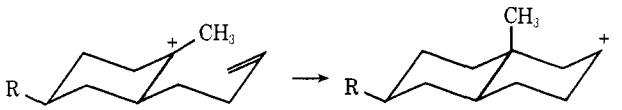
Alicyclic Cations in Biogenetic-Like Olefin Cyclizations

Sir:

Many examples of stereoselective synthesis of polycyclic fused-ring compounds by nonenzymic, cationic cyclization of polyolefins are known.[1,2] The potential involvement of alicyclic cations (*e.g.*, **1**) as short-lived intermediates in such reactions has been the subject of considerable discussion.[1,2a,3-6] If alicyclic cations are intermediates, the observed stereoselectivity can be rationalized only if attack of the olefinic double bond on the cationic center occurs with a high preference for formation of an equatorial C–C bond (**1** → **2**). The

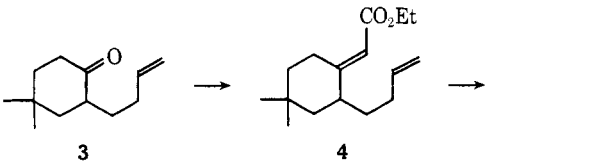


1 **2**

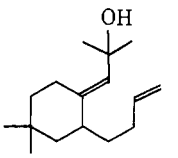
observation that reaction of solvent and other nucleophiles with intermediates derived from acid treatment of cyclohexanol systems gives both axial and equatorial attack[7] has been considered evidence against selectivity of this type.

On the basis of modern concepts of conformational analysis and organic transition state structures, we have presented arguments[8] that the intramolecular attack of a double bond on a conformationally rigid cyclohexyl cation such as **1** should be expected to lead to stereoselective formation of a trans fused ring system. We now report the initial results of our cyclization studies with alcohol **5** which offer the first direct evidence in support of the above proposition.

Alkylation of 4,4-dimethylcyclohexanone[9] with 4-bromobutene using Stork's metalloenamine procedure[10] gave the alkylated ketone **3**[11a] in 77% yield (95% pure by vpc; oxime mp 83–83.5°[11b]) after distillation[12] at 86° (0.18 mm). Treatment of this ketone with a fourfold excess of the magnesium salt of ethoxyethyne followed by acid hydrolysis[13] and distillation[12] at 105° (0.05 mm) gave α,β-unsaturated ester **4** in 90% yield.[11] The *E* configuration for the exocyclic double bond is predicted on the basis of steric arguments[14] and is supported by the nmr spectrum of this compound, which shows absorption for the 6-equatorial proton as a doublet of triplets at δ 3.75 ppm.[15] Addition of excess methylmagnesium bromide to ester **4**, followed by a neutral aqueous workup[16] to minimize dehydration, gave alcohol **5** in quantitative yield.[13a] This



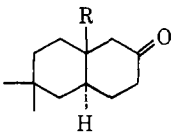
3 **4**

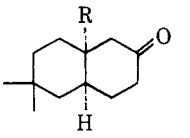


5

material was not stable to distillation and was used directly for cyclization studies.

Treatment of alcohol **5** with anhydrous formic acid at room temperature for 30 min effected cyclization to bicyclic products in high yield. Removal of hydrocarbon products by preparative tlc gave bicyclic formates,[11a] ir (film) 1720 cm^{-1}, in 85% yield. Vapor phase chromatography[17a] showed two predominant peaks with an area ratio of >85:15. Cleavage of the formate group followed by oxidation with Jones reagent[18] gave a mixture consisting primarily of ketones **6** and **7** in 70% overall yield from alcohol **5**. Vapor phase chromatography[17b] showed the ratio of peak areas to be ~90:10. Recrystallization gave pure trans ketone **6**, mp 73.5–74°.[11]





6, R = CH=CMe$_2$ **7**, R = CH=CMe$_2$
8, R = CN **9**, R = CN
10, R = COOH **11**, R = COOH

The structure and stereochemistry of ketones **6** and **7** were established by comparison with compounds of known stereochemistry. Authentic *trans*- and *cis*-6,6-dimethyl-9-carboxy-2-decalone (**10** and **11**) were

(1) For reviews of some extensive investigations see: W. S. Johnson, *Accounts Chem. Res.*, 1, 1 (1968); E. E. van Tamelen, *ibid.*, **1**, 111 (1968).

(2) For some recent papers in this area see: (a) D. J. Goldsmith and C. F. Phillips, *J. Amer. Chem. Soc.*, **91**, 5862 (1969); (b) G. Stork and P. A. Grieco, *ibid.*, **91**, 2407 (1969); (c) E. E. van Tamelen and J. W. Murphy, *ibid.*, **92**, 7204 (1970); (d) K. B. Sharpless, *ibid.*, **92**, 6999 (1970); (e) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *ibid.*, **93**, 4332 (1971); (f) R. E. Ireland, M. I. Dawson, J. Bordner, and R. E. Dickerson, *ibid.*, **92**, 2568 (1970), and references cited within these papers.

(3) G. Stork and A. W. Burgstahler, *ibid.*, 77, 5068 (1955).

(4) (a) W. S. Johnson, *Trans. N. Y. Acad. Sci., II*, **29**, 1001 (1967); (b) W. S. Johnson and J. K. Crandall, *J. Org. Chem.*, 30, 1785 (1965).

(5) E. E. van Tamelen and J. P. McCormick, *J. Amer. Chem. Soc.*, **91**, 1847 (1969).

(6) A. Eschenmoser, D. Felix, M. Gut, J. Meier, and P. Stadler in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Connor, Ed., J. and A. Churchill, Ltd., London, 1959.

(7) Two studies which show preferential axial attack on intermediates derived from acid treatment of tertiary cyclohexanols are (a) S. D. Elakovich and J. G. Traynham, *Tetrahedron Lett.*, 1435 (1971); (b) P. J. Beeby and S. Sternhell, *Aust. J. Chem.*, **25**, 809 (1971).

(8) (a) K. E. Harding, Ph.D. Thesis, Stanford University, 1968; (b) K. E. Harding, *Bioorg. Chem.*, submitted for publication.

(9) R. F. Miller and R. Adams, *J. Amer. Chem. Soc.*, **58**, 787 (1936); E. B. Reid and T. E. Gompf, *J. Org. Chem.*, **18**, 661 (1953).

(10) *Cf.* G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(11) (a) The ir and nmr data obtained for this compound were consistent with the assigned structure. (b) A satisfactory elemental analysis was obtained for this compound.

(12) Evaporative bulb-to-bulb distillation using a Büchi kugelröhrofen.

(13) G. Stork, A. Meisels, and J. E. Davies, *J. Amer. Chem. Soc.*, **85**, 3419 (1963).

(14) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); C. Szantay, L. Töke, and P. Kolonits, *J. Org. Chem.*, **31**, 1447 (1966).

(15) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, 31, 3128 (1966).

(16) J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **88**, 3408 (1966).

(17) (a) 0.25 in. × 6 ft 10% SE-30 column at 178°; (b) 0.25 in. × 6 ft Carbowax 20M column at 189°.

(18) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

synthesized using procedures developed by Nagata.[19] Hydrocyanylation of 6,6-dimethyl-$\Delta^{1,9}$-2-octalone[11,20] with potassium cyanide and ammonium chloride in dimethylformamide gave two cyano ketones, mp 66–66.5°[11] and mp 83–83.5°,[11] in a ratio of 5:2 after separation by preparative tlc. Hydrocyanylation using triethylaluminum and hydrogen cyanide gave the same products in a ratio of 17:1 by vpc analysis. On the basis of the close analogy of these results to those obtained by Nagata with $\Delta^{1,9}$-2-octalone, the major product, mp 66–66.5°, is assigned the trans configuration **8**. The cyano ketones were converted to the trans ketoacid **10**, mp 85–86°,[11] and cis ketoacid **11**, mp 120–121°,[11] by alkaline hydrolysis using the procedures reported by Nagata.

Ozonolysis of ketone **6** followed by oxidation of the ozonide with Jones reagent[21] gave a ketoacid, mp 85–86°, identical (melting point, ir, and nmr) with the authentic trans acid **10**. A sample consisting predominantly of a 50:50 mixture of ketones **6** and **7** was ozonized and the acidic product was esterified with diazomethane. Vapor phase chromatography of this material showed two peaks with retention times identical with those of the methyl esters of acids **10** and **11**.

The absence of dehydration–reprotonation reactions in the cyclization was shown by conducting the cyclization in the presence of deuterium. Ketones **6** and **7** isolated from a cyclization with deuteriotrifluoroacetic acid at −78° were shown by mass spectrometric analysis (comparison of P, P + 1, and P + 2 ions) to contain no more deuterium than material isolated from a similar cyclization with trifluoroacetic acid.

The results obtained with alcohol **5** show that generation of a decalin ring system by intramolecular attack of a monosubstituted double bond on a conformationally rigid cyclohexyl ring system with one sp^2-hybridized carbon is highly stereoselective. It should be noted that cyclizations in which the double bond is a nonterminal double bond or in which axial substituents are present on the six-membered ring should exhibit even greater stereoselectivity than shown in the present case.[8b,22]

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(19) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.*, **11**, 226 (1963).

(20) We thank Mr. Chung-ye Tseng for preparing this compound from the pyrollidine enamine of 4,4-dimethylcyclohexanone and methyl vinyl ketone.

(21) A. S. Narula and Sukh Dev, *Tetrahedron Lett.*, 1733 (1969).

(22) Our results suggest that formation of cis fused products in relatively high proportion in some previous studies[23] may be a result of elimination to a cyclohexenyl system from which concerted protonation–cyclization leading to cis products[3] competes with reprotonation to the cation.[8b]

(23) *Inter alia* R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Amer. Chem. Soc.*, **94**, 2056 (1972); P. T. Lansbury, P. C. Briggs, T. R. Demmin, and G. E. DuBois, *ibid.*, **93**, 1311 (1971); P. T. Lansbury and G. E. DuBois, *Chem. Commun.*, 1107 (1971).

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Mechanisms of Photochemical Reactions in Solution. LXXVII. A New Method for the Determination of Intersystem Crossing Yields[1]

Sir:

We describe a new technique for the determination of intersystem crossing quantum yields in fluid solution and report some preliminary results obtained with this technique. The method is a combination of two previously reported procedures: the sensitized cis–trans isomerization method of Lamola and Hammond[2] and the flash spectroscopic method of Wilkinson and coworkers which utilizes heavy-atom enhancement of intersystem crossing.[3] While the method described here is applicable to most aromatic compounds, it is especially useful for substituted benzenes, compounds for which the two previously mentioned techniques are only marginally applicable.[4]

Our experimental procedure involves measurement of relative fluorescence intensities of an aromatic compound A and relative yields for isomerization of a "triplet counter" C in solutions with constant concentrations of A and C but with varying concentrations of heavy-atom fluorescence quencher H. The processes of interest are shown in the kinetic scheme below.

$$A_0 \xrightarrow{h\nu} A^{*(1)} \quad (1)$$

$$A^{*(1)} \xrightarrow{k_2} A_0 + h\nu' \quad (2)$$

$$A^{*(1)} \xrightarrow{k_3} A_0 \quad (3)$$

$$A^{*(1)} + C \xrightarrow{k_4} A_0 + C \quad (4)$$

$$A^{*(1)} \xrightarrow{k_5} A^{*(3)} \quad (5)$$

$$A^{*(1)} + H \xrightarrow{k_6} A^{*(3)} + H \quad (6)$$

$$A^{*(3)} \xrightarrow{k_7} A_0 \quad (7)$$

$$A^{*(3)} + C \xrightarrow{k_8} A_0 + C^{*(3)} \quad (8)$$

$$C^{*(3)} \xrightarrow{k_9} C \quad (9)$$

$$C^{*(3)} \xrightarrow{k_{10}} T \quad (10)$$

We carried out experiments with 0.05–0.10 *M* *cis*-2-pentene as the triplet counter and monitored the appearance of *trans*-2-pentene (T) by glpc. The heavy-atom fluorescence quencher was xenon, which has been shown to quench singlets by inducing intersystem crossing.[3]

The effect of fluorescence quenching by C in the absence of H is given by eq 11.[6,7] Equation 12 de-

(1) Part LXXVI: G. F. Vesley and G. S. Hammond, *J. Amer. Chem. Soc.*, submitted for publication.

(2) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

(3) A. R. Horrocks and F. Wilkinson, *Proc. Roy. Soc., Ser. A*, **306**, 257 (1968), and references cited therein.

(4) The limitations of the Lamola–Hammond method have been discussed.[5] The procedure of Horrocks and Wilkinson[3] cannot be used for benzene derivatives because they generally do not show triplet–triplet absorption in flash spectroscopy.

(5) W. Ferree, Jr., J. B. Grutzner, and H. Morrison, *J. Amer. Chem. Soc.*, **93**, 5502 (1971), and references cited therein.

(6) Values of k_4 ranged from *ca.* 10^7 M^{-1} sec^{-1} (mesitylene) to *ca.* 10^8 M^{-1} sec^{-1} (anisole).

(7) F' and F^0 are the fluorescence intensities of A with and without C; τ_f' and τ_f^0 are the corresponding singlet lifetimes. Y_T' is the yield of T in the absence of H. F, τ_f, and Y_T refer to quantities with both C and H present.