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STUDIES ON THE CONFORMATIONAL MOBILITY OF ARACHIDONIC ACID. FACILE MACROLACTONIZATION OF 20-HYDROXYARACHIDONIC ACID.

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Summary: 20-Hydroxyarachidonic acid is converted to the corresponding 21-membered lactone via the 2-thiolpyridine ester in > 90% yield and at a rate which is approximately 100 times that for the saturated analog, evidence that only a modest increase in free energy is required to bring the ends of the chain into proximity.

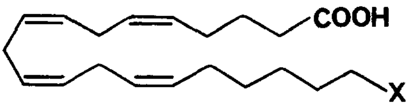
It is now clear that arachidonic acid (**1**) plays a versatile role in mammalian life processes, as a constituent of phospholipid in membranes and as a predecessor of prostanoids, leukotrienes and various hydroxy acids. Although the polyfunctionality of **1** accounts in part for this versatility, another factor may be an unusual conformational flexibility. Because of this flexibility it is possible for arachidonic chains to assume a wide variety of shapes in membranes or in enzyme pockets.

Several years ago we reported a remarkably selective transfer of the distal oxygen of peroxyarachidonic acid to the 14,15-double bond and proposed that this was due to two factors: (1) "linearity" of the transition state for S_N2-like displacement by the olefinic π-electrons at the back side of the peroxy O-O linkage, and (2) the low energy of the bent, J-like conformation which brings C(1) in proximity to the 14,15-double bond.[1] Extensive conformational search by computer and potential energy calculations performed for arachidonic acid allowed the identification of global energy minima and provided an independent indication of the conformational mobility of **1**.[2] Over 20 conformers were found to be within 1 kcal. of the minimum energy molecular geometry and over 250 conformers within 3 kcal.[2] Among these low energy conformers are several in which the ends of the chain are in proximity. This last finding suggests the desirability of further chemical studies on reactions which bring together the alpha and omega portions of **1** and its relatives. This note describes the results of a study of the lactonization of 20-hydroxyarachidonic acid (**2**). Macrolactones derived from eicosnoids have previously been investigated[3-6] and are of interest for other reasons as well.

20-Hydroxyarachidonic acid **2** was synthesized from methyl 14,15-epoxyarachidonate[1] commencing with reaction with 1 : 1.9 : 4.3 1.2 M perchloric acid-water-tetrahydrofuran (THF) at 23° for 10 hr. to form the methyl 14,15-dihydroxyarachidonate (R_f 0.31 vs 0.78 for starting epoxide on silica gel plates with 2:1 ether-hexane development) (73% yield) followed by glycol cleavage with lead tetraacetate in methylene chloride at -20° for 20 min. to afford the aldehyde **3** (>95% yield).[7,8] The Wittig reagent was prepared from the phosphonium salt **4** by reaction with 1 equiv. of *n*-butyllithium in THF at -78° for 30 min. and allowed to react in THF-hexamethylphosphorictriamide (5:1) with the aldehyde **3** for 1 hr. at -78° and then at -78 to -20° for 1.5 hr. to give after extractive isolation and chromatography the methyl ester tetrahydropyranyl ether of 20-hydroxyarachidonic acid in >90% yield. Cleavage of the THP group (0.1% tosic acid in methanol at 23° for 1.5 hr.) and saponification (2 : 1 : 0.2 THF - 1 *M* aqueous lithium hydroxide - methanol at 23° for 1.5 hr.) afforded 20-hydroxyarachidonic acid (**2**) (85% yield).

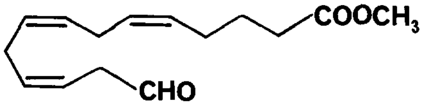
Treatment of **2** with 6 equiv. of triethylamine and 1.5 equiv. of 2-thiopyridine chloroformate[9] in methylene chloride at 0° produced the 2-pyridinethiol ester **5** which was obtained by extractive isolation as a colorless oil (homogeneous by tlc analysis, 92% yield) and subjected to lactonization by the "double activation" procedure.[10,11] Both the rate of lactonization and yield of product were found to be unusually high for formation of a 21-membered ring. When the thiol ester **5** was heated in dry toluene solution at 80° lactonization occurred with a half life estimated to be *ca.* 30 min. (or less), and workup after 4 hr. afforded a 90% isolated yield of pure 21-membered product **6**. Under these conditions the saturated analog of **5**, i.e., the 2-thiopyridyl ester of 20-hydroxyeicosanoic acid affords only about 5% yield of the 21-membered lactone after 4 hr. and 23% after 24 hr. It is estimated that the ratio of rates of cyclization of **5** and its perhydro analog is about 100. By comparison, only small variations in rates (factor of 4 maximum) were previously observed for the conversion of 2-thiopyridyl esters of saturated ω-hydroxy acids to lactones of ring size 14 to 21.[12,13]

Reaction of sodium arachidonate with iodine in water produces, not unexpectedly, a high yield of the 6-iodo-δ-lactone,[14] through involvement of the 5,6-double bond. This is also the major product from the reaction of arachidonic acid with hydrogen peroxide and iodide ion in the presence of the enzyme lactoperoxidase (a hypoiodite generating system).[15] However, in the latter case two isomeric macrolactones resulting from addition to the 14,15-double bond were found to be minor products,[15] an observation consistent with facile accessibility of conformers which bring C(1) and the 14,15-double bond into proximity. Studies on the iodolactonization of the silver salt of 5,6-dehydroarachidonic acid[16] (1.1 equiv. of iodine in carbon tetrachloride) in this laboratory indicated that the 14,15-double bond was the principal site of addition (confirmed by isolation of iodolactone and transformation by treatment with (1) methanolic triethylamine, (2) ethereal CH_2N_2 and (3) hydrogen-palladium (Lindlar) catalyst into the known methyl 14,15-epoxyarachidonate[1]).



1 X = H

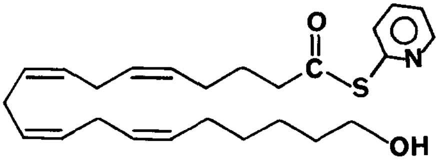
2 X = OH



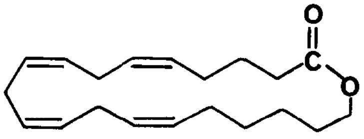
3

$\mathrm{THPO(CH_2)_6\overset{+}{P}Ph_3\ I^-}$

4



5



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In contrast, intermolecular reactions of arachidonic acid (or ester) with peroxyacids[17] or $^1\Delta_g$ oxygen[18] are non-selective with regard to the locus of attack.

The facile macrolactonization of **2** provides especially clear evidence of the low energy requirement for bringing the ends of the arachidonic acid chain into proximity. The details of this key experiment are as follows:

20-Hydroxyarachidonic Acid 1→20 lactone (**6**). 20-Hydroxyarachidonic acid (**2**,[19] 84.3 mg, 0.264 mmol) was azeotropically dried in vacuo with 3 3-ml. portions of dry benzene, dissolved in 5.0 ml. of dry methylene chloride under argon and cooled to -20°C. Triethylamine (75 μl, 2.0 equiv.) was added with stirring followed by 1.0 equiv. of 2-thiopyridylchloroformate,[9] added slowly over a 5-minute period. Tlc analysis after 30 min. showed complete conversion of acid **2** to the 2-pyridinethiol ester **5**. The reaction was quenched with 2 ml. of ice cold 10% (w/v) aqueous sodium bicarbonate, transferred to a separatory funnel with 20 ml. of ice cold methylene chloride and washed with 10 ml. of ice cold 10% sodium bicarbonate, 10 ml. of ice cold 0.02 N hydrochloric acid and 20 ml. of saturated sodium chloride. Drying ($MgSO_4$) and evaporation left 102.7 mg. of ester **5** as a yellow oil which contained only trace amounts of impurities by tlc analysis and which was subjected forthwith to lactonization. To a dry flask were added 100.7 mg. (0.244 mmol) of the ester **5**. The oil was azeotropically dried in vacuo with 3 5-ml. portions of dry benzene. Dry toluene (30 ml.) was added and the reaction was heated to 80°C for 4 hr. The mixture was concentrated in vacuo and purified directly by preparative tlc on silica gel plates (elution with 1:5 ether-hexane) to give 75 mg. of lactone **6** (90%); M^+, 302; IR max. 1738 cm.$^{-1}$ (neat); pmr peaks at 5.34-5.44 δ (m, 8H, olefinic), 4.10 (t, J=6.3Hz, 2H $C(20)H_2$),2.80-2.87 (m, 6H, bis allylic CH_2), 2.34 (t, J=6.6Hz, 2H, $C(2)H_2$), 2.04-2.14 (m, 4H allylic $C(4)H_2$ and $C(16)H_2$), 1.37-1.75 (m, 8H, non-allylic CH_2).[20]

References and Notes

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7. For isolation of the sensitive aldehyde **3** the reaction mixture was rapidly filtered through a pad of silica gel and concentrated *in vacuo*. Traces of acetic acid were removed from **3** by two azeotropic distillations of toluene *in vacuo*.
8. Satisfactory infrared, pmr, and mass spectral data were obtained for reaction products using chromatographically purified and/or homogeneous samples.
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13. We have also converted the 2-thiolpyridine ester of 15-HETE to the corresponding 1→15-lactone This cyclization is considerably slower than that of **5**; 6 hr. heating at 115° (toluene as solvent) was required to obtain 50% conversion to lactone.
14. (a) E. J. Corey, J. O. Albright, A. E. Barton and S. Hashimoto, *J. Am. Chem. Soc.*, **102**, 1435 (1980); (b) E. J. Corey and S. Hashimoto, *Tetrahedron Lett.*, **22**, 299 (1981).
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19. The *Z* geometry of the 14,15-double bond in **2** is indicated by the pmr spectrum as well as the method of preparation. The 14,15-*E*-isomer of **2** was also prepared by a non-stereoselective Wittig coupling in THF alone as solvent. The 14,15-*E* and *Z* isomers of **2** were readily distinguished by tlc and pmr.
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