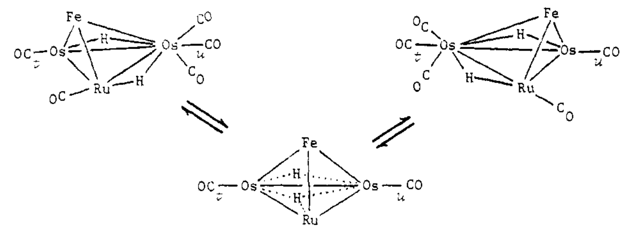
Scheme I



average environment to *t* and *u*, and the observation that *t* and *u* become equivalent provides strong support for this mechanism.

The second effect of the intrametallic rearrangement in C_1 occurs when the Fe atom moves away from Ru and generates the Fe-Os_1-Os_2 triangle with the bridging COs. This movement results in isomerization to the C_s isomer and is the final averaging process. It begins at 40 °C, and results in the averaging of all carbonyls on both isomers. It is important to note that the variable-temperature ^{1}H NMR spectra[22] indicate that the $C_s \rightleftharpoons C_1$ isomerization occurs in the same temperature range as shown by the ^{13}C NMR spectra. Studies are currently in progress employing $H_2FeRu_2Os(CO)_{13}$, $H_2Ru_4(CO)_{13}$, and phosphine derivatives of $H_2FeRu_3(CO)_{13}$ to elucidate further the nature of these fluxional processes.

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(22) The ^{1}H NMR spectrum of $H_2FeRuOs_2(CO)_{13}$ at −50 °C exhibits a singlet at τ 29.5 due to C_s and a pair of doublets at 29.7 and 29.8 (J_{H-H} = 1.3 Hz) due to C_1, in an approximate C_s/C_1 ratio of 2.3. These resonances coalesce at 50 °C and sharpen to a singlet at 90 °C, establishing that the two isomers interconvert at elevated temperatures.
(23) Spectra for the sample enriched to 40% with ^{13}CO were recorded using 3:1 $CHFCl_2/CDCl_3$, $CDCl_3$, and toluene-d^8 solvents for the appropriate temperature ranges. In each case spectra were recorded at the same temperature in different solvents and were identical except for very small chemical shift changes.
(24) The assignment of the upfield resonance to carbonyl *r* trans to hydrogen is internally consistent with our earlier assignment derived from the ^{1}H coupled-decoupled spectra. These clearly showed that the carbonyls trans to hydrogen give the most upfield resonances.

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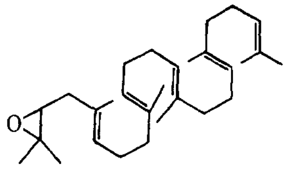
Cyclization Studies with Nor- and Homosqualene 2,3-Oxide

Sir:

In order to learn more about the critical initial phase in the bioorganic polycyclization of squalene 2,3-oxide and related terpenoid epoxides,[1] syntheses and reactivity studies of 4-norsqualene 2,3-oxide (**1**) and homosqualene 2,3-oxide (**2**)



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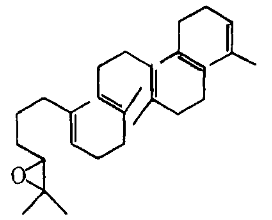
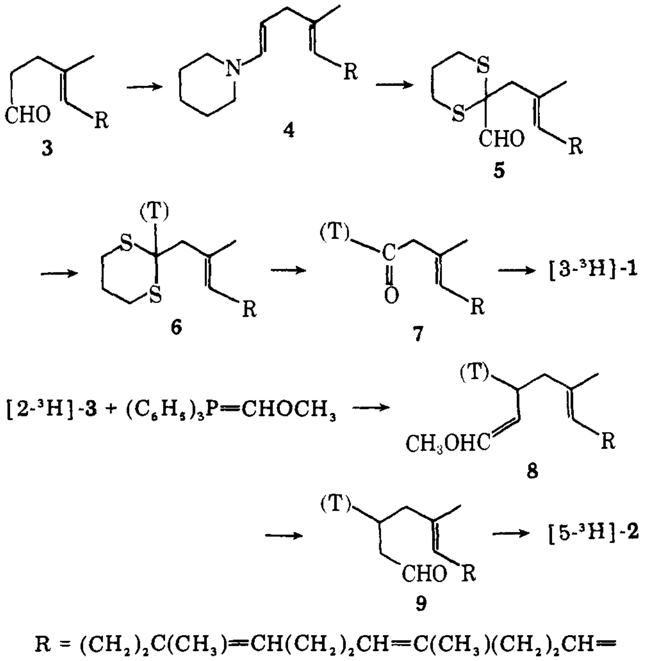


2

were carried out. The behavior of these two analogues under biological and abiological conditions not only bears on the physical organic mechanism of A-ring formation,[1] but also suggests that a comparatively high degree of enzyme control is exercised to achieve the oxide/neighboring π-bond juxtaposition necessary for initiating cyclization of the normal substrate.

In connection with the favored synthetic approach to oxide **1**, we faced the need for a selective method of degrading a given aldehyde to the noraldehyde, applicable even where the product is the sensitive β,γ-unsaturated type. Toward this end the enamine **4** of aldehyde **3**,[2] on treatment with trimethylene di-

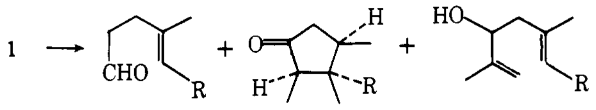


R = $(CH_2)_2C(CH_3){=}CH(CH_2)_2CH{=}C(CH_3)(CH_2)_2CH{=}$
$C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$

thiotosylate[3] in Et_3N/CH_3CN, was converted (65% from **3**) to the α-ketoaldehyde trimethylene dithioketal **5**, which, on cleavage[4] with sodium methoxide in $Me_2SO/H_2O(T_2O)$, gave rise to (radiolabeled) dithioacetal **6**[5] (85%). After generation of the parent crude aldehyde **7** by S-methylation and subsequent hydrolysis (CH_3I and $CaCO_3$ in H_2O/CH_3CN), reaction with diphenylsulfonium isopropylide in THF produced after preparative TLC (benzene, EtAc/hexane-silica) the desired epoxide, [3-^{3}H]-**1** (69% from **6**):[5] NMR (CCl_4) δ 1.20 (3 H, CH_3CO), 1.24 (3 H, CH_3CO), 1.5-1.7 (18 H, $C{=}CCH_3$), 1.9-2.1 (16 H, $C{=}CCH_2$-), 2.15 (2 H, -CH_2CO), 2.6 (1 H, HCO), 4.9-5.3 (5 H, $C{=}CH$).

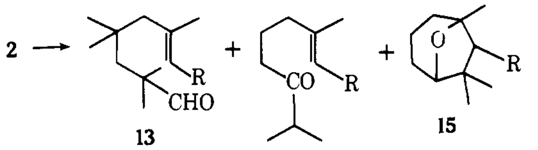
In order to secure the homologue **2**, tris noraldehyde [2-^{3}H]-**3** was first subjected to a Wittig reaction with ylide generated from triphenyl(methoxymethyl)phosphonium chloride (n-C_4H_9Li/Et_2O),[6] affording (65%) enol ether **8** as a mixture of cis and trans isomers (IR and NMR).[5] On hydrolysis (glyme/CH_3CO_2H/H_2O), the enol ether mixture yielded the homoaldehyde **9**, which without purification was transformed (41%), as in the case of **1**, to the homo epoxide [5-^{3}H]-**2**,[5] purified by preparative TLC (EtAc/hexane-silica): NMR (CCl_4) δ 1.18 (3 H, CH_3CO), 1.22 (3 H, CH_3CO), 1.3-1.5 (4 H, $CH_2CH_2CC{=}C$), 1.6 (18 H, $C{=}CCH_3$), 1.8-2.2 (18 H, $C{=}CCH_2$), 2.45 (1 H, HCO), 4.9-5.3 (5 H, $C{=}CH$).

Nonenzymic cyclization experiments were carried out with 0.15-0.35 equiv of catalyst in benzene at 7 °C. Epoxide **1** was isomerized (BF_3) to acyclic aldehyde **10** (78%),[5] cyclopentanone **11** (10%), and allylic alcohol **12** (5%), all noncrystalline products which were separated and purified by TLC (EtAc/petroleum ether-silica gel). The structure of **10** was confirmed by independent synthesis involving two successive α-methylations (CH_3I/hexane-THF)[7] of the *tert*-butylimine of aldehyde **3**, each methylation being preceeded by formation of the imine anion through the action of lithium diisopropylamide. The cyclization product was identified as **11** by its carbonyl stretch at 1750 cm^{-1} and by its NMR spectral properties ($CDCl_3$)—δ 0.63 (s, 3 H, t-CH_3), 0.93 (d, J = 7 Hz, 3 H, *sec*-CH_3), 0.99 (d, J = 7 Hz, 3 H, *sec*-CH_3), 1.59 (br s, 12 H, $C{=}CCH_3$), 1.67 (s, 3 H, $C{=}CCH_3$), 1.80-2.56 (m, 20 H, -CH_2-), 5.13 (br s, 4 H, $C{=}CH$)—including comparison with those of structurally similar, known 1,2,3-trimethylcyclopentanes.[8-10]



10 11 12

With $SnCl_4$, epoxide **2** generated the precedented (vide supra)[11,12] rearrangement products **13**-**14** (a mixture with **13** predominating, 50%), monocarbocyclic bridged ether **15** (27%), and, as in the case of **1**, some acyclic allyl alcohol (0.5%), structural assignments to which were made on the basis of IR and NMR spectral data as well as analogy to other epoxide cyclization results.[11,12] For example, in addition to paralleling the bicyclo[2.2.1] ether type observed earlier,[11,12] the bridged ether structure **15** was assigned on the basis of its IR (ether stretch at 1080 cm^{-1}) and NMR spectrum (C_6D_6): δ 1.00 (s, 3 H, t-CH_3), 1.17 (s, 3 H, t-CH_3), 1.20-2.44 (br m, 38 H, overlapping CCH_3), 1.42 (s, 3 H, CH_3CO), 3.72 (d, 1 H, HCO), 5.37 (m, 4 H, $C{=}CH$).

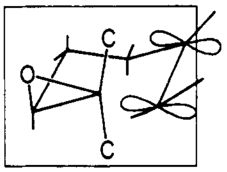


13 14 15

Although participation firmly governs production of 4-hydroxycyclohexyl cation through acid-catalyzed cyclization of appropriately substituted hexa-1,5-diene 1,2-oxide,[1] a similar course of action in the norsqualene oxide case (**1**) cannot be followed, in that the colinear arrangement of C-2, C-6, and oxygen required for an S_N2-like ring-closure process[13] is not possible, in keeping with the argument made elsewhere[1] for the mechanism of A-ring formation. We believe that the modest amount of cyclic product **11** is likely formed by unassisted S_N1-like epoxide opening, followed by interaction of the resulting carbonium ion or ion pair with the neighboring π bond.[14,15] In the case of homosqualene oxide **2**, entropic factors presumably are responsible for a decrease in the yield of cyclization product from the level observed with squalene oxide and related systems (as high as 67%), with consequent formation instead of acyclic materials in greater yield.

Under circumstances[18] (incubation at 37 °C using resuspended microsomes) where substantial cyclization of squalene oxide and many of its analogues[18] occurs, radiolabeled **1** (20 μg, 4.68 × 10^5 dpm) and **2** (20 μg, 1.82 × 10^5 dpm) (each in 0.4 mL of enzyme preparation) do not form detectable amounts (<0.5%) of any cyclization products. In both cases, although small amounts of the corresponding glycol may have been formed, most of the starting epoxide was recovered, results indistinguishable from those using denatured enzyme (controls run with boiled microsomal preparation). In parallel runs, squalene oxide was converted to lanosterol in 66-70% yields.

That the cyclase cannot take advantage of nonenzymic cyclization pathways open to **1** and **2** implies to us that the constraints employed by the enzyme to optimize the stereoelectronic opportunities for ring-A formation by a concerted process are considerable, highly specific, and thus not conducive to cyclization by other mechanistic means, all consequences of the special structural character and binding capability in this region of the enzyme. In turn, substrate structural requirements in the epoxide/neighboring π-bond area—in contrast to other parts of the substrate[18,19]—are correspondingly high and specific: no variation in the distance between these structural units is permitted, and the relative orientations necessary for their anchimeric involvement must be achievable and optimized.[20] These views, taken together with previous conclusions,[19] allow the proposal that an intact hepta-2,6-diene 2,3-oxide moiety, which is conformationally oriented as shown in **16**, is per se necessary for cyclase action.



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(15) In that (anchimerically unassisted) solvolysis of pent-4-enyl sulfonate does not give rise to the relatively high energy cyclopentyl cation,[16,17] it might be assumed that the low yield, and therefore low cyclization rate, of **1** is due to an equally high $\Delta H^{\ddagger}$ for formation of an analogous cationic species. Although this factor may contribute, it should be pointed out that the starting material **1** features epoxy oxygen as the triggering group, a comparatively high energy unit which should result in a distinctly lower $\Delta H^{\ddagger}$ than that of the pent-4-enyl sulfonate solvolysis. Similarly, this effect may overshadow any energy differences due to varying steric contributions of substituents in the formation of cyclopentyl and cyclohexyl cationic types in the cyclization of **1** and squalene oxide (or related systems), respectively.
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(20) Binding without subsequent cyclization, and the absence of binding, presumably differentiable through appropriate competitive inhibition experiments with **1**, **2**, and squalene oxide, can both be thought of as possible consequences of the same special character and specificity of the enzyme postulated above, based upon the presence in the natural substrate of epoxide and π-bond moieties a prescribed distance apart.

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Inelastic Electron Tunneling Spectroscopy of a Chemically Modified Surface

Sir:

Chemical modification of metal oxide surfaces for electrochemical purposes has attracted a considerable amount of attention since the first report by Murray.[1-5] The modifications can be performed in a controlled manner using commercially available silane derivatives and the technique provides a novel approach for studying and controlling surface reactions. Fundamental to this objective, however, is the need to understand clearly the bonding and structural aspects of the bonded molecules. Thus, it becomes attractive to take advantage of the very sensitive inelastic tunneling spectroscopy (IETS), which will give vibrational structure information of organic monolayers on metal oxide surfaces. The silylation approach of covalently bonding organic moieties to a metal oxide surface provides an alternative to the vapor and liquid phase surface doping techniques[6] generally used in IETS studies. We now present some preliminary results of such a study.

The metal/insulator/metal sandwiches of 1-mm^2 cross section were prepared on clean 10 × 15 mm glass slides. First an aluminum strip 1 mm wide was vacuum evaporated using the appropriate shadow mask and immediately oxidized by admitting pure oxygen into the vacuum system. The plate was next immersed in an anhydrous benzene solution containing the molecule of interest, for example triethoxyvinylsilane (1% v/v) and allowed to stand for 5 min. The excess reagent was removed by rinsing the plate with six portions of fresh benzene. The entire silylation process was carried out under an anhydrous nitrogen atmosphere since the presence of trace amounts of moisture will generate thick polymeric films. A 1-mm-wide strip of lead was subsequently evaporated for the counter electrode. The junction resistances were in the range of 50-5000 Ω/mm^2. The junction was next mounted for cooling to 4.2 K as previously described.[6]

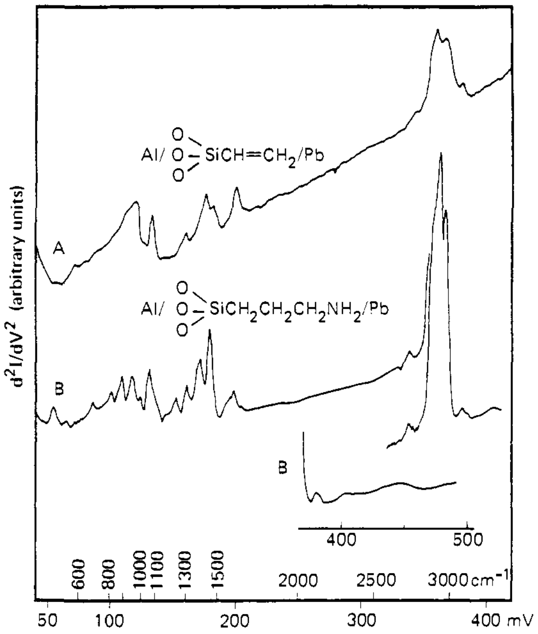

Figure 1. Tunneling spectra at 4.2 K of covalently bonded vinylsilyl (A) and 3-aminopropylsilyl (B) derivatives.

As can be seen in Figure 1, good tunneling spectra (d^2I/dV^2 vs. V) are obtained of the organic material when it is introduced into the sandwich junction by a chemical reaction as an alternative to the normal[6] doping procedures. The IETS spectrum for the vinylsilyl derivative (A) is relatively simple and compares well with the IR spectrum for trichlorovinylsilane.[7] While not shown in Figure 1, plot A reveals only a very small broad peak in the region near 3600 cm^{-1} suggesting the extensive removal of surface OH groups.[6] Of particular interest is the presence of bands at 1070, 2853, and 2944 cm^{-1} which indicates the presence of -OCH_2CH_3 groups on the surface. When the aluminum surface is silylated with excess triethoxyvinylsilane and not rinsed, then these bands become much stronger plus other weaker bands appear as expected. The simplest conclusion is that some ethoxy groups survive the silylation reaction and remain intact as Si-O-CH_2CH_3. This result shows that during the reaction of the triethoxysilyl derivative with the surface some Si-OCH_2CH_3 groups remain and may be available for reaction with Lewis bases. The region 800-1100 cm^{-1} is not well resolved which is unfortunate since it could provide some insight into the Si-O-Si and Si-O-Al bonding structure.[8]

The spectrum for the 3-aminopropylsilyl derivative (B) shows somewhat better resolution than the IR spectrum for the starting material, 3-aminopropyltriethoxysilane.[7] The major difference is the position and the weakness of the N-H stretching bands at 3320 and 3250 cm^{-1} which are displaced to lower frequencies by ~80 cm^{-1}. While this shift is appropriate for the presence of intermolecular hydrogen bonding,[8] it is dangerous to draw definite conclusions on the molecular structure of the 3-aminopropylsilyl insulator layer without understanding clearly the influence of the deposited lead contact.

Silylation of the aluminum oxide surface using 3-(2-aminoethylamino)propyltrimethoxysilane also produced a good sandwich junction and the resulting IETS spectra is similar to that of the 3-aminopropylsilyl derivative. A general observation is that the resistivity of the junction increases with increasing molecular size of the covalently bonded molecule suggesting that this factor may be a limitation for studying