Table I. Incorporation of Labeled Precursors into Geldanamycin

	Precursor			Geldanamycin isolated		
Compound	Spec Activity (mCi/mmol)	Amount (μmol)	Spec Activity (μCi/mmol)	Isotope dilution	Amount (mg)	% incorp
[Methyl-14C]methionine	42.6	0.86	34.60	1.22×10^3	169.8	22.66
Sodium [carboxy-14C]propionate	54.9	0.73	14.40	3.82×10^3	60.5	3.71
Sodium [carboxy-14C]acetate	52.9	0.28	0.35	1.51×10^5	247.1	0.90
Sodium [carboxy-14C]malonate	40.0	1.00	1.12	3.59×10^4	58.3	0.27
Sodium 14C-formate	41.7	0.96	0.09	4.63×10^5	160.2	0.04
[Methyl-13C]methionine[a]		1333		9.00	70.0	1.16[b]
Sodium [carboxy-13C]propionate[a]		6400		6.00	130.0	0.60[b]

[a] 90% carbon-13. [b] Calculated from enrichment (determined by mass spectrometric analysis) and yield of geldanamycin vs. enrichment and amount added of the 13C-labeled precursors.
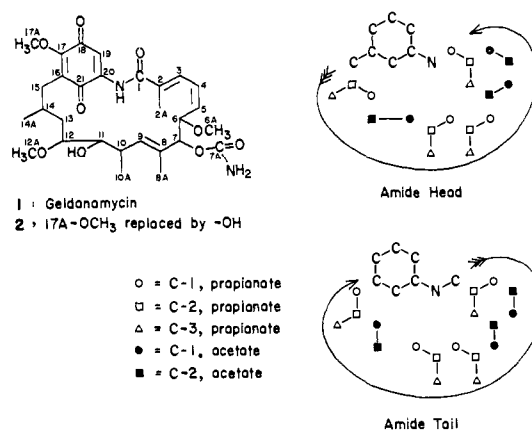
each of the three (see following) labeled carbons. The cmr spectrum of methionine-labeled geldanamycin clearly showed that only the three methoxyl peaks, at 56.0, 56.5, and 61.0 ppm (relative intensities 1.08:1.08:0.86), were enriched by 13C. The peak at 61.0 ppm is assigned to C-17A, since it was missing in the cmr spectrum of 2. That at 56.5 ppm is assigned to C-12A from its upfield shift in the spectrum of geldanamycin acetate.[6] That at 56.0 ppm must then be C-6A. The carbamate carbon, C-7A, was not labeled.

Geldanamycin from propionate was 65% unlabeled, 18% mono-, 10% di-, 5% tri-, and 2% tetralabeled, or an average of 15% labeled at each of the four (see following) labeled carbons. The cmr spectrum of propionate-labeled geldanamycin showed four highly enriched peaks at 31.0, 80.6, 131.9, and 169.1 ppm (relative intensities 1.17:0.90:1.14:0.79), and no others. The first three were identified as C-13, C-7, and C-9, respectively, by specific decoupling of the attached protons at δ 1.45, 4.90, and 5.52.[6] The fourth absorption (at 169.1 ppm) was identified as the amide carbonyl (C-1) by its chemical shift, nearly identical with that of the amide carbonyl in the cmr spectrum of streptovaricin D.[2,4] Labeling of C-1, C-7, C-9, and C-13 corresponds perfectly to the pattern for the amide-head[2,4] direction of biosynthesis (Figure 1) but would not agree with an amide-tail direction, while labeling of C-1 and C-13 argues for a continuous sequence of propionate–acetate units from C-14 through C-1. This is the same pattern found for streptovaricin[2,4] and rifamycin.[5] The benzoquinone unit and its attached carbon (C-15 through C-21) were not labeled by propionate or methionine.

The origin of C-15 through C-21 is still under active investigation. However, it seems clear that the remaining C7N unit of geldanamycin (C-15 through C-21 and the attached nitrogen) corresponds to part of the naphthoquinonoid units in streptovaricin and rifamycin. Although streptovaricin has a methyl group at C-25,[2,4] which corresponds to C-19 of geldanamycin, we have now shown that this methyl group (as well as the methoxyl and methylenedioxy groups) comes from methionine,[12] extending the previous studies,[2,4] which demonstrated that it did not come from propionate.

I : Geldanomycin
2 : 17A-OCH₃ replaced by -OH

o = C-1, propionate
□ = C-2, propionate
△ = C-3, propionate
● = C-1, acetate
■ = C-2, acetate

Figure 1. Geldanamycin (1), des-O-methylgeldanamycin (2), and two potential biosynthetic pathways for the formation of 1. The amide head pathway is correct. Carbons 6A, 12A, and 17A are labeled by methionine.

Ronald D. Johnson, Arthur Haber, Kenneth L. Rinehart, Jr.*

*Roger Adams Laboratory, University of Illinois
Urbana, Illinois 61801*

Received December 8, 1973

Allene Oxide–Cyclopropanone Isomerization. A Low Barrier Pathway on the CNDO/2 Energy Surface

Sir:

There has been considerable interest recently in the cyclopropanone (III) allene oxide (I) isomerization reaction[1–3] and in the postulated intermediate oxyallyl

(1) J. K. Crandall and W. W. Conover, *J. Chem. Soc., Chem. Commun.,* 340 (1973).
(2) J. K. Crandall, W. H. Machleder, and S. A. Sojka, *J. Org. Chem.,* **38,** 1149 (1973).
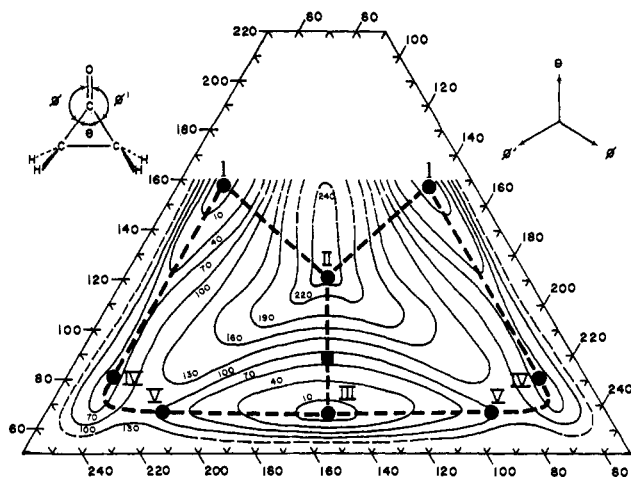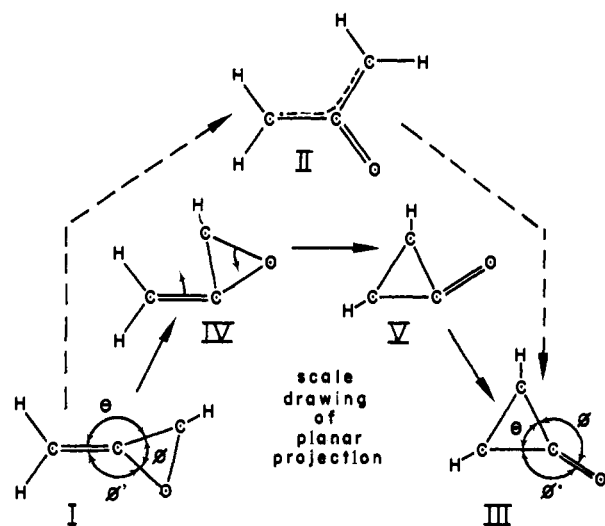(3) Y. N. Kuo and M. J. Nye, *Can. J. Chem.,* **51,** 1995 (1973).

Figure 1. Contour diagram of the CNDO/2 energy surface for the allene oxide–oxallyl–cyclopropanone system. The contour spacing is 30 kcal/mol.

Scheme I

(II)[4–6] (Scheme I). In the case of 1,3-di-*tert*-butyl-allene oxide, the half-life for the isomerization to the corresponding cyclopropanone is ∼5 hr at 100°,[7] implying an activation barrier of about 40 kcal or less. This result agrees with the measured 40.1 kcal for the enthalpy of activation for the conversion of 2-methyl-methylenecyclopropane to ethylidenecyclopropane.[8]

Several quantum mechanical computations on the cyclopropanone–allene oxide system have recently appeared[4–6,9,10] in which it is assumed that a planar oxyallyl intermediate or transition state is involved in the isomerization mechanism. These calculations indicate that oxyallyl is a very high energy structure, whereas the allene oxide energy is ∼2.3 kcal/mol higher than cyclopropanone. The activation energy (in kcal/mol)

computed as the difference between the energy of oxyallyl and cyclopropanone is as follows: EHT = −23,[9] INDO (CNDO) = 232,[4–6] MINDO = 78,[10] and *ab initio* SCF (POLYATOM) = 83.[4] If the actual mechanism is uncomplicated by heterogeneous catalysis, intermolecular reaction, enol formation,[11] etc., these results seem to be too high (except for EHT which is now considered to be invalid for this system).

This paper reports results of a successful search on the CNDO/2 energy surface for an isomerization pathway involving a lower barrier. A contour map of the CNDO/2 energy surface is shown in Figure 1. Here the energy is plotted as a function of θ (vertical), ϕ (right), and ϕ' (left), the $C_2C_1C_3$, C_2C_1O, and C_3C_1O bond angles, respectively. A triangular plot is convenient since, for structures in which the oxygen and three carbon atoms are restricted to lie in a plane, $\theta + \phi + \phi' = $ constant $= 360°$. The surface, which is symmetrical around the vertical bisector of the triangle, was generated by means of interpolation and extrapolation from approximately 30 points spaced roughly at 20° intervals.

The energy at each computed point (selection of θ and ϕ) was obtained by minimizing the energy as a function of the remaining 15 independent coordinates. An approximate minimum was found by guessing a value for each of the 15 bond lengths and angles, then sequentially minimizing the energy with respect to each coordinate by passing a parabola through three computed points obtained by adding and subtracting a small increment to the guessed value. The SCF energy for each configuration was computed to ±0.0002 hartree (0.1 kcal/mol) by means of the Dobosh–Pople CNDO/2 program[12] modified to run on an IBM 360-44 computer. With a sufficiently accurately guessed structure, it was demonstrated[13] that one cycle through the 15 coordinates served to minimize the energy to within <5 kcal/mol. It was also observed that the C–H bond lengths and H–C–H angles were quite insensitive to location on the surface; hence, these parameters were varied only at major points. It is felt that the total minimizational and computational error at each computed point is less than 30 kcal/mol on general regions of the surface and less than 10 kcal/mol along the reaction pathway. With more extensive minimization, small changes may occur but the general features of the surface are not likely to be materially altered.

On the CNDO/2 energy surface, Figure 1, oxyallyl (defined by $\theta = 120$, $\phi = 120$)[14] is most stable with all atoms in a plane but represents nearly the highest energy structure on the surface. Thus, to the extent that the CNDO/2 surface is accurate, a cyclopropanone–allene oxide isomerization pathway through oxyallyl must be very unlikely. Yet these have been the only pathways considered computationally to date. In fact,

(4) A. Liberles, A. Greenberg, and A. Lesk, *J. Amer. Chem. Soc.*, **94**, 8685 (1972).

(5) A. Liberles, S. Kang, and A. Greenberg, *J. Org. Chem.*, **38**, 1923 (1973).

(6) J. F. Olsen, S. Kang, and L. Burnelle, *J. Mol. Struct.*, **9**, 305 (1971).

(7) R. L. Camp and F. D. Greene, *J. Amer. Chem. Soc.*, **90**, 7349 (1968).

(8) J. P. Chesick, *J. Amer. Chem. Soc.*, **85**, 2720 (1963).

(9) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1476 (1968).

(10) N. Bodor, M. J. S. Dewar, A. Harget, and E. Haselback, *J. Amer. Chem. Soc.*, **92**, 3854 (1970).

(11) D. B. Sclove, J. F. Pazos, R. L. Camp, and R. D. Greene, *J. Amer. Chem. Soc.*, **92**, 7488 (1970).

(12) J. A. Pople, D. L. Beveridge, and P. A. Dobosch, *J. Chem. Phys.*, **47**, 2026 (1967).

(13) C. K. Johnson, M.S. Thesis, Wichita State University, 1973.

(14) Liberles[4,5] and Olsen[6] define oxyallyl to be the totally planar molecule with $\phi = \phi'$ (the vertical bisector of Figure 1) then proceed to minimize the energy as a function of θ, yielding a minimum of over 200 kcal/mol due to nonbonded H repulsion at $\theta = 90°$ (■ in Figure 1). On the lowest energy path from III to II the methylene groups are perpendicular to the CCCO plane at $\theta = 90°$, with energy less than 80 kcal/mol.

all prior computations have been performed at point I and along the vertical path from III to II, where disrotary and conrotary ring openings were studied.

The novel pathway I → IV → V → III for the allene oxide–cyclopropanone isomerization has a CNDO/2 barrier of less than 110 kcal/mol, which is less than half that of previously computed CNDO/2 or INDO barriers. No secondary minima were detected in the region near oxyallyl suggesting that, if CNDO/2 is correct, oxyallyl cannot exist as an intermediate as often proposed. It must be admitted, however, that oxyallyl may be a necessary transition state in cycloaddition[15,16] reactions and reactions of allene with ozone.[1] There is one reported isolation of an oxyallyl but for this case the evidence is weak.[17]

The proposed pathway is intuitively quite reasonable in that bending is known to require less energy than bond stretching. Delocalization stabilization in oxyallyl is apparently insufficient to compensate for destabilization due to bond breakage. On the CNDO/2 energy surface, the three-membered ring is preserved intact until bending allows another ring to form with minimal bond stretch. The reliability of this result is hard to assess since CNDO/2 is known to overestimate bond force constants, thereby strongly resisting bond stretching motions, and ring strain may be improperly estimated. Also, the usual uncertainties involving application of semiempirical single determinant SCF schemes apply, and only the closed shell singlet configuration was studied (compare ref 19). Dynamic factors as discussed by Wang and Karplus[18] may also be important, and correlation changes as the conformation is altered from the equilibrium geometry may not be negligible. However, the total error should be much less than the >120 kcal/mol difference between the two paths.

The newly discovered low energy isomerism pathway may shed light on the following. The retention of optical activity when Feist's ester undergoes rearrangement may be more easily explained by a mechanism analogous to that proposed above, than by nonplanar open shell singlet trimethylenemethane[19] or complicated 45° methylene rotations.[20] By completing the upper portion of Figure 1, an analogous pathway may be found for converting I (left) to I (right), which represent different isomers of the product of epoxidation of 1,1-dimethylallene[11,16] or 1,1-di-tert-butylallene.[21] The relative barriers for conversion between cyclopropanone and the two allene oxide isomers would be of interest as well as the relative energy of the three isomers.

In conclusion, the above results illustrate the danger of considering a restricted number of possible reaction pathways. The results indicate that perhaps too much emphasis has been placed on the stability of delocalized configurations. Perhaps, many reaction

mechanisms could be profitably reevaluated by considering unusually large distortions of angles (bending) rather than bond stretching. It is hoped that this work will stimulate a check of the proposed mechanism using more accurate and/or more reliable quantum mechanical computational schemes. Spot checking shows that the INDO energy surface is essentially equivalent to the CNDO/2 surface for this system.

Melvin E. Zandler,* Charles E. Choc, Carolyn K. Johnson
*Department of Chemistry, Wichita State University
Wichita, Kansas 67208*

Simultaneous Participation of Three Neighboring Groups in the Transition State for a Radical-Forming Perester Decomposition. A New Route to Hypervalent Compounds of Sulfur and Iodine[1]

Sir:

Several years ago work in these laboratories[2] established the importance of neighboring group participation in the decomposition of ortho-substituted *tert*-butyl perbenzoates, an effect anchimerically accelerating the decomposition of o-phenylthioperbenzoate (**1b**) by a

1a, X = H
b, X = SPh
c, X = I

2
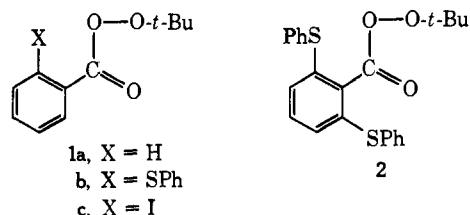
factor of ca. 10^6 (at 0°) relative to **1a**. Further work in related systems[3] led us to an unsuccessful search[1a] for evidence for simultaneous participation at both carbonyl oxygen and peroxy oxygen by the two o-thiophenyl substituents of **2**; peresters **2** and **1b** decompose at about the same rate (Table I).

Recent success in the isolation of stable diaryldialkoxysulfuranes[4] led us to study perester **3a** as a possible precursor to sulfurane **5a**. We here present evidence for a highly concerted reaction of **3a**, simultaneously involving three neighboring groups in a reaction leading through transition state **4a** directly to sulfurane **5a** and two *tert*-butoxy radicals.

Perester **3a** (mp 44.5° dec) was prepared by treating the corresponding acid chloride with potassium *tert*-

(1) (a) Part VII of a series on anchimerically accelerated bond homolysis; for Part VI see T. H. Fisher and J. C. Martin, *J. Amer. Chem. Soc.*, **88**, 3382 (1966). (b) This is also Part XIII of a series on sulfuranes; for Part XII see J. C. Martin, and E. F. Perozzi, *ibid.*, **96**, 3155 (1974).
(2) J. C. Martin and W. G. Bentrude, *Chem. Ind. (London)*, 192 (1959); W. G. Bentrude and J. C. Martin, *J. Amer. Chem. Soc.*, **84**, 1561 (1962).
(3) (a) J. C. Martin, D. L. Tuleen, and W. G. Bentrude, *Tetrahedron Lett.*, 229 (1962); (b) D. L. Tuleen, W. G. Bentrude, and J. C. Martin, *J. Amer. Chem. Soc.*, **85**, 1938 (1963); (c) T. W. Koenig and J. C. Martin, *J. Org. Chem.*, **29**, 1520 (1964); (d) J. C. Martin and T. W. Koenig, *J. Amer. Chem. Soc.*, **86**, 1771 (1964).
(4) J. C. Martin and R. J. Arhart, *J. Amer. Chem. Soc.*, **93**, 2339 (1971).

(15) R. Noyori, Y. Baba, S. Makino, and H. Takaya, *Tetrahedron Lett.*, 1741 (1973); S. Ito, H. Ohtani, and S. Amiya, *ibid.*, 1737 (1973).
(16) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).
(17) M. H. Fisch and J. H. Richards, *J. Amer. Chem. Soc.*, **90**, 1547 (1968).
(18) I. S. Y. Wang and M. Karplus, *J. Amer. Chem. Soc.*, **95**, 8160 (1973).
(19) M. J. S. Dewar and J. S. Wasson, *J. Amer. Chem. Soc.*, **93**, 3081 (1971).
(20) W. von E. Doering and L. Birladeanu, *Tetrahedron*, **29**, 499 (1973); W. von E. Doering and H. D. Roth, *ibid.*, **26**, 2825 (1970).
(21) J. K. Crandall and W. H. Machleder, *J. Amer. Chem. Soc.*, **90**, 7347 (1968).