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PATHWAYS FOR MIGRATION AND CLEAVAGE OF THE S-PEPTIDE UNIT OF THE LEUKOTRIENES

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Summary: Sulfoxides of leukotriene C (2) and various analogs (5, 8) undergo a 1,7-migration of sulfur (forming diastereomers 3, 6, and 9, respectively) with noteworthy facility. Generation of the S-halo derivatives of leukotriene C in water results in heterolysis of the C-S bond to give (5S,12R)- and (5S,12S)-6-trans-leukotriene B in a process which mimics biochemical deactivation.

The unique lipopeptide nature of the slow reacting substances (SRSs), leukotrienes (LTs) C, D, and E raises the intriguing question as to how these molecules function as biological agents and, in particular, whether chemically reactive intermediates are involved in the expression of this activity or in metabolic deactivation. Some time ago we initiated tests to determine whether divalent sulfur plays a role of this sort, as might be the case, for instance, if sulfonium ion formation or oxidation at sulfur is a key biochemical event. That divalent sulfur is not essential for bioactivity on airways or smooth muscle was indicated by the finding that one (but only one) of the two diastereomeric LTD sulfoxides (the less polar) is highly active (ca. 0.1 x LTD).[1,2] Continuation of these studies on the S-oxidation products of leukotrienes has led to a number of striking findings which form the subject of this note. The results which have been obtained are of general chemical interest and are also relevant to the mechanisms for biological deactivation of SRSs.

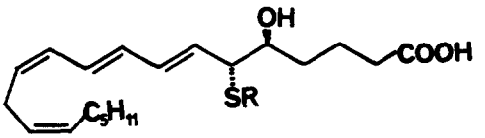
Reaction of LTC (1) in pH 6.8 phosphate buffer (0.25 mg/ml) with excess sodium periodate (ca. 20 equiv) at 23°C for 1 hr produced a 4:1 mixture of two diastereomeric sulfoxides (2) having reversed phase HPLC (RP-HPLC) retention volumes (R_v) of 2.6 and 2.7, respectively, in system A.[3] The diastereomer R_v = 2.6 showed UV max in CH_3OH at 286 nm[4] and that of R_v = 2.7 at 285 nm,[4] and as was the case in the LTD series[1] the more polar isomer (lower R_v) was the less active. Each diastereomer underwent a remarkably facile rearrangement involving overall migration of sulfur from C(6) to C(12) resulting in a mixture of four diastereomeric 6,8,10-trans-sulfoxides 3 having UV max (H_2O, pH 6.8) at 279.0 nm.[4] The half life for this rearrangement at 23°C was roughly 4 hr. The structure 3 for the diastereomeric rearrangement products was confirmed by independent synthesis from the two known diastereomers of the 12S-glutathionyl-6,8,10-trans analog of LTC[5] by periodate oxidation and careful comparison of the resulting diastereomeric sulfoxides (UV, RP-HPLC in several solvent systems) with the sulfoxides produced by rearrangement of 2. The four diastereomers 3 were resolved by RP-HPLC into two peaks with R_vs of 2.4 and 2.7 in system B,[3] in which system the two LTC sulfoxides 2 are unresolved with R_v = 5.0. It is likely that the two unresolved components in each peak differ in absolute configuration at sulfur and have the same chirality at C(12).

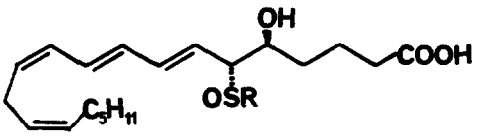
The rearrangement of sulfoxides 2 to 3 represents a novel 1,7-migration of sulfur which is, to our knowledge, without precedent. Among the mechanistic possibilities for rationalizing this 1,7-shift are the following: (1) [2,3]-sigmatropic rearrangement of 2 to form a sulfenic ester with oxygen attached to C(8)[6] followed by heterolysis to a heptatrienyl sulfenate ion pair which undergoes collapse with bonding between sulfur and C(12) to afford 3; (2) two successive [2,3]-sigmatropic rearrangements of 2 to form a C(10) sulfoxide, a further [2,3]-sigmatropic rearrangement to a C(12)-sulfenic ester, and finally, heterolysis to an ion pair followed by collapse to the C(12) sulfoxide 3; or (3) protonation of 2 at the sulfinyl oxygen followed by heterolysis to a heptatrienyl cation and nucleophilic recombination of sulfur of the peptide-SOH fragment with C(12) of the cation to form 3. The third of these possibilities can be excluded by virtue of the observation that the rate of the rearrangement of 2 to 3 is no more than a factor of 2 faster at pH 4 than at pH 7. Alternatives (1) and (2) are consistent with the data at hand on the transformation of 2 into 3 and also with the recently discovered facility of multiple [2,3]-sigmatropic rearrangement of 2,4-pentadienylic sulfoxides.[7] The sulfone of LTC[8] was prepared and found not to undergo allylic migration of sulfur at pHs between 7 and 3.5, a result to be expected if the shift of sulfur in 2 is a consequence of [2,3]-sigmatropic rearrangement rather than initial C(6)-S-heterolysis (possibility (3)).[9] During the preparation of the sulfone of LTC by the oxidation of LTC with Oxone reagent in water[10] at 23°C and pH 3.6, the two diastereomeric sulfoxides of LTC (2) are produced rapidly and two competing reactions ensue: (1) rearrangement of 2 to diastereomeric mixture 3 and (2) slower oxidation of 2 to the sulfone of LTC. Because of this competition only a poor yield of LTC sulfone results under these conditions; better results were obtained at -5°C in water containing a little ethanol (24% yield of LTC sulfone, UV max 281 nm,[4] R_v 3.8 system A). The competition between rearrangement and further oxidation of 2 had not been appreciated previously.[8]

N-Acetyl-LTD (4, prepared from LTD and acetic anhydride in water at 0°C) was oxidized by periodate to a diastereomeric mixture of two sulfoxides (5) which underwent migration of the sulfinyl group from C(6) to C(12) (in a manner paralleling 2⟶3) to form the diastereomeric sulfoxide mixture 6.[11] Similarly, the conjugate of LTA (7) with isopropyl mercaptan was oxidized to the two diastereomeric sulfoxides 8 which were observed to undergo C(6) ⟶ C(12) rearrangement to give diastereomeric mixture 9.[12]

Although the C(6) to C(12) migration of sulfur could be observed with substrates 2, 5, and 8, it is not a completely general process. For example, the pair of diastereomeric sulfoxides derived from LTD and also N-trifluoroacetyl LTD were found not to undergo the C(6) ⟶ C(12) migration to an appreciable extent (10%) even after 72 hr, corresponding to almost 20 half lives for the rearrangement 2 ⟶ 3. It is clear that the rate of the sulfur migration can be influenced strongly by the structural factors such as internal hydrogen bonding to the sulfinyl oxygen.[13]

The conversion of LTC (1) to the two diastereomeric sulfoxides 2 can be effected not only by periodate and Oxone reagent, but also by excess hydrogen peroxide (pH 6) or by N-chloro- and N-bromosuccinimides or by hypochlorous acid. In the case of the reaction with the positive halogen reagents another course of reaction was observed, conversion to a mixture of (5S,12R)- and (5S,12S)-6-*trans*-LTB (10), UV max 268.5 nm,[4] R_v 8.1, 9.1 (respectively) in system B (R_v for LTC = 6.8). The assignment of structure 10





1 SR = glutathionyl

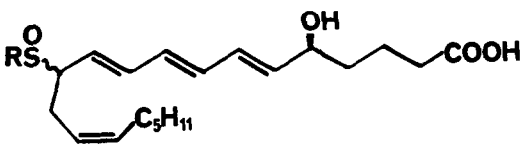
4 SR = N-acetyl cysgly

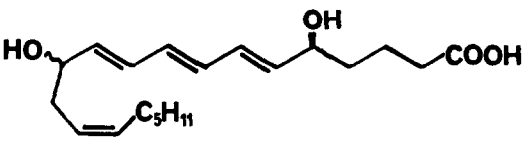
7 R = i-Pr

2 SR = glutathionyl

5 SR = N-acetyl cysgly

8 R = i-Pr





3 SR = glutathionyl

6 SR = N-acetyl cysgly

9 R = i-Pr

10

was supported by HPLC, UV and mass spectral comparison with compounds prepared by unambiguous total synthesis.[14] The formation of the two diastereomeric sulfoxides 2 and the two C(12)-diastereomers of 6-trans-LTB (10) from LTC can be explained in terms of an S-halosulfonium ion intermediate which undergoes either nucleophilic attack by water (or OH^-) at sulfur to form 2 or heterolysis to a heptatrienyl cation which is attacked by water to form 10.[5,14,15] Remarkably, LTC is also converted to the sulfoxides 2 and the dihydroxy acids 10 biochemically by polymorphonuclear leukocytes stimulated by phorbol myristate acetate (simulating activation of white blood cells by bacteria, etc.).[16] Thus it appears that oxidation and cleavage reactions at sulfur may be involved in the biochemistry and/or deactivation of the leukotrienes.[17]

References and Notes

1. R. A. Lewis, J. M. Drazen, K. F. Austen, M. Toda, F. Brion, A. Marfat, and E. J. Corey, Proc. Natl. Acad. Sci. USA, 78, 4579 (1981).
2. A dependence of bioactivity on stereochemistry about sulfur was also evident, since it was found that the more polar (MP) of the two diastereomeric LTD sulfoxides displays only low activity (ca. 0.1% of LTD). Periodate oxidation of LTD produces the MP and LP sulfoxides in a ratio of ca. 4:1.
3. System A: Waters Associates C_{18} column using CH_3CN-H_2O-HOAc (35:65:0.1) buffered to pH 5.8 with NH_4OH. System B: Waters Associates C_{18} column using CH_3OH-H_2O-HOAc (65:35:0.1) buffered to pH 5.6 with NH_4OH. System C: Waters Associates C_{18} column using CH_3OH-H_2O-HOAc (74:26:0.074) buffered to pH 5.6 with NH_4OH. None of these systems are capable of resolving the C(12) sulfoxide mixtures 3, 6, or 9 into the four components.
4. Shoulders at ca. 10 nm higher and lower wavelength relative to the main peak were also evident.
5. E. J. Corey and D. A. Clark, Tetrahedron Letters, 21, 3547 (1980).
6. See, (a) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, J. Am. Chem. Soc., 90, 4869 (1968); (b) D. A. Evans and G. C. Andrews, Accts. Chem. Res., 7, 147 (1974).
7. E. J. Corey and D. J. Hoover, Tetrahedron Letters, preceding article.
8. Y. Girard, M. Larue, T. R. Jones, and J. Rokach, Tetrahedron Letters, 23, 1023 (1982).
9. It should be noted that attack by nucleophilic sulfur on a C(6)-C(12) heptatrienyl cation unit can be expected to occur at C(12) to form two C(12) epimers having the all trans-6,8,10-triene system; see ref. 5.
10. B. M. Trost and D. P. Curran, Tetrahedron Letters, 22, 1287 (1981).
11. For 4, UV max 281, R_V 8.0 in system B. For 5 (mixture of 2 diastereomers), R_V 6.5, 6.9 in system B. For 6, UV max 279 nm (mixture of 4 diastereomers resolvable into peaks of R_V 2.6, 3.0 in system B). Four diastereomers of 6 were independently synthesized from the corresponding pair of C(12)-epimeric C(12)-sulfides (prepared according to ref. 5) by periodate oxidation (diastereomers at sulfur not resolved by HPLC) and compared by HPLC with 6 produced from 5 to establish identity.
12. Sulfide 7 was prepared from LTA and isopropyl mercaptan and triethylamine in methanol; UV max 280 nm, R_V 21.4 in system C. For 8 (doubtless a mixture of two diastereomers at sulfur) R_V 8.5, unresolved in system C, UV max 284.5 nm. For 9 (mixture of 4 diastereomers), R_V 3.7, 3.9 in system C.
13. Such hydrogen bonding which could stabilize the sulfoxide against rearrangement could involve the α-NH of the cys unit and the C(5) hydroxyl.
14. E. J. Corey, A. Marfat, D. J. Hoover, Tetrahedron Letters, 22, 1587 (1981).
15. E. J. Corey, P. B. Hopkins, J. E. Munroe, A. Marfat, and S. Hashimoto, J. Am. Chem. Soc., 102, 7984 (1980).
16. C. W. Lee, R. A. Lewis, E. J. Corey, A. Barton, H. Oh, A. Tauber, and K. F. Austen, Proc. Natl. Acad. Sci. USA, 79, July 1982.

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