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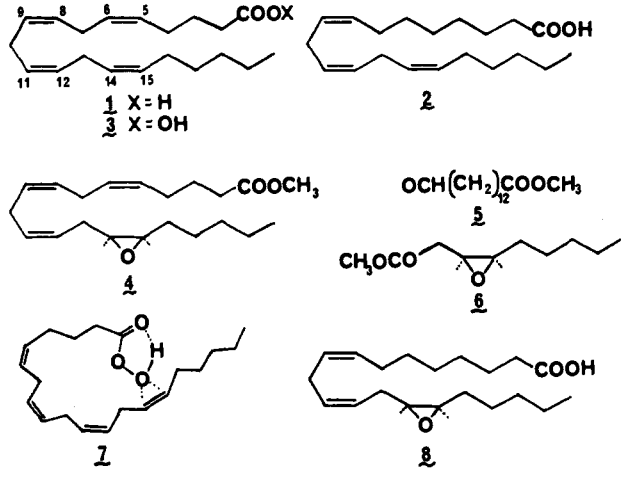
Communications to the Editor

Selective Epoxidation of Eicosa-*cis*-5,8,11,14-tetraenoic (Arachidonic) Acid and Eicosa-*cis*-8,11,14-trienoic Acid

Sir:

The key role of arachidonic acid (**1**) as the predecessor of a large family of biologically important substances including prostaglandins (PG's), thromboxanes, SRS-A, HETE, and prostacyclin (members of the "arachidonic cascade" [1]) depends on highly selective enzymatic oxidation of this substrate as a primary event. Similarly, selective oxidation of eicosa-*cis*-8,11,14-trienoic acid (**2**) initiates the series of transformations leading to PG_1 derivatives. Despite the great interest in such controlled biological oxidations of **1** and **2**, and despite the obvious utility of the primary oxidation products as intermediates for the synthesis of various metabolites of **1** and **2**, there has been no demonstrated example of selective *chemical* oxidation of these polyunsaturated substrates. This communication describes the first successful approach to this chemical problem, specifically new methodology for epoxidation of either the double bond *closest* or *farthest* from the carboxyl function of **1** or **2**.



Direct epoxidation of **1** or **2**, or their esters, by peroxy acid reagents, e.g., *m*-chloroperoxybenzoic acid, is essentially nonselective and leads to a mixture of all possible oxides.[2] In contrast, *internal* epoxidation of **1** or **2** under the proper conditions has now been found to be *highly* selective.

The preparation of peroxyarachidonic acid (**3**) by previously detailed methods proved to be elusive. However, it was possible to generate solutions of this self-reactive intermediate by the following new method. A soultion of *pure* (>99%) **1** in dry methylene chloride was allowed to react with 1.05 equiv of carbonyldiimidazole at 25 °C for 20 min to form arachidonylimidazole and this solution was added over 2 min to a cold (0 °C), anhydrous solution (~3.5 M) of hydrogen peroxide (20 equiv) in ether containing 0.01 equiv of lithium imidazolide as basic catalyst.[3] After 3-min stirring, additional methylene chloride was added along with 15 equiv of finely powdered anhydrous potassium bisulfate and the resulting mixture was stirred for 3 min.[4] Separation of the cloudy supernatant solution and addition of anhydrous sodium sulfate provided a dry solution of the peroxy acid **3**.[5]

Upon standing at 20 °C, the peroxy acid **3** gradually was transformed into a more polar product which showed a slightly lower R_f than **1**. Esterification of the reaction product with diazomethane gave after isolation >98% yield of essentially pure[6] epoxy ester **4**.[7] The structure of **4** was ascertained by catalytic hydrogenation (in tetrahydrofuran (THF) over Pd/C catalyst at 1 atm) to the saturated epoxy ester and subsequent cleavage with periodic acid in aqueous THF (or alternatively in two steps with (a) perchloric acid–water–dimethoxyethane for glycol formation and (b) lead tetraacetate) to give in 85% yield (after extractive isolation) the ester aldehyde **5** which was fully characterized by ^1H NMR, IR, and mass spectra and by oxidation (dichromate) and esterification (CH_2N_2) to dimethyl 1,12-tetradecanedioate (compared with an authentic

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sample by ^{1}H NMR, IR, and mass spectra, TLC, mp and mmp 42–43 °C). In addition, oxidation of **4** by sodium periodate–potassium permanganate in basic medium followed by methylation (CH_2N_2) and chromatography gave methyl 3,4-epoxynonenoate (**6**) in good yield.

This remarkably selective and unprecedented[8] internal epoxidation of peroxyarachidonic acid **3** to form 14,15-epoxyarachidonic acid, which clearly occurs by intramolecular oxygen transfer, indicates that the 15-membered cyclic structure **7** is energetically quite favorable compared with alternative geometries involving more proximate double bonds and smaller rings. It is clear from examination of space-filling models that structure **7** is free of serious internal nonbonded repulsion or angle strain, as would, for example, be associated with internal epoxidation of the $\Delta^{5,6}$ double bond of **3**. The sizable preference for **7** over the alternative structures suggests that there may be a tendency of arachidonic acid itself to adopt a strongly bent, "J"-like shape and that the favored transition state for oxygen transfer may be an (S_N2 like) arrangement with the center of the C=C π cloud attacking oxygen back side to and colinear with the O—O bond being broken.

Using a different reaction scheme the 5,6-oxide of arachidonic acid could also be obtained selectively. Treatment of pure arachidonic acid in THF–water (1.7:1) with 5 equiv of potassium bicarbonate and 8 equiv of potassium triiodide at 0–5 °C for 3 days, followed by rapid extractive isolation, afforded an unstable iodo δ-lactone as the only neutral product (R_f values of the lactone and **1**, 0.82 and 0.20, respectively, on silica gel plates using CH_2Cl_2–CH_3OH, 95:5). The oily iodo lactone was immediately treated with excess 0.2 N lithium hydroxide in THF–water (3:2) at 25 °C for 3 h. Extractive isolation and methylation of the product by diazomethane in ether afforded after chromatography 68% methyl 5,6-epoxyarachidonate,[9] the structure of which was established by hydrogenation (over Pd/C in ethyl acetate) to a saturated epoxide which was identical with methyl *cis*-5,6-epoxyeicosenoate.[10] The R_f values for the methyl esters of 5,6-epoxy- and 14,15-epoxyarachidonate (**4**) were 0.37 and 0.46, respectively, by TLC (silica gel) using hexane–ether (4:1).

In a similar way eicosa-*cis*-8,11,14-trienoic acid (**2**) could be converted in high yield into the corresponding peroxy acid derivative which at 0 °C for 70 h in ether–methylene chloride solution transferred oxygen preferentially to the $\Delta^{14,15}$ double bond to form the $\Delta^{14,15}$-epoxide of **2** in 94% isolated yield and >95% purity (TLC (silica gel) analysis).[11] The structure of the product (**8**) was demonstrated by comparison with an authentic sample[2] and by methylation (CH_2N_2) and hydrogenation (Pd/C in ethyl acetate) to methyl 14,15-epoxy-*cis*-eicosenoate, identical with a sample obtained as described above starting from **1**. The TLC (silica gel) R_f values found for the 14,15-, 11,12-, and 8.9-epoxides of **2** (cf. ref 2) were 0.36, 0.31, and 0.27, respectively (two developements using 95:5 methylene chloride–methanol).

The scope of these and related internal epoxidation reactions as a technique for selective oxidation of polyunsaturated fatty acids remains to be determined. Internal epoxidation does not seem to be a very favorable pathway in the case of peroxyoleic acid, since it was found with this substrate that internal epoxidation (i.e., reaction in very dilute solution) was relatively slow and further that an equimolar mixture of peroxyoleic acid and methyl oleate (each 0.15 M in methylene chloride–ether) was converted into a mixture of epoxyoleic acid and methyl epoxyoleate in a ratio of ~1:1.

As a result of the experiments described above, a multitude of new research opportunities present themselves. We are currently investigating logical extensions and a variety of approaches to internal selective epoxidation of polyunsaturated fatty acids, as well as biologically and chemically significant transformations of the products derived therefrom.[12]

References and Notes

(1) See T. K. Schaaf, *Annu. Rep. Med. Chem.*, **12**, 182 (1977).
(2) See S.-K. Chung and A. I. Scott, *Tetrahedron Lett.*, 3023 (1974). Studies in this laboratory have shown that intermolecular epoxidation of **1** yields each of the four possible monooxides which are readily separable as the methyl esters by chromatography on silica gel.
(3) To accelerate the reaction of the acylimidazole with hydrogen peroxide, presumably by generating a small concentration of the nucleophile HOO^-. In the absence of this catalyst the reaction was much slower. Anhydrous ethereal solutions of H_2O_2 were prepared by dissolving 90% H_2O_2 in ether and drying first over Na_2SO_4 and then two times over anhydrous $CaSO_4$.
(4) The function of the potassium bisulfate is to remove imidazole from the solution. Unless this is done, the peroxy acid **3** is rapidly reduced to the carboxylic acid **1**.
(5) Effectively complete conversion to peroxy acid occurs under these conditions. The formation or disappearance of peroxy acid **3** may be monitored by thin layer chromatographic analysis on silica gel using KI–starch spray for visualization and CH_2Cl_2–CH_3OH (95:5) for development (R_f values for **1** and **3**, ~0.2 and 0.6, respectively). The rate of the reaction **3** → epoxy acid is concentration independent. The peracid **3** showed infrared absorption due to carbonyl at 1748 cm^{-1} (in CCl_4) compared with 1700 cm^{-1} for **1**.
(6) By TLC (silica gel) and ^{1}H NMR analysis.
(7) Assigned structure fully consistent with ^{1}H NMR, IR, and mass spectral data.
(8) For fascinating examples of internally directed epoxidation reactions of a different character, see (a) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973); (b) R. Breslow and J. M. Maresca, *Tetrahedron Lett.*, 623 (1977); and (c) B. M. Trost and T. N. Salzmann, *J. Chem. Soc., Chem. Commun.*, 571 (1975).
(9) For some other examples of the use of this technique for internal epoxidation, see (a) E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 311 (1970); (b) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *J. Am. Chem. Soc.*, **84**, 2614 (1962); (c) P. A. Bartlett and J. Myerson, *ibid.*, **100**, 3950 (1978); (d) E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, and S. Yoo, *ibid.*, **100**, 4618 (1978); and (e) E. J. Corey and T. Hase, *Tetrahedron Lett.*, in press.
(10) Prepared by successive reaction of *cis*-5-eicosenoic acid (Applied Science Laboratories) with diazomethane and *m*-chloroperoxybenzoic acid.
(11) Peroxy acid **3** shows higher selectivity in internal oxygen transfer to the $\Delta^{14,15}$ bond than does peroxy-**2**, as evidenced by the fact that the internal epoxidation with peroxy-**2** produces detectable amounts (~10%) of other epoxides at 25 °C in contrast to **3**.
(12) This work was assisted financially by a grant from the National Science Foundation.

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Proof of Existence of Cyclic $C_4H_7^+$ Ions in the Dilute Gas State

Sir:

In contrast to the impressive body of structural, spectroscopic, and kinetic data concerning cyclopropylcarbinyl and cyclobutyl cations in condensed media,[1,2] very little is known about the corresponding gaseous species, whose very existence has not been substantiated.

Gaseous $C_4H_7^+$ ions, to be sure, have long been detected by mass spectrometry, and appearance potentials of species labeled as "cyclobutyl" or "methylcyclopropyl" ions are listed in many compilations.[3] However, most authorities carefully point out the lack of experimental evidence for the cyclic structure of the species observed, and it is generally agreed[4] that the ionization and fragmentation of a cyclic neutral parent may well entail rearrangement to a linear structure. Such cautious positions are dictated, inter alia, by the very close values of the appearance potentials of the $C_4H_7^+$ ions obtained from cyclobutane and from the butenes.

Theoretical approaches have led to somewhat conflicting conclusions[5] concerning the relative stability of the $C_4H_7^+$ ions. The results of the most recent STO-3G calculations identify the cyclopropylcarbinyl cation in the bisected configuration as the most stable cyclic $C_4H_7^+$ structure, to which others, such as planar and puckered cyclobutyl cations, are predicted to

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