b] and John D. Roberts

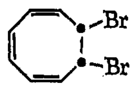
Contribution No. 3358 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. *Received March 31, 1966*

Abstract: The rate of ring inversion in 3,5,7-cyclooctatrienone was determined by the temperature dependence of the nmr spectrum of the methylene protons adjacent to the carbonyl group. Inversion does not occur by rapid reversible formation of hydroxycyclooctatetraene because deuterium exchange of the methylene protons is much too slow for the operation of such a mechanism. It is suggested that a nearly planar transition state is involved. The activation energy for ring inversion was determined to be 11.9 ± 0.5 kcal/mole.

The rates and activation energies of bond shift and/or ring inversion in cyclooctatetraene (I),[2] fluorocyclooctatetraene (II),[3] and *cis*-1,2-dibromo-3,5,7-cyclooctatriene (III)[4] have been determined by nuclear magnetic resonance spectroscopy. We report here a similar investigation of ring inversion of 3,5,7-cyclooctatrienone (IV)[5,6] from the temperature dependence of its proton nmr spectrum.

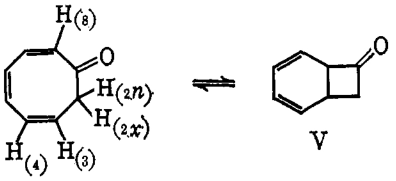


I, R=H
II, R=F



III

A possible complication in the study of ring inversion of IV arises from the fact that infrared[5] and nmr measurements[7] indicate that at equilibrium at 20° IV contains about 5% of the valence tautomer V. However, the proportion of IV decreases rapidly with decreasing temperature[7] and the equilibrium between IV and V is established rather slowly.[7] For this reason,



IV
V

we have assumed that the equilibrium IV ⇄ V has no appreciable effect on the rate of ring inversion of IV.

The temperature dependence of the proton nmr spectrum of IV was studied with the aid of a Varian Model HR-60 spectrometer equipped with a special low-temperature probe using a 25% by volume solution of IV in carbon disulfide with tetramethylsilane (TMS) as internal standard.

The spectrum of IV at room temperature (Figure 1a) shows a doublet (two protons) centered on δ 2.97, assigned to the protons on C(2); a quartet (one proton), split further, and centered on δ 5.77, assigned to the proton on C(3); and a complex jumble of lines (five

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[1] (a) Supported in part by the National Science Foundation; (b) participant in the Undergraduate Research Program of the National Science Foundation.

[2] F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 671 (1962); F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *ibid.*, **86**, 3576 (1964).

[3] D. E. Gwynn, G. M. Whitesides, and J. D. Roberts, *ibid.*, **87**, 2862 (1965).

[4] R. Huisgen and G. Boche, *Tetrahedron Letters*, No. 23, 1769 (1965).

[5] A. C. Cope and B. D. Tiffany, *J. Am. Chem. Soc.*, **73**, 4158 (1951).

[6] We wish to thank Dr. A. G. Anastassiou of the Central Research Dept. of E. I. du Pont de Nemours and Co. for the sample of 3,5,7-cyclooctatrienone used in this work: *cf.* A. G. Anastassiou, *J. Am. Chem. Soc.*, **87**, 5512 (1965).

[7] R. Huisgen, F. Mietzsch, G. Boche, and H. Seidl, Special Publication No. 19, The Chemical Society, London, 1965, pp 3–20.

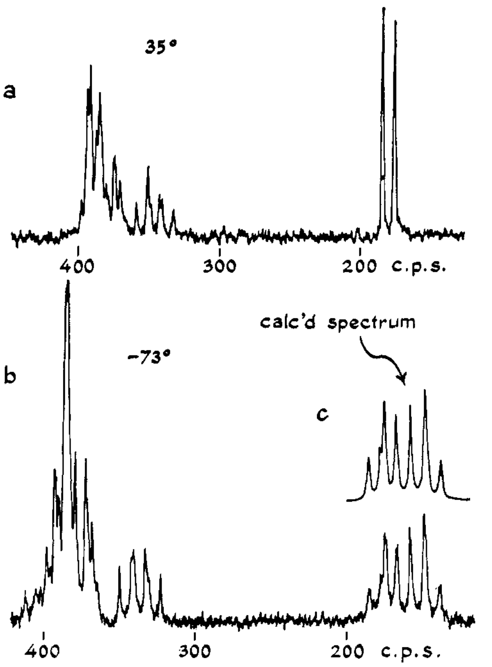
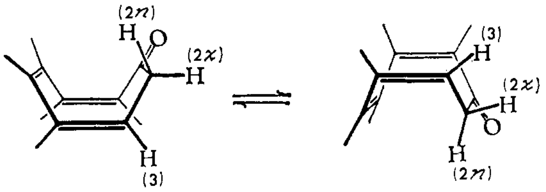


Figure 1. (a) Observed spectrum of 3,5,7-cyclooctatrienone at 35°, (b) observed spectrum of 3,5,7-cyclooctatrienone at −73°, and (c) calculated AB part of frozen-out ABX spectrum.

protons) between δ 6.1 and 6.6 assigned to the protons on C(4) through C(8).

At temperatures above −20°, the rate of inversion is sufficiently rapid that only a doublet resonance is observed for the two C(2) protons (Figure 1a). This doublet corresponds roughly to the AB part of an ABX spectrum [A = H(2*n*), B = H(2*x*), X = H(3)] with $\delta_{AB} \sim 0$ as would be expected for interchange of the magnetic environments of the C(2) protons by ring inversion as shown in eq 1. As the temperature is



(1)

lowered, the doublet coalesces and at −43 to −44° a broad singlet is observed. At still lower temperatures, the signal of the protons at C(2) sharpens to take the appearance of the AB part of an ABX spectrum with $\Delta\nu_{AB} \sim 25$ cps (Figure 1b). No further change occurs below −80°.

The three-spin ABX-type system with slow inversion was analyzed with the aid of the computer program developed by Ferguson[8] on the assumption that the effect of the coupling between the X proton on C(3) and the protons on C(4) through C(8) could be neglected for the AB part of the spectrum. The parameters which gave good agreement for the AB part of the spectrum were $\nu(2n) = 165.4$, $\nu(2x) = 190.7$, $\nu(3) = 344.0$, $J(2n, 2x) = -10.0$, $J(2n, 3) = 9.0$, and $J(2x, 3) = 7.2$ (all values in cps with chemical shifts from TMS as internal standard). The observed and calculated spectra with these parameters are compared in Figures 1b and c.

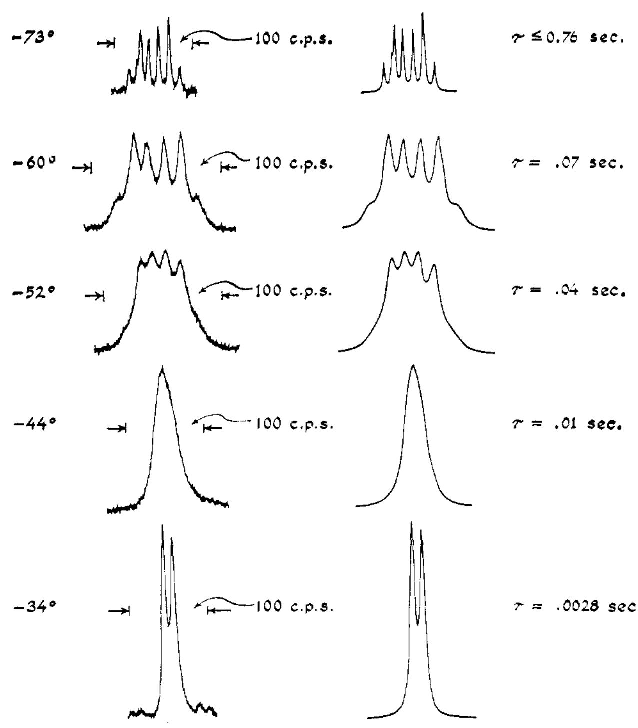


Figure 2. Observed (left) and calculated (right) spectra of the AB part [H(2*n*), H(2*x*)] of 3,5,7-cyclooctatrienone as a function of τ.

Trial calculated spectra with $J(2n, 8)$ and $J(2x, 8)$ assigned values from 0 to 1 cps, $J(2n, 4)$ from 0 to −1.7 cps, and $J(2x, 4)$ from 0.2 to 1.1 cps[9] showed no significant changes in the AB part of the spectrum other than small broadening effects.

The assignment of the *endo* proton H(2*n*) giving resonance at higher field than the *exo* proton H(2*x*) is based on an expected substantial shielding effect of the C(3)–C(4) double bond. Such an effect has been observed for *cis*-1,2-dibromo-3,5,7-cyclooctatriene (III).[4]

For the tub structure (see eq 1), if the bond angles are taken to have their normal values, the carbonyl bond bisects the angle between the C(2) protons. The dihedral angle is then approximately 10° between H(3) and H(2*n*) and approximately 130° between H(3) and H(2*x*). The Karplus relation[10] between dihedral angles and vicinal proton–proton coupling constants indicates that, for the actual couplings, $J(2n, 3)$ and $J(2x, 3)$, the dihedral angles are likely to be somewhat larger than 10 and 130°. Study of models shows that a bending of the carbonyl bond approximately 10° outward to a more equatorial-like position results in changing the dihedral angles at the 2 and 3 positions to more reasonable values; the resulting distorted tub form is quite likely to be energetically more favorable than the simple structure because the distortion moves the carbonyl bond closer to coplanarity with the C(7)–C(8) double bond.

Spectra were taken from −85 to +35° in order to evaluate the activation energy, E_a, for ring inversion. The rate of inversion at each temperature was deter-

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[8] R. C. Ferguson and D. M. Marquardt, *J. Chem. Phys.*, 41, 2087 (1964).

[9] These signs and values for the allylic coupling constants, $J(2n,4)$ and $J(2x, 4)$, were chosen in accordance with dihedral angles estimated from models using the theoretical treatment of long-range proton spin–spin coupling across four bonds in unsaturated hydrocarbons proposed by M. Barfield, *ibid.*, 41, 3825 (1964).

[10] M. Karplus, *ibid.*, 30, 11 (1959).

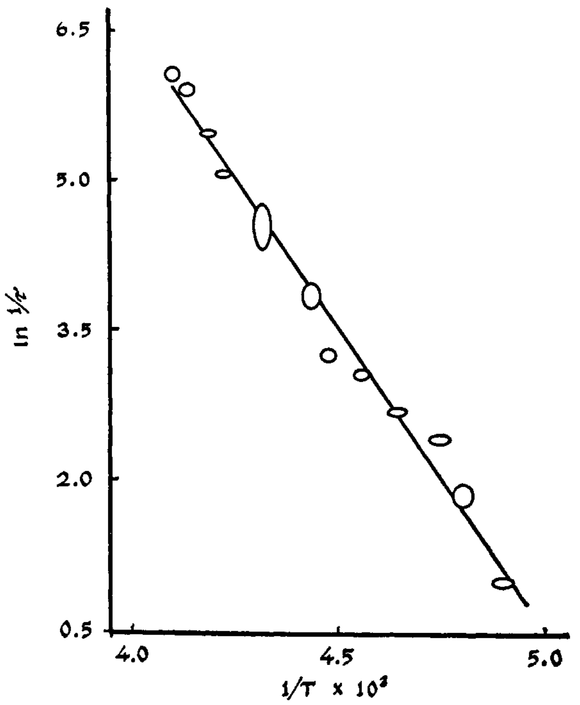

Figure 3. Arrhenius plot for inversion process. The points are shaped to accord with the estimated uncertainties in temperature or in matching curves to obtain τ.

mined with the aid of calculated theoretical spectra having various values of the mean half-life (τ) calculated by means of a Fortran IV coded program.[11] In each case, τ was adjusted until the theoretical spectra were as nearly superimposable as possible on the observed spectra. Representative observed and calculated spectra are shown in Figure 2. An activation energy of E_a = 11.9 ± 0.5 kcal/mole for the inversion process was obtained from a least-squares fit to the Arrhenius plot of Figure 3. It is interesting to compare this value with energies for bond shift in cyclooctatetraene (13.7 kcal)[2] and fluorocyclooctatetraene (~12 kcal),[3,12] and for inversion in cyclooctatetraenyldimethylcarbinol (14.7 kcal)[2] and *cis*-1,2-dibromo-3,5,7-cyclooctatriene (13 kcal).[4,12]

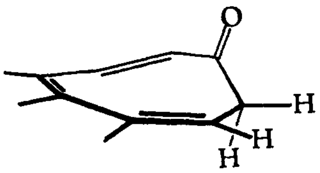

Figure 4. Possible transition state for inversion of 3,5,7-cyclooctatrienone.

The possibility that the inversion of IV might occur by a facile equilibration with hydroxycyclooctatetraene (VI) was ruled out by the finding that IV does not undergo deuterium exchange easily; in fact, extensive exchange was observed only after 35 min in a refluxing solution of dioxane containing a 20 molar excess of 5% sodium deuterioxide in deuterium oxide. Five protons were replaced by deuterium, those at C(2), C(4), C(6), and C(8).

IV VI

A possible transition state for ring inversion of IV, suggested by Fieser models, is shown in Figure 4 wherein the three double bonds are almost coplanar. For such a transition state some gain of conjugation energy might well compensate the increase in strain energy. A similar inversion process is probably also effective in *cis*-1,2-dibromo-3,5,7-cyclooctatriene (III).

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(11) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, 43, 602 (1965). This program was adapted for our use by Dr. J. T. C. Gerig.

(12) This value is for the free energy of activation.