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(12) Cf., inter alia: (a) J. T. Edward and J.-M. Ferland, *Can. J. Chem.*, **44**, 1317 (1966); (b) H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C*, 2459 (1967); (c) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970). See also: (d) B. M. Trost and T. N. Salzmann, *J. Chem. Soc., Chem. Commun.*, 571 (1975); (e) G. W. Schaffer, E. H. Eschinasi, K. L. Purzycki, and A. B. Doerr, *J. Org. Chem.*, **40**, 2181 (1975).

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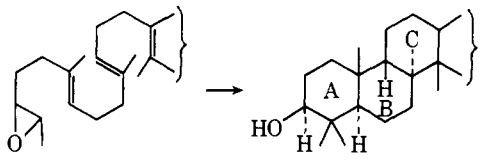
Overall Mechanism of Terpenoid Terminal Epoxide Polycyclizations[1]

Sir:

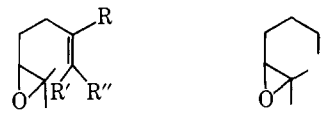
Past studies have revealed that in the nonenzymic generation of the AB[2] and ABC[3] ring systems of polycyclic terpenoids (including the lanosterol type) from polyene terminal epoxides (e.g., **1** → **2**), cyclizations do not proceed through partially



1 **2**

cyclized intermediates with newly formed π bonds requiring protonation for further reaction, or through equilibrating mono- and bicyclic carbonium ion conformers or other related species, but are more concerted, possibly involving intermediate "frozen" carbonium ions or ion pairs. We present herein a new body of results which, taken together with certain other considerations, (1) indicate that the A ring is formed with a high degree of neighboring π-bond participation during S_N2-like epoxide ring opening, and (2) suggest that the overall annulation process is not completely concerted, but involves a series of conformationally rigid carbocyclic cationic intermediates.[4] These conclusions are incorporated into an overall picture which represents the most detailed mechanistic interpretation to date of this fundamental cyclization process, a notable example of which is the biological conversion of squalene 2,3-oxide (**3**) to lanosterol (**4**) (Scheme I).

Anchimeric assistance in the epoxide ring opening process is revealed by comparison of the reaction rates of diene monoepoxides, e.g., **5a**[5] and **5b**, with saturated counterparts. For example, under conditions (8.65×10^{-4} M $SnCl_4$ in benzene at 5–7 °C) similar to those where under total polyene epoxide cyclization can be as high as 67%,[6] epoxide **6** is >90% recov-

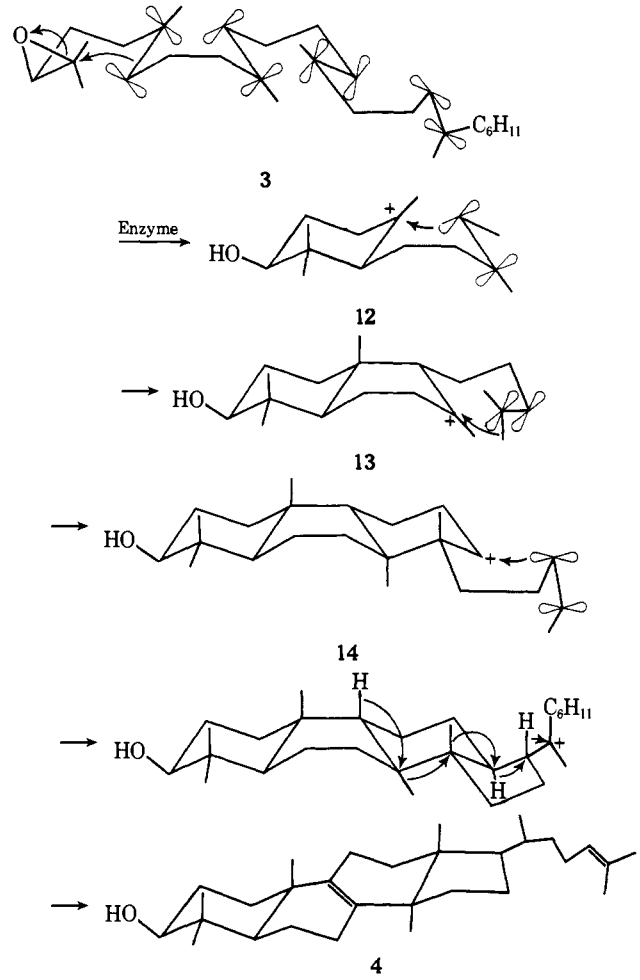


5 **6**

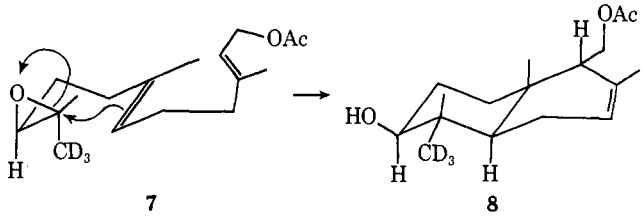
a, R = CH_3; R' = R'' = H
b, R = H; R' = R'' = CH_3
c, R = R'' = CH_3; R' = H

ered after 15 h, while the unsaturated epoxide **5b** reacts completely within 5 min[7] (competitive rates of disappearance of substances in the same vessel). In support of a concerted process, the 12,12,12-trideuterio-10,11-oxido-*trans,trans*-farnesyl acetate racemate, in which the 10-H and 11-CD_3 are cis (**7**),[8] cyclizes under conditions already described[6c] to a trideuteriohydroxydriminol (**8**) in which, as in the enzymic cycliza-

Scheme I

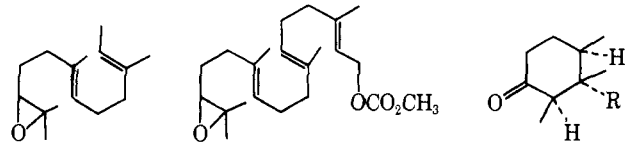


tion,[10] the isotopically labeled methyl group has maintained its stereochemical integrity and appears as an 4α-substituent, as revealed by the absence in **8** of the δ 0.98 ($CDCl_3$, 100 Hz) NMR signal assigned to the corresponding 4α-methyl in the undeuterated case.[9]



7 **8**

In an attempt to detect participation of additional π bonds in systems of the type where bicyclization and tricyclization can be extensive,[6] the rate of disappearance of diene monoepoxide **5c**[11] was compared (as in **5b**/**6** above) with that of triene monoepoxide **9**[11] and of tetraene monoepoxide **10**.[6b] Half-lives for **5c**, **9**, and **10** were ~75, 100, and 100 min, respectively, with rate ratios **5c**/**9** = 1.4 ± 0.1 and **5c**/**10** = 1.3 ± 0.2. Under these conditions, the total yield of cyclization product from, e.g., **10**, was ≥57% (>20% of previously described tricycles[6b] and 37% of 2,3,4-trimethylcyclohexanone(**11**), resulting from monocyclization and subsequent



9 **10** **11**

rearrangement). In the cyclization of epoxides **9** and **10**, no substances other than starting material and final cyclization products can be detected by VPC means. Also, monocarbocyclic olefin and bridged ether,[6c,d] potential intermediates generated by partial cyclization of starting epoxide, are not converted to higher cyclization products under conditions where epoxide is transformed to such materials.

In regard to nonenzymic epoxide cyclizations, entropy considerations, although suggesting no exceptional barrier to the formation of the first six-membered ring by the assisted opening of the oxide unit, render less likely an entirely concerted single transition state reaction in which two or more rings are formed. Further, except for the remote possibility that in the polycyclization of epoxide **9** or **10** a less favorable $\Delta S^{\ddagger}$ for the concerted process is fortuitously compensated by a decreased $\Delta H^{\ddagger}$, so as to maintain the same rate as that of **5c**, the rate findings above signify that additional π bonds do not participate in this overall polycyclization. Similarly, in the enzymic cyclization of squalene 2,3-oxide, we surmise that the entropic control by the enzyme must be less than maximal, as indicated by the fact that the biological conversion to lanosterol-type product is not markedly affected by replacement in squalene oxide of (1) the *cis*-1-CH_3 by C_2H_5,[12] (2) 6-,[13,14] 10-,[15] or 15-CH_3[16] by H, (3) γ,γ-dimethylallyl terminus by H,[17] or (4) saturation of the Δ^{18} π bond,[18] structural changes which would have had a more profound adverse affect on the cyclization, were a perfect "lock and key" arrangement of substrate and enzyme mandatory.

Even under circumstances (e.g., in an enzyme system) where all parts of the starting material are rigidly held and positioned for reaction as well as possible without increasing the energy through buildup of intermolecular repulsive interactions, a single transition state for a complex polycyclization seems, in the strictest sense, implausible—the principle that molecular motion is slower than electronic motion clearly signifies that interruptions in the overall reaction course will occur whenever movements associated with reaction in one area of the large starting molecule are not suitable for, and entirely synchronous with, motions required for reaction in another, distant area, in fact an inescapable circumstance. Thus, all the foregoing considerations force us to conclude that the oxide-triggered polycyclization proceeds specifically through particular ground-state carbocyclic carbonium ion conformers which, enroute to higher polycycles, do not undergo equilibration with other conformers unsuitably disposed for conversion to the same end products.

The enzymic and nonenzymic transformations leading to the lanosterol system also compare closely with respect to: the nature of the starting material; electronic mechanism, a cationic process which includes initiation by epoxide opening, cyclization, and the characteristic twofold hydrogen and methyl migrations preceding final proton loss; and gross structure, as well as stereochemistry, of the complex cyclization product.[6] For these various reasons, we believe that the overall mechanistic pathways, including conformational behavior, of the enzymic and nonenzymic cyclization routes are fundamentally equivalent and thus propose that steps **3** → **12** → **13** → **14** operate in the biological process.[19,20]

Acknowledgment. The authors are grateful to the National Institutes of Health (GM 10421) and the National Science Foundation (CHE 75-17622) for grant support, to Professor J. Brauman for valuable discussion, and to Dr. L. Durham for assistance with NMR spectral determinations.

References and Notes

(1) Presented in part at the Organic Chemistry Centennial Symposium, 171st National Meeting of the American Chemical Society, New York, N.Y., April 5–9, 1976.
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(4) Mechanistic considerations based on studies of terpenoid terminal epoxide cyclizations do not necessarily apply to other types of nonenzymic conversions of polyenes to polycycles. For example, in certain bicyclizations where allylic hydroxyl is the leaving group, acceleration by the more distant unsaturated center has been observed (P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkmann, *J. Am. Chem. Soc.*, **95**, 7502 (1973)).
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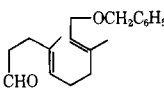
(8) Synthesis:



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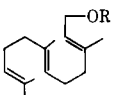
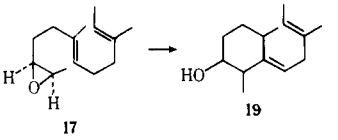


16
(trans,trans,trans)

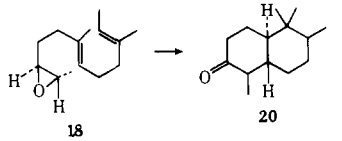
a, R = $CH_2C_6H_5$; R′ = $CO_2C_2H_5$
b, R = $CH_2C_6H_5$; R′ = CD_2OH
c, R = $CH_2C_6H_5$; R′ = CD_3
d, R = $COCH_3$; R′ = CD_3

15 → **16a**: $(C_6H_5)_3PC(CH_3)CO_2C_2H_5$
16a → **16b**: AlD_3
16b → **16c**: $CH_3SO_2Cl/(C_2H_5)_3N$; AlD_3
16c → **16d**: Li/NH_3; $(CH_3CO)_2O/C_5H_5N$
16d → **7**: NBS/H_2O—THF; K_2CO_3

(9) In keeping with this mechanistic trend, J. P. McCormick discovered (unpublished results, Stanford University) that *cis*- and *trans*-epoxides **17** and **18** gave rise, under otherwise identical conditions, to two different major cyclization products, assigned structures **19** and **20** on the basis of NMR spectral analysis.

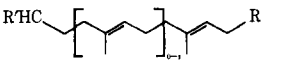


17 19



18 20

(10) K. J. Stone, W. R. Roeske, R. B. Clayton, and E. E. van Tamelen, *Chem. Commun.*, 530 (1969).
(11) Polyene epoxides **5c**, **9**, **17**, and **18** were prepared according to the general route:



a, R = $OCOCH_3$; R′ = $(CH_3)_2C$
b, R = $OCOCH_3$; R′ = $(CH_3)_2CO$
c, R = $OCOCH_3$; R′ = $(CH_2O)_2$
d, R = H; R′ = $(CH_2O)_2$
e, R = H; R′ = O

a → **b**: NBS/H_2O—THF
b → **c**: aq $HClO_4$; aq $NaIO_4$; $(CH_2OH)_2/H^+$
c → **d**: $Li/C_2H_5NH_2$
d → **e**: aq H^+
e → ; $(C_6H_5)_2SCR''$, R′′′

(12) E. E. van Tamelen, R. B. Clayton, and O. Crosby, *Chem. Commun.*, 532 (1969).
(13) (a) E. E. van Tamelen and J. H. Freed, *J. Am. Chem. Soc.*, **92**, 7206 (1970); (b) E. E. van Tamelen, J. A. Smaal, and R. B. Clayton, *ibid.*, **93**, 5279 (1971).
(14) E. J. Corey, A. Krief and H. Yamamoto, *J. Am. Chem. Soc.*, **93**, 1493 (1971).
(15) E. E. van Tamelen, R. P. Hanzlik, R. B. Clayton, and A. L. Burlingame, *J. Am. Chem. Soc.*, **92**, 2137 (1970).
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(19) For previous stereochemical interpretations of lanosterol biosynthesis, see G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(20) In many epoxide cyclization experiments, significant amounts of acyclic ketone resulting from simple rearrangement are formed, despite the greatly enhanced reaction rate due to the neighboring π bond.[6] As an explanation for this and other cyclization results, there may be generated with participation some type of partially cyclized intermediate cation common to all processes, reacting with external nucleophiles (or bases) to give acyclic and monocyclic material as well as with further double bonds to give polycyclics. As a particularly attractive feature, this hypothesis (proposed by Professor J. Brauman) accounts both for the rate acceleration in production of noncyclized material as well as the lack of extra acceleration in the rate of polycycle formation.

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Structural and Dynamic Stereochemistry of α-$Mo_8O_{26}^{4-}$

Sir:

Rational synthesis of novel, large polyoxoanions is virtually impossible due to a scarcity of experimental data from which principles governing reaction mechanism may be inferred. We report here the results of a dynamic ^{17}O NMR solution study and a solid-state x-ray diffraction study which, for the first time, provide experimental evidence for a simple structure-reactivity relationship and its more general implications.

When ^{17}O enriched α-$[(n\text{-}C_4H_9)_4N]_4Mo_8O_{26}$ (**1**) is dissolved in acetonitrile containing a small amount of water, ^{17}O NMR spectra shown in Figure 1c-e are obtained as the temperature is lowered. Since infrared studies[1] have established an α-β $Mo_8O_{26}^{4-}$ equilibrium in acetonitrile and x-ray diffraction studies[2,3] have determined the structures of α- and β-$Mo_8O_{26}^{4-}$ (see Figure 1a, b), the resonances may be assigned by comparison with the spectrum of ^{17}O enriched β-$[(n\text{-}C_4H_9)_4N]_3KMo_8O_{26}\cdot 2H_2O$ (**2**) in acetonitrile, shown in Figure 1f, using the ^{17}O NMR chemical shift scale described elsewhere.[4] Although the spectra shown in Figure 1c-e are not of sufficient quality to allow quantitative interpretation, several distinctive features may be noted: (1) as the temperature increases, resonances for O_B and O_C in α-$Mo_8O_{26}^{4-}$ broaden significantly, while resonances for O_A and O_D do not, (2) the H_2O triplet is observed at 30 °C, and (3) the O_B resonance broadens more rapidly than the O_C resonance as the temperature increases. From these features, one may conclude that (1) the O_B and O_C resonances broadening is due to a nuclear site exchange process, not quadrupolar broadening, (2) the site exchange process does not involve water, and (3) the exchange process involves exchange between the O_B site (two oxygens) and the O_C site (six oxygens). A simple mechanism consistent with this site exchange scheme is reorientation of the tetrahedral molybdate unit within the α-$Mo_8O_{26}^{4-}$ structure, either inter- or intramolecularly. Such a mechanism involves breaking and subsequent re-forming of bonds between O_C and the octahedrally coordinated molybdenums (Mo_I) in α-$Mo_8O_{26}^{4-}$, and the rapid reaction rate implies their being weak bonds.

Detailed examination of the α-$Mo_8O_{26}^{4-}$ structure, obtained from single crystals of α-$[(n\text{-}C_3H_7)(C_6H_5)_3P]_4Mo_8O_{26}\cdot H_2O\cdot CH_3CN$ (**3**),[5] confirms the weakness of these bonds. Although the α-$Mo_8O_{26}^{4-}$ ion in **3** possesses only inversion symmetry, deviations from idealized D_{3d} symmetry are slight (see Table I). Three features of the structure indicate the weakness of the Mo_I-O_C bonds and the potential lability of the MoO_4^{2-} unit within the α-$Mo_8O_{26}^{4-}$ ion. First, the average Mo_I-O_C distance of 2.425 Å implies a bond order[6] of less than 0.1. Second, the significant variation of Mo_I-O_C distances, ranging from 2.369 (3) to 2.444 (3) Å, reflects the ease with which these bonds may be stretched.[7] Finally, the average Mo_{II}-O distance within the tetrahedral coordination sphere is 1.764 Å, which agrees, within standard deviations, with the average of 1.772 Å found in $Na_2MoO_4\cdot 2H_2O$.[8] Thus the MoO_4^{2-} unit could be reoriented with only a slight deformation of its geometry. As a result of these three considerations, α-$Mo_8O_{26}^{4-}$ may be accurately represented by the

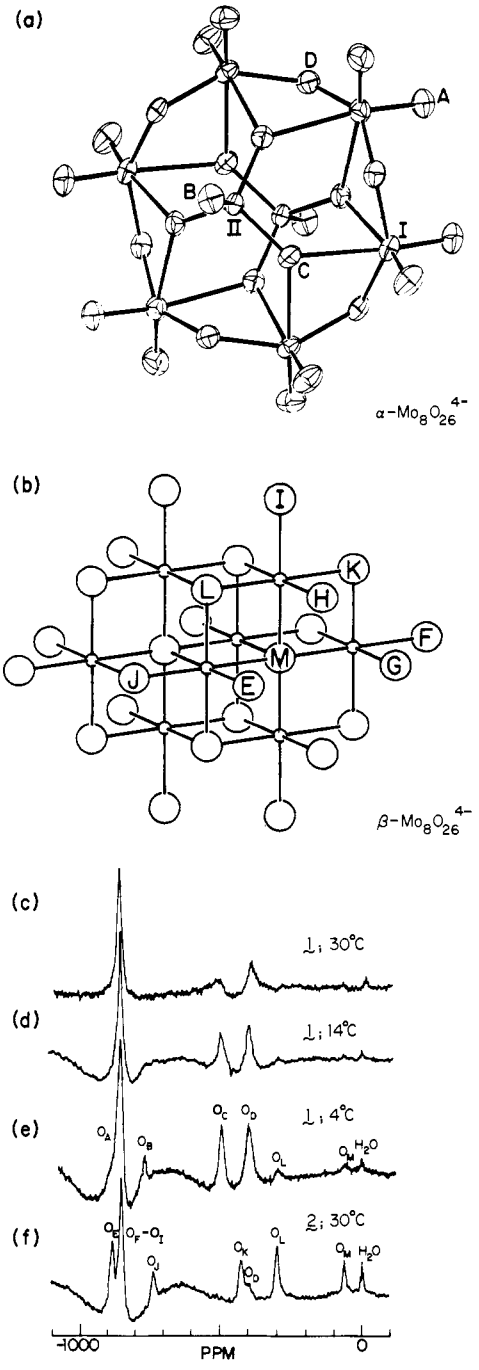

Figure 1. (a) ORTEP drawing of α-$Mo_8O_{26}^{4-}$ as observed in **3**. All atoms are represented by thermal vibration ellipsoids of 50% probability. Assuming idealized D_{3d} symmetry, nonequivalent oxygen atoms are labeled with letters and nonequivalent molybdenum atoms are labeled with numerals. (b) C_{2h} idealized view of β-$Mo_8O_{26}^{4-}$, where small circles represent molybdenum atoms, and large circles represent oxygen atoms. Nonequivalent oxygen atoms are labeled with letters. All molybdenum coordination polyhedra are drawn as idealized octahedra. (c)-(e) ^{17}O FT NMR spectra of 25 atom % ^{17}O enriched α-$[(n\text{-}C_4H_9)_4N]_4Mo_8O_{26}$ (**1**) in hydrated acetonitrile, [Mo] = 0.16 M. (f) ^{17}O FT NMR spectrum of 34 atom % ^{17}O enriched β-$[(n\text{-}C_4H_9)_4N]_3KMo_8O_{26}\cdot 2H_2O$ (**2**) in acetonitrile, [Mo] = 0.05 M. Pure water at 30 °C is assigned a chemical shift of 0 ppm on the scale shown at the bottom of the figure.