free-energy increment is an enthalpic effect and not an entropic effect is quite contrary to previous analyses[11] and contrary also to suggestions[12-14] that restriction of internal motion of hydrocarbon chains in water is an important feature.

Finally, I wish to point out that the hydrophobic effect can most logically be discussed only by assessing the expected thermodynamic parameters for solution in water in the absence of any unusual or hydrophobic effect. Thus, $\Delta G_t°$ for transfer of *n*-hexane from *n*-hexane solvent to water is very positive (7.8 kcal mol^{-1}); however, not all of this is due to a hydrophobic effect, because $\Delta G_t°$ for transfer from *n*-hexane solvent to many other solvents is also positive, e.g., 2.6 kcal mol^{-1} to Me_2SO and 3.9 kcal mol^{-1} to ethylene glycol. Only by factoring out the expected or normal solvent effect for transfer to water can the unusual or hydrophobic effect quantitatively be obtained. Similarly, $\Delta H_t°$ for transfer of *n*-hexane from *n*-hexane solvent to water is 0; this does not mean that there is no enthalpic contribution to the hydrophobic effect but is the result of a positive hydrophobic enthalpic effect (about 2.5 kcal mol^{-1}) in combination with a negative normal solvent effect for transfer to water.

(11) W. Kauzmann, *Adv. Protein Chem.*, **14**, 1 (1959). See also the review by F. Franks in "Water, a Comprehensive Treatise", Vol. 2, Plenum Press, New York, 1973, p 323.
(12) R. H. Aranow and L. Witten, *J. Phys. Chem.*, **64**, 1643 (1960).
(13) O. W. Howarth, *J. Chem. Soc., Faraday Trans. 1*, **71**, 2303 (1975).
(14) M. Osinga, *J. Am. Chem. Soc.*, **101**, 1621 (1979).

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Received January 24, 1980

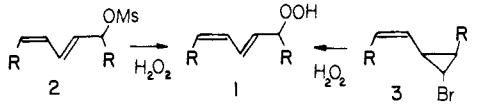
A New Route to Lipid Hydroperoxides: Orbital Symmetry Controlled Ring Opening of Vinylcyclopropyl Bromides

Sir:

Recent reports that diene hydroperoxides are formed from polyunsaturated fatty acids by enzymes present in platelets and polymorphonuclear leukocytes have stimulated interest in this class of compounds. Arachidonic acid (5,8,11,14-eicosatetraenoic acid, 20:4), for example, is converted to 12-(hydroperoxy)eicosatetraenoic acid (12-HPETE) by a platelet enzyme,[1,2] and an enzyme present in leukocytes converts this fatty acid into 5-(hydroperoxy)eicosatetraenoic acid[3] (5-HPETE). The spectrum of biological activity of these hydroperoxides remains to be fully determined, but it has been suggested that these compounds play an important role in inflammation. 5-HPETE, in particular, is the proposed intermediate in the biosynthesis of SRS-A,[3] a compound believed to be involved in the allergic response.

Fatty acid hydroperoxides are also formed in free-radical autoxidation, and random oxidation of lipid may play an important biological role. It has, in fact, been suggested that heart attacks and strokes may be essentially lipid peroxidation diseases.[4,5]

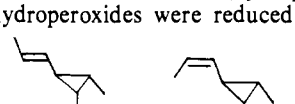
While we have earlier reported on chromatographic methods for purification of fatty acid hydroperoxides formed by singlet oxygen[6] or free-radical oxidation[7] of the fatty acid, these procedures, while convenient, provide relatively low conversion from fatty acid to isolated hydroperoxide products. Recently, direct peroxide displacement to diene mesylates (prepared in an elegant scheme from the starting fatty acid) **2** → **1** has been used[8,9] to



2 1 3

prepare specific diene hydroperoxides. We have also utilized direct peroxide displacement[10,11] (silver ion assisted displacement of halides)[12,13] for preparation of prostaglandin endoperoxides and allylic hydroperoxides, and we report here a method for the preparation of lipid hydroperoxides by the use of this silver ion/hydrogen peroxide reagent. The known orbital symmetry control of stereochemistry in the ring opening of cyclopropyl halides[14] suggested that the route **3** → **1** might provide a vehicle for the preparation of the target compound. While the reaction of alkyl-substituted cyclopropyl halides has been studied extensively[14,15] with regard to mechanism, vinylcyclopropyl halides like **3**, on the other hand, have not been thoroughly investigated.[16]

Treatment of the model bromides **4** or **5**[17] with excess silver trifluoroacetate/hydrogen peroxide in diethyl ether at 25 °C led to a mixture of geometric isomers of 2-(hydroperoxy)-3,5-heptadiene. The hydroperoxides were reduced with triphenyl-



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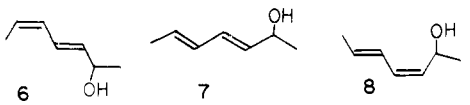
phosphine, and the resulting alcohols were analyzed on a 25-m SCOT Carbowax column. The product alcohols **6**–**8** were in-



6 7 8

dependently prepared by reduction of the known[18] 3,5-heptadien-2-ones with lithium aluminum hydride. Bromide **4** leads to a 50:50 mixture of alcohols **6** and **7** while **5** gives a 92:8 mixture of these diene alcohols. None of the *cis,trans*-diene alcohol **8** was detected in the reaction of either **4** or **5** with Ag^+/H_2O_2.

With the validity of the approach established, we next sought a route that would be generally useful for the preparation of trans,cis- and trans,trans-substituted diene hydroperoxides. Lipid hydroperoxides with both trans,cis and trans,trans stereochemistry are formed in autoxidation, and the factors that control product stereochemistry in free-radical oxidation have only recently been established.[19] We chose the 12-hydroperoxides **15a** and **15b** as target molecules since they are representative of the general class of fatty acid hydroperoxides, and we had earlier[6] prepared these compounds by singlet oxygen methods.

The synthesis, which is general for fatty acid hydroperoxides, proceeds[20] from the dihydropyran **9** to **10** by addition of di-

(1) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3400.
(2) Nugteren, D. H. *Biochim. Biophys. Acta* **1975**, *380*, 299.
(3) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2463, 7865.
(4) Salmon, J. A.; Smith, D. R.; Flowers, R. J.; Moncada, S.; Vane, J. R. *Biochim. Biophys. Acta* **1978**, *523*, 250.
(5) Moncada, S.; Gryglewski, R. J.; Bunting, S.; Vane, J. R. *Prostaglandins* **1976**, *15*, 12.
(6) Porter, N. A.; Logan, J.; Kontoyiannidou, V. *J. Org. Chem.* **1979**, *44*, 3177.
(7) Porter, N. A.; Wolf, R. A.; Yarbro, E. M.; Weenen, H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 1058.
(8) Corey, E. J.; Marfat, A.; Falik, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.
(9) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S. I. *J. Am. Chem. Soc.* **1980**, *102*, 1435.
(10) Porter, N. A.; Byers, J. D.; Holden, K. M.; Menzel, D. B. *J. Am. Chem. Soc.* **1979**, *101*, 4319.
(11) Porter, N. A.; Byers, J. D.; Ali, A. E.; Eling, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 1183.
(12) Kopecky, K. R.; van de Sande, J. H.; Mumford, C. *Can. J. Chem.* **1968**, *46*, 25.
(13) Cookson, P. G.; Davies, A. G.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* **1976**, 1022.
(14) Schleyer, P. von R.; Su, T. M.; Saunders, M.; Rosenfeld, J. C. *J. Am. Chem. Soc.* **1969**, *91*, 5174.
(15) Parham, W. E.; Yong, K. S. *J. Org. Chem.* **1970**, *35*, 683.
(16) Landgrebe, J. A.; Becker, L. W. *J. Org. Chem.* **1968**, *33*, 1173.
(17) The model cyclopropyl bromides **4** and **5** were prepared in a manner similar to bromides **14a** and **14b**. Details of this study will be subsequently published.
(18) Kluge, A. F.; Lillya, C. P. *J. Org. Chem.* **1971**, *36*, 1988.
(19) Porter, N. A.; Weber, B. A.; Weenen, H.; Khan, J. A. *J. Am. Chem. Soc.*, in press.
(20) Woods, G. F.; Sanders, H. *J. Am. Chem. Soc.* **1946**, *68*, 2483.

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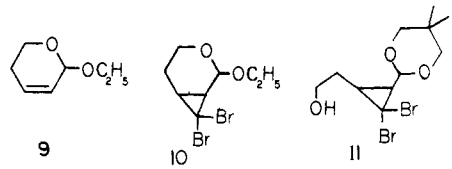
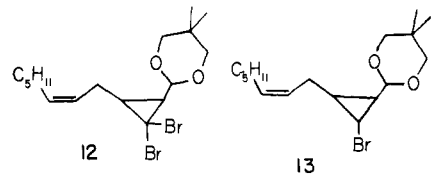
bromocarbene.[21,22] Reaction of **10** with dimethylpropanediol and



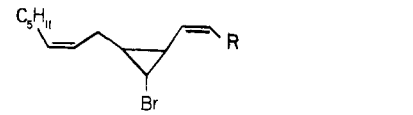
9 10 11

a trace of toluenesulfonic acid gave the acetal **11** (55%) that was oxidized to the corresponding aldehyde (75%) with pyridinium chlorochromate for 10 h.[22] The aldehyde was reacted with the ylide $PPh_3CHC_5H_{11}$ in THF at 0 °C for 2 h, giving the acetal **12** in 71% isolated yield. Reaction of **12** with methyllithium in



12 13

ether at −78 °C followed by workup by addition of water gave the bromocyclopropane **13** (80%). Only one bromine was removed in the methyllithium exchange, and published work[23] suggests that the acetal directs the methyllithium to remove the *cis*-bromine. Hydrolysis of the acetal with 88% formic acid for 31 h at 0 °C led to the corresponding aldehyde (88%) and reaction of this aldehyde with the ylide $PPh_3CH(CH_2)_6COOCH_3$ or $PPh_3CHCH_2CH{=}CH(CH_2)_3COOCH_3$ gave the target cyclopropyl bromides **14a** or **14b** in 85% isolated yield. The synthesis

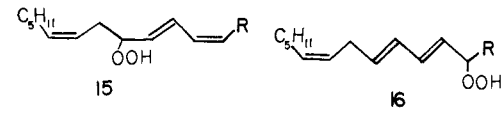


14 a, R = $-(CH_2)_6COOCH_3$

b, R = $-CH_2CH{=}CH(CH_2)_3COOCH_3$

of **14** is economical in terms of time and starting materials. Further, a judicious choice of Wittig reagents should make a variety of appropriately substituted cyclopropyl bromide precursors available for study.

Ring opening of **14a** was affected with excess silver trifluoroacetate and hydrogen peroxide present. In a typical reaction, 40 mg of **14a** and 950 μL of hydrogen peroxide in 6.6 mL of ether at 0 °C was treated with 758 mg of silver trifluoroacetate for 5 min. Chromatography of the product mixture after workup (bicarbonate and aqueous wash) on 10-μm silica showed two peroxide products (total yield 70–80%) formed in a 60:40 product ratio (**15**/**16**). The hydroperoxide **15a** was chromatographically



15 16

a, R = $-(CH_2)_6-COOCH_3$

b, R = $-CH_2CH{=}CH{-}(CH_2)_3COOCH_3$

identical with authentic material prepared by singlet oxygen oxidation of eicosatrienoic acid methyl ester. Reduction of **15a** and **16a** gave the corresponding alcohols which were characterized by IR, UV, and ^1H and ^{13}C NMR.[6,22] Hydrogenation, silylation and GC/MS analysis requires that **15a** is 12-substituted and **16a** has oxygen functionality at carbon 8. The infrared spectra confirm that **15a** has trans–cis-conjugated diene stereochemistry while **16a** has the trans,trans-substituted diene[24] structure.

The reaction of **14b** with silver trifluoroacetate and hydrogen peroxide provides the hydroperoxides **15b** and **16b**. In addition to IR, UV, GC/MS, and NMR characterization of the corresponding alcohols, decoupling experiments on the hydroperoxides, themselves, establish the stereochemistry as shown. Thus, the vinyl region of **15b** consists of signals at δ 6.57 [dd, H_{10}, $J_{10,11}$ = 15 Hz (trans 10,11)] and δ 5.95 [dd, H_9, $J_{8,9}$ = 11.3 Hz (cis 8,9)] while that of **16b** has signals at δ 6.27 [dd, H_9, $J_{9,10}$ = 15 Hz (trans 9,10)], δ 6.06 (dd H_{10}), and δ 5.72 [dt, H_{12}, $J_{11,12}$ = 15 Hz (trans 11,12)].

The ring-opening reaction of vinylcyclopropyl bromides thus affords lipid diene hydroperoxides with stereochemical control. The products formed in the ring opening of cyclopropyl bromide **14** are consistent with a mechanism involving formation of an intermediate pentadienyl cation. The preference for the thermodynamically less stable[25] trans,cis product **15** over the trans,trans isomer **16** is puzzling, however. Experiments designed to exploit the synthetic potential of this approach[26] and to provide mechanistic details of the ring-opening reaction are currently in progress.

Acknowledgments. This work was supported by NIH Grant HL-17921. N.A.P. gratefully acknowledges an RCDA 1977–1982.

Supplementary Material Available: Experimental details for the synthesis of compounds **9–16** are available upon request (8 pages). Ordering information is given on any current masthead page.

(21) Makosza, M.; Fedorynski, M. *Rocz. Chem.* **1976**, *50*, 2223.

(22) All new compounds were characterized by NMR (^1H and ^{13}C) and gave satisfactory C,H analyses. Details of the synthetic procedures may be obtained in the Supplementary Material to this communication.

(23) Taylor, K. G.; Chaney, J. *J. Am. Chem. Soc.* **1976**, *98*, 4158.

(24) Chan, H. W. S.; Levett, G. *Lipids* **1977**, *12*, 99.

(25) Chan, H. W. S.; Levett, G.; Matthew, J. A. *Chem. Phys. Lipids* **1979**, *24*, 245.

(26) Methods for hydrolysis of lipid hydroperoxide methyl esters have recently been reported. Thus, not only the methyl esters but also the free acids are available by this approach. See ref 8 and 9. While the base hydrolysis methods reported do lead to fatty acid hydroperoxides, we have found that hog pancreas lipase (ref 10 and 11) is a far superior reagent for hydrolysis.

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Received March 31, 1980

Reversible Conformational Changes Induced by Light in Poly(L-glutamic acid) with Photochromic Side Chains

Sir:

Polypeptides containing photoisomerizable azo aromatic chromophores were first investigated by Goodman and associated in 1966–1967 with ORD techniques.[1] In connection with more recent CD studies[2,3] in different laboratories, we report here some preliminary data indicating the possibility of producing, by irradiation, reversible $\beta \rightleftharpoons$ coil transition in water-soluble poly(L-glutamates) containing azobenzene groups in the side chains. In particular, it is shown that the pK value for the order–disorder conformational transition depends, in these polymers, on the dark and light conditions.

The photochromic polymers (Scheme I) were prepared from high molecular weight poly(L-glutamic acid) ($\bar{M}_v$ 200 000), fractionated by gel-filtration chromatography on Sephadex G50, by reaction with *p*-aminoazobenzene in the presence of dicyclohexylcarbodiimide and *N*-hydroxybenzotriazole[4] in dimethylformamide. Samples containing 13–56 mol % of azo groups were

(1) (a) Goodman, M.; Kossoy, A. *J. Am. Chem. Soc.* **1966**, *88*, 5010–5015. (b) Goodman, M.; Falxa, M. L. *Ibid.* **1967**, *89*, 3863–3867.

(2) Houben, J. L.; Pieroni, O.; Fissi, A.; Ciardelli, F. *Biopolymers* **1978**, *17*, 799–804.

(3) (a) Ueno, A.; Anzai, J.; Osa, T.; Kadoma, Y. *J. Polym. Sci., Polym. Lett. Ed.* **1977**, *15*, 407–410; (b) *Bull. Chem. Soc. Jpn* **1979**, *52*, 549–554.

(4) König, W.; Geiger, R. *Chem. Ber.* **1973**, *106*, 3626–3635.

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