H_8 6.09 d, H_{10} 6.18 d, H_{11} 7.46 dxd, H_{12} 6.06 ppm d, $J_{7,8}$ = 12.5 and $J_{11,12}$ = 14.5 Hz; 7,9-dicis H_7 5.97 d, H_8 6.60 d, H_{10} 6.14 d, H_{11} 7.52 dxd, H_{12} 6.03 d, $J_{7,8}$ = 12.0, $J_{11,12}$ = 15 Hz). Direct or sensitized irradiation of these tetraene ketone isomers results in conversion to a mixture of the 7-trans isomers as indicated by complete replacement of the singlet at 1.50 ppm (C_5–Me in 7-cis isomers) by a broad lower field singlet between 1.70 and 1.75 ppm, corresponding to the C_5-Me's in 7-trans isomers.

An obvious trend in this series of compounds is that geometric isomerization around the 7,8-double bond,[12] when the conjugation involves four double bonds or longer, shows a decay ratio prohibitively in favor of the trans. This somewhat unexpected result, however, can be rationalized by the excited state tortional potential curve around the 7,8-bond. Because of higher ground state and $S_0 \rightarrow T_1$ excitation energies, cis triplets are expected to be much higher in energy than the trans. If one further assumes, in agreement with the calculated results for tetraenes,[4a] that any intermediate structures in going from trans to cis are higher in energy than the trans, when one expects excitation from either isomer will result in the exclusive formation of the trans. The photochemical results, therefore, simply reflect the distorted shape of the potential curve. It is worth noting that the excited state potential curve for the slightly less hindered 11-*cis*-retinal is available in the literature[13] which takes the general shape of our postulated model for the 7-cis compounds. It is also interesting to note that extension of our results would predict that 7-*cis*-retinal isomers should not be present in significant amounts in the photostationary state mixture. This agrees with present knowledge of retinal photochemistry which is based on study starting from the 7-trans isomers.[14] A more definitive confirmation of this prediction would be irradiation of the 7-cis isomers. The preparation of such hindered retinal isomers is in progress in our laboratory.[15]

(12) IId is probably more appropriately considered as a tetraene. For example, the triplet energy of a trienealdehyde (43.5 kcal/mol) is known to be much lower than that of hexatriene (48): D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

(13) (a) J. R. Wiesenfeld and E. W. Abrahamson, *Photochem. Photobiol.*, **8**, 487 (1968); (b) J. Langlet, B. Pullman, and H. Berthod, *C. R. Acad. Sci.*, 1616 (1969).

(14) A. Kropf and R. Hubbard, *Photochem. Photobiol.*, **12**, 249 (1970).

(15) This work was supported by the National Eye Institute, Public Health Service, Research Grant No. EY-AM 00918.

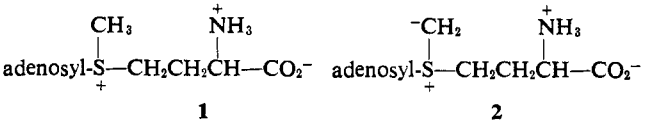
V. Ramamurthy, R. S. H. Liu*
Department of Chemistry, University of Hawaii
Honolulu, Hawaii 96822

Received May 8, 1974

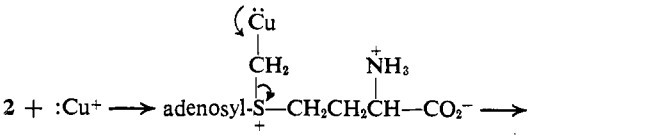
A Laboratory Model for the Biosynthesis of Cyclopropane Rings. Copper-Catalyzed Cyclopropanation of Olefins by Sulfur Ylides

Sir:

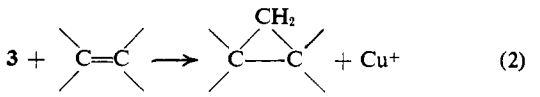
The biosynthesis of the cyclopropane ring in a number of natural products is known to occur by the transfer of a methylene group from the methyl group of *S*-adenosylmethionine (**1**) to an unactivated olefin such as an oleic ester.[1] It has been suggested[2] that the process involves the corresponding ylide (**2**) but a viable scheme for the *in vivo* methylene transfer from **2** to the olefin has never been advanced. The copper-induced cyclopropanation of unactivated olefins by diazoalkanes[3] and the electronic and behavioral analogy between diazoalkanes and ylides[4,5] suggest that transition metal-induced transfer of a methylene group from **2** to the olefin *via* a metal–carbene complex (such as **3**) may be occurring. Equations 1 and 2 illustrate the process for the case of copper(I);[4] copper(II) salts used in diazoalkane decompositions may be reduced to copper(I) *in situ*.[5] It is of considerable interest to note that the binding of the metal ion to the ylide (**2**), derived from *S*-adenosylmethionine (**1**), and/or the cleavage of the C–S bond may be facilitated by strain-free chelate formation involving strategically placed electronegative atoms (see **4**).[6]



1 **2**



3 (1)



(2)

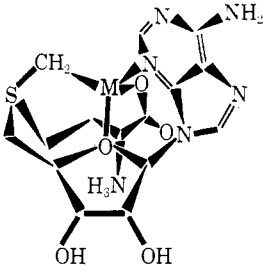
The credibility of this biosynthetic scheme has been demonstrated by the cyclopropanation of the following olefins by diphenylsulfonium methylide (**5**) in tetrahydrofuran solution at room temperature in the presence of the soluble complex cupric acetylacetonate (glpc yields, based on sulfonium salt, in parentheses): 1-heptene (39%), isobutyl vinyl ether (45%), *trans*-2-octene (48%), *cis*-2-octene (41%), cyclohexene (35%), 3-methylcyclohexene (31%, two stereoisomers produced), tetramethylethylene (yield not determined).[7,8]

(3) D. J. Cardin, B. Cetinkaya, M. J. Doyle, and M. F. Lappert, *Chem. Soc. Rev.*, **2**, 99 (1973); V. Dave and E. W. Warnhoff, *Org. React.*, **18**, 217 (1970); C. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 119 (1970).

(4) B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 138 (1967).

(5) Ylides have recently been used as models for diazoalkanes in a mechanistic study of the copper-induced decomposition of the latter: R. G. Salomon and J. K. Kochi, *J. Amer. Chem. Soc.*, **95**, 3300 (1973).

(6) The tetrahedral bonding of the metal is appropriate for a d^{10} complex.

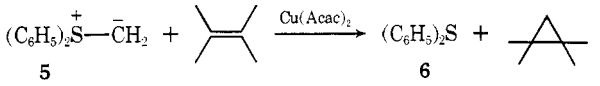


4

(7) The only other reported example of metal ion induced cyclopropanation by an ylide is that of Trost who recognized the analogy between diazoalkanes and ylides.[4] He demonstrated that 7-benzoylnorcarane is generated in 5% yield by reaction of the stabilized ylide dimethylsulfonium phenacylide and cyclohexene in the presence of cupric sulfate.

(8) No reaction occurs without the catalyst.

All the cyclopropanes, except that from *trans*-2-octene, were compared by glpc and mass spectrometry to authentic samples prepared by the Simmons–Smith procedure.[9] That from *trans*-2-octene proved to be a single stereoisomer, presumably *trans*-1-methyl-2-*n*-pentylcyclopropane, which had similar but nonidentical gas chromatographic and mass spectrometric behavior with the corresponding cis isomer. The latter, contaminated with 7% of the trans isomer, was produced from a sample of *cis*-2-octene which contained 6% trans isomer. Thus, the cyclopropanations appear to be stereospecific with retention as in the corresponding reactions with diazomethane.[10] The yields of diphenyl sulfide (**6**) varied from 81% to nearly quantitative.



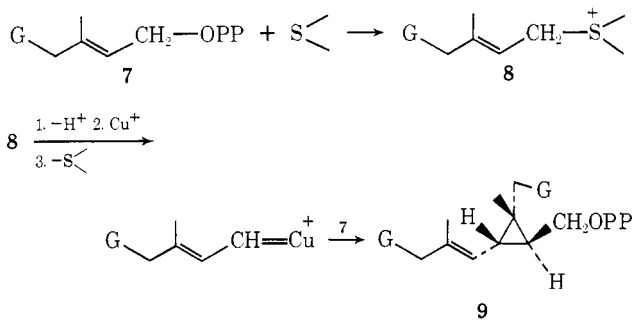
5 6

Ethylene (6%) was detected as a by-product in the cyclopropanation of cyclohexene.

The best yields were obtained when the ylide was generated (3.47 mmol of methyldiphenylsulfonium tetrafluoroborate[11] and 6.79 mmol of sodium hybride were used) in the presence of the olefin (5 ml) and catalyst (1.52 mmol)[12] in the THF (8 ml) solution, but the olefin and catalyst can also be added to the preformed ylide in THF solution. In the case of cyclohexene, cyclopropanation does not occur with dimethylsulfonium methylide; a likely explanation is that, as expected, diphenyl sulfide is a better leaving group than dimethyl sulfide.

In experiments designed to assess the ease of conversion of sulfonium salts to ylides, without the use of strong bases such as the sodium hydride which we used, the disappearance of the methyl signal in the nmr spectrum of methyldiphenylsulfonium tetrafluoroborate was monitored in D_2O. Exchange was complete after 4 hr in a solution containing Na_2CO_3 (0.2 g/25 ml); during the same time no change occurred in the aromatic region. Thus, it is not unreasonable to expect a basic function of an enzyme to be capable of deprotonating sulfonium salts *in vivo*.

A reasonable biosynthetic route for presqualene pyrophosphate (**9**), based on the same concept, involves reaction of farnesyl pyrophosphate (**7**) with a sulfide, deprotonation at the allylic position of the resulting sulfonium salt (**8**), and metal-induced transfer of the carbene to the 2-double bond of a farnesyl pyrophosphate molecule. Precisely the correct stereochemistry about both the cyclopropane ring and the double bonds is expected from this route; indeed presqualene alcohol has been prepared by zinc iodide induced decomposition of an appropriate diazoalkene in the presence of farnesol,[13] a reaction which presumably involves a metal–carbene complex. Previous suggestions[14] for presqualene biosynthesis involve reactions which are not applicable to cyclopropanation of olefins by *S*-adenosylmethionine (**1**). The hypothesis presented here has the attractive feature that it is capable of explaining, by a single mechanistic concept, the two major types of cyclopropanation reactions in nature.



7 8

8 → 9

G = geranyl

This method of cyclopropanation may have theoretical and synthetic value. It is apparently the only method of generation of copper–carbenes other than the rather severely limited diazoalkane procedure; the safety and ease of preparation of ylides may make the latter most attractive precursors of these reactive intermediates. Moreover, unlike N_2, the diarylsulfide leaving group is subject to modification which should allow changes in the ease of reaction as well as a study of the encumbrance of the carbenoid by the leaving group. Investigation of these factors as well as of extensions of this principle of carbenoid generation to other types of progenitors is in progress.

Acknowledgment. We wish to thank the Health Research and Services Foundation and the National Science Foundation (Science Development Grant GU-3148) for support of this work.

(9) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973).

(10) W. Kirmse, M. Kapps, and R. B. Hager, *Chem. Ber.*, **99**, 2855 (1966).

(11) V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961). The sulfonium salt was best prepared using Meerwein's reagent: E. J. Corey, M. Jantelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967).

(12) Increasing the quantity of catalyst does not improve the yield.

(13) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1783 (1971).

(14) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **93**, 1780 (1971); H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *ibid.*, **93**, 1783 (1971); W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1970); J. Edmond, G. Popjak, S. Wong, and V. P. Williams, *ibid.*, **246**, 6254 (1971); B. M. Trost and W. G. Biddlecom, *J. Org. Chem.*, **38**, 3438 (1973).

Theodore Cohen,* Glen Herman
Toby M. Chapman, David Kuhn
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received April 29, 1974

Mechanism of Hydrogen Exchange in Amides

Sir:

There has been considerable recent interest in hydrogen exchange in amides.[1] It seems to be generally accepted that the mechanism for the acid-catalyzed ex-

(1) (a) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970); (b) M. S. Miller and I. M. Klotz, *J. Amer. Chem. Soc.*, **95**, 5694 (1973), D. L. Hunston and I. M. Klotz, *J. Phys. Chem.*, **75**, 2123 (1971); (c) R. S. Molday, S. W. Englander, and R. G. Kallen, *Biochemistry*, **11**, 150 (1972), R. S. Molday and R. G. Kallen, *J. Amer. Chem. Soc.*, **94**, 6739 (1972); (d) M. Liler, *J. Chem. Soc., Perkin Trans. 2*, 720, 816 (1972); (e) L. C. Martinelli, C. D. Blanton, and J. F. Whidby, *J. Amer. Chem. Soc.*, **93**, 5111 (1971), *J. Phys. Chem.*, **75**, 1895 (1971); (f) R. L. Vold, E. S. Daniel, and S. O. Chan, *J. Amer. Chem. Soc.*, **92**, 6771 (1970); (g) M. Sheinblatt, *ibid.*, **92**, 2505 (1970); (h) C. Y. S. Chen and C. A. Swenson, *ibid.*, **91**, 234 (1969); (i) T. Schleich, R. Gentzler, and P. H. von Hippel, *ibid.*, **90**, 5954 (1968).