Mechanism of the Rearrangement of Vinyl Allene Oxide to 2-Cyclopenten-1-one

B. Andes Hess, Jr.,*[,†] Lidia Smentek,[†,‡] Alan R. Brash,[§] and Jin Kun Cha*[,⊥]

Department of Chemistry, Vanderbilt University Nashville, Tennessee 37235
Institute of Physics, N. Copernicus University 87-100 Toruń, Poland
Department of Pharmacology, Vanderbilt University Medical Center, Nashville, Tennessee 37232
Department of Chemistry, University of Alabama Tuscaloosa, Alabama 35487

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Prostaglandins (PGs) and structurally related cyclopentanoids have been found in both the plant and animal kingdoms. In mammals, PGs result from cyclooxygenase-catalyzed metabolism of unsaturated fatty acids. On the other hand, the mechanistic details of cyclopentanoid biosynthesis in marine organisms remain unresolved. Implicated as potential precursors to PGs and related cyclopentanoids in plants and marine organisms are allene oxides, which are produced by the enzymatic dehydration of a lipoxygenase-derived unsaturated fatty acid hydroperoxide.[1,2] Vinyl allene oxide is thought to first open to vinyl oxyallyl (i.e., 2-oxidopentadienyl cation), which then undergoes a conrotatory ring closure to give the cyclopentenone product. Biomimetic studies on the cyclopentenone annulation are also known.[3] However, the possibility of a concerted rearrangement of vinyl allene oxide to cyclopentenone has not been addressed in any previous work. Herein we report the first detailed theoretical study on the rearrangement of vinyl allene oxide to 2-cyclopenten-1-one and discuss its implication in the hitherto unknown geometry of the double bond in naturally occurring allene oxides.[4]

We have recently reported an ab initio study on the rearrangement of the parent allene oxide (methyleneoxirane) to cyclopropanone via the oxyallyl intermediate,[5] in which the density functional method (DFT) was demonstrated to be appropriate for treating zwitterions (or diradicals). Hence, all calculations[6] were done with the DFT method using the 6-31G* basis set[7] with Becke's three-parameter functional, (U)B3LYP.[8,9]

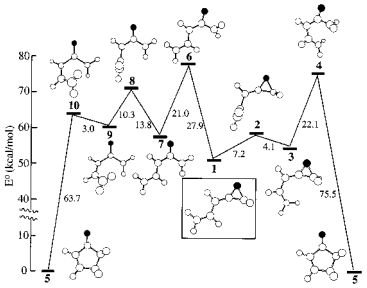

Figure 1. Relative energies of **1**−**10**.

We found that vinyl allene oxide can exist in two energetically similar conformations, *s-trans* (**1**), with a planar carbon skeleton, and *s-cis* (**3**), with a nonplanar carbon skeleton, linked by a transition structure **2**, with **1** more stable than **3** (see Figure 1).[10,11] A concerted rearrangement to 2-cyclopenten-1-one (**5**) could occur from the *s-cis* conformer, which is in equilibrium with the *s-trans* conformer. Indeed, a transition structure **4** for the concerted rearrangement was located, and IRC calculations[9] showed it linked **3** with **5**. The transition structure **4** has S_N2 characteristics, with the C−O bond breakage assisted from the back side by attack of the double bond π electrons.

The second pathway from **1** to **5** was found to involve two conformations of vinyl oxyallyl. The *s-trans* conformer **7** was found to be only 6.9 kcal/mol higher in energy than **1**.[12] However, the transition structure **6** linking **1** and **7** lies 27.9 kcal/mol above **1**, which suggests that **1** should be reasonably stable in the absence of Lewis acids, polar solvents, or nucleophiles. The transition structure **6** is characterized by a significant degree of ring opening of the epoxide, as well as rotation of the methylene group toward planar **7**. A conformational change of **7** to the *s-cis* isomer **9** must then precede ring closure to 2-cyclopenten-1-one. The transition structure **8**, with its vinyl group orthogonal to the oxyallyl function, was found to link **7** to **9**, with the *cis* conformer 3.5 kcal/mol higher in energy than the *trans* conformer. The *s-cis* isomer **9** has a nonplanar structure because of steric crowding of the hydrogens on the two terminal methylene groups.[13,14] Finally, **9** undergoes conrotatory ring closure via **10** to **5**, with an activation energy of only 3 kcal/mol. The "early" transition structure **10** differs from **9** by conrotatory rotation of the two methylene groups and the distance between the termini forming the new carbon−carbon bond (3.19 Å in **9** and 2.65 Å in **10**). Note that the rate-determining step in the zwitterionic pathway is the initial ring-opening step, i.e., **1** → **7**, whereas that in the concerted rearrangement is the ring-closing step, i.e., **3** → **5**. The energy of the transition state for the concerted rearrangement of the minor

† Vanderbilt University.
‡ N. Copernicus University.
§ Vanderbilt Medical Center.
⊥ University of Alabama.

(1) (a) Vick, B. A.; Zimmerman, D. C. *Biochem. Biophys. Res. Commun.* **1983**, *111*, 470. (b) Corey, E. J.; Matsuda, S. P. T.; Nagata, R.; Cleaver, M. B. *Tetrahedron Lett.* **1988**, *29*, 2555. (c) Hamberg, M.; Miersch, O.; Sembdner, G. *Lipids* **1988**, *23*, 521.

(2) (a) Brash, A. R.; Baertschi, S. W.; Ingram, C. D.; Harris, T. *M. Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3382. (b) Song, W.-C.; Baertschi, W.; Boeglin, W. E.; Harris, T. M.; Brash, A. R. *J. Biol. Chem.* **1993**, *268*, 6293. (c) Koljak, R.; Boutaud, O.; Shieh, B.-H.; Samel, N.; Brash, A. R. *Science* **1997**, *277*, 1994.

(3) (a) Kim, S. J.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613. (b) Malacria, M.; Rournestant, M. L. *Tetrahedron* **1977**, *33*, 2813. (c) Bertrand, M.; Dulcere, J. P.; Gil, G.; Rournestant, M. L. *Tetrahedron Lett*. **1979**, 1845. (d) Doutheau, A.; Gore, J.; Diab, J. *Tetrahedron* **1985**, *41*, 329 and references therein.

(4) This paper deals with only the *E*-vinyl allene oxide isomer. The corresponding *Z*-isomer is not applicable to the present work.

(5) Hess, B. A., Jr.; Eckart, U.; Fabian, J. *J. Am. Chem. Soc*. **1998**, *120*, 12310.

(6) Calculations were performed with GAUSSIAN 94: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *GAUSSIAN 94,* Revision DA; Gaussian Inc.: Pittsburgh, PA, 1995.

(7) Harriharan, P. C.; Pople, J. A. *Chem. Phys. Lett*. **1972**, *66*, 217.

(8) Becke, A. J. *J. Chem. Phys*. **1993**, *98*, 5648.

(9) Several structures gave restricted solutions which were unstable, and for these the unrestricted form of the single-determinant-based DFT method was used. Harmonic frequencies were used to characterize all stationary points and to compute zero-point energies.[10] Intrinsic reaction coordinate (IRC) calculations (Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys*. **1989**, *90*, 2154) were performed for all transition structures.

(10) For geometries, see Figure S1; for total energies, zero-point energies, and energies relative to 2-cyclopenten-1-one, see Table S1.

(11) Planar *s-cis*-vinyl allene oxide (**11**) is a transition structure linking the two enantiomeric conformers of **3**. The potential surface here is extremely flat, with the energies of **3** and **11** (see Figure S1 and Table S1) essentially the same, but frequency calculations for **3** gave only real frequencies and one imaginary frequency for **11**.

(12) A comparable calculation[5] gives an energy difference between allene oxide and oxyallyl of 16.2 kcal/mol, which suggests that the zwitterion (or diradical) is significantly stabilized by the vinyl group.

(13) The planar "conformation" of *s-cis*-vinyl oxyallyl (**12**) was located (1.9 kcal/mol above **9**, see Table S1 and Figure S1) and is a transition structure linking the two enantiomeric conformations of **9**.

(14) A reviewer suggested that a "nonsynchronous pathway in the conversion of **3** to **5**" might exist. This would presumably involve the intermediacy of **9**. A search for a transition structure linking **3** to **9** failed, with all attempts leading to **4**. Hence, it is likely that no such TS exists.

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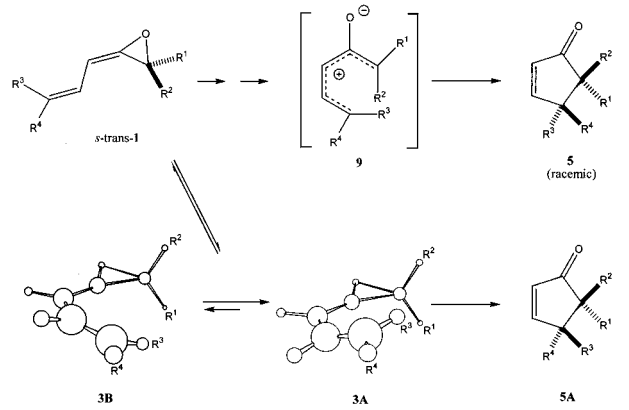
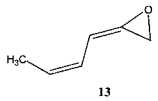
Scheme 1. (R^1 Is Larger than R^2)



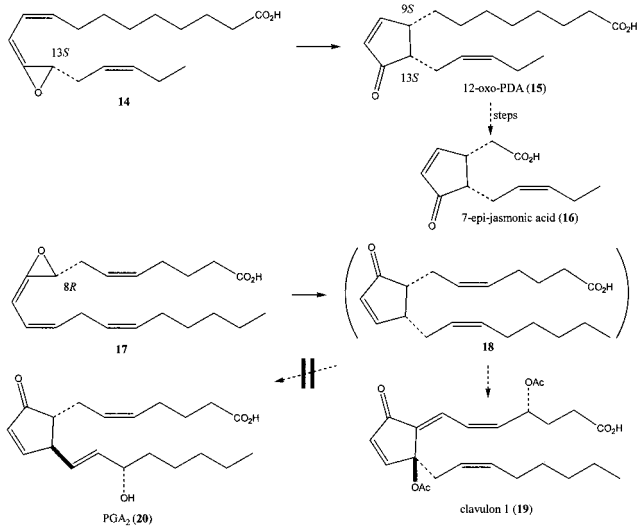
s-cis conformer **3** is slightly lower than that of **6** in the alternate zwitterionic pathway (vide supra), and therefore the Curtin−Hammet postulate predicts that the concerted pathway should be slightly favored over the zwitterionic pathway.

The presence of additional substituents not only raises the issue of diastereoselectivity but also is likely to affect the relative energies of the transition states involved in these two competing reaction paths. Therefore, the rearrangement of a prototype, (*Z*)-1-propenyl allene oxide (**13**), was examined. The two reaction



pathways were also found to be competitive: 26.7 kcal/mol for **3′** → **4′**, 27.1 kcal/mol for **13** (**1′**) → **6′**, 6.0 kcal/mol for **13** → **2′**, and 2.7 kcal/mol for **3′** → **2′**.[9,15] However, in this case the zwitterionic pathway was found to be slightly more favorable than the concerted pathway. Stereochemistry could be a characteristic guide for distinguishing between the occurrence of these two competing mechanisms (Scheme 1). The stereochemistry of the zwitterionic pathway should be determined by the initial ring-opening of the epoxide, as well as by orbital symmetry considerations for the ring-closing step. The W-shaped oxyallyl **9** (where R^1 is larger than R^2) should be favored over the sickle-shaped isomer,[16] but the chirality of the starting material is, of course, lost. Subsequent conrotatory ring closure then affords racemic cyclopentenone **5**. On the other hand, steric effects would be of primary importance in the concerted rearrangement reaction. Of the two possible diastereomeric *s-cis* conformers, **3A** and **3B**, the

Scheme 2



conformer **3A** is expected to be of lower energy than **3B**, because in the latter R^3 is in close proximity to a larger R^1 substituent vis-à-vis a smaller R^2 substituent in **3A**. The same should hold for the transition structures linking **3A** and **3B** to cyclopentenone. Consequently, the enantioselective formation of the diastereomer, as generalized as **5A**, is preferred over the other possible diastereomer (i.e., **5**), the opposite diastereochemical outcome to that of the oxyallyl rearrangement.[17]

In practice, the rearrangement of substituted vinyl allene oxides to the corresponding 2-cyclopenten-1-ones can take place with conrotatory diastereofacial stereoselectivity but with predominant inversion of configuration at the epoxide stereogenic center. Increased racemization is expected with increasing polarity of solvent, as the oxyallyl mechanism would be operative in a polar medium. A "hybrid" mechanism would seem plausible in view of the similar activation energies of the two limiting mechanisms[18,19] and further augmentation by the action of an enzyme. A main role of an enzyme might be to shield one face of the epoxide, resulting in enantioselective torquoselectivity.[20] An enzyme could also facilitate cyclization by preorganizing the sterically less favorable *s-cis* substrate in preference to the *s-trans* conformer. In this connection, it should be noted that enzymatic conversion of the allene oxide **14** to 12-oxo-PDA (**15**) indeed takes place with complete inversion of configuration at C-13 (Scheme 2).[21] On this basis, we propose that the hitherto unknown geometry of the allene oxide double bond in **14** most likely has the *E*-configuration, as indicated in Scheme 2.[22]

In summary, an ab initio study on the rearrangement of vinyl allene oxide to cyclopentenone indicates that either a concerted mechanism or an oxyallyl pathway can be operative and that the competing paths have comparable activation energies. Under suitable conditions, the rearrangement reactions of substituted vinyl allene oxides are predicted to take place with excellent diastereoselectivity, as well as with predominant inversion of configuration at the epoxide stereogenic center.

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Supporting Information Available: Energies (Tables S1 and S2) and geometries (Figures S1 and S2) of **1**−**12** and the methyl-substituted derivatives **1′**−**10′** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For geometries, total energies, zero-point energies, and energies relative to 4-methyl-2-cyclopenten-1-one, see Figure S2 and Table S2.

(16) Cf.: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1.

(17) In the present study, where $R^1 = R^2 = H$, conformers **3A** and **3B** are enantiomeric and thus isoenergetic.

(18) Conceptually, this "hybrid" pathway can be regarded as *midway* between typical S_N1 (oxyallyl) and S_N2 (concerted) mechanisms.

(19) There is only one report on the stereochemistry of the oxidative rearrangement of vinyl allenes to cyclopentenones, where excellent diastereocontrol was rationalized by conrotation.[3a]

(20) For the first use of "torquoselectivity", see: (a) Kirmse, W.; Rondan, N.; Houk, K. N. *J. Am. Chem. Soc*. **1984**, *106*, 7989. (b) Kallel, E. A.; Houk, K. N. *J. Org. Chem*. **1989**, *54*, 6006.

(21) This transformation is known to play a pivotal role in the biosynthesis of the growth hormone jasmonic acid in plants. Analogous transformations may be involved in the synthesis of marine eicosanoids such as the clavulones (**17** → **18** → **19**). While Brash and co-workers obtained racemic **18** during the isolation of **17**, the former compound could be a product generated nonenzymatically during isolation. Moreover, recent evidence suggests that the biosynthesis of PGA_2 in sea coral is directed by a cyclooxygenase, not by a lipoxygenase pathway: Varvas, K.; Järving, I.; Valmsen, K.; Brash, A. R.; Samel, N. *J. Biol. Chem.* **1999**, *274*, 9923.

(22) Another obvious mechanism of chiral transfer by an enzyme is to confer a chiral environment around the otherwise planar zwitterionic intermediate **9** such that a single enantiomer (e.g., **15**) of the *cis*-4,5-disubstituted 2-cyclopenten-1-one product is formed. Should the double bond of naturally occurring allene oxides have the *Z*-configuration, the observed chirality transfer would require such a scenario.