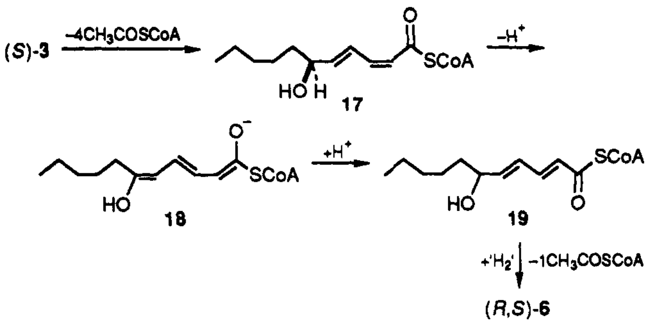
Scheme II



(*R*)-γ-nonanolides biosynthesized from dideutero (14*S*)-**10** the structures **11** and **12**, respectively. Thus, during the degradation of C_{19} (14*S*)-**10** to (4*R*)- and (4*S*)-4-hydroxydecanoic acid, the loss of the hydrogen atom originally located on the hydroxyl-substituted carbon atom occurs, at some point, only from that species that undergoes inversion of configuration. In support of this view are the results of feeding experiments with (14*R*,*S*)-**16**-*14-d*, prepared from **13** by way of **14** and **15**.[17] The γ-nonanolide that was isolated after a 34-h incubation was a 72:28 mixture of the *S* enantiomer (95.2% monodeuterated, 4.8% undeutrated) and the *R* enantiomer (38.9% monodeuterated, 61.1% undeuterated). NMR analysis indicated that the retained deuterium atom is located on C-4 of **6**. It thus seems that both enantiomers of homocoriolic acid (**3**) are converted into γ-nonanolide (**6**), but at different rates and by different mechanisms. The *S* enantiomer of **3** is metabolized at a faster rate, and the deuterium atom at C-14 is lost from that fraction of the material that is converted into (*R*)-**6**. The *R* enantiomer of **3** is degraded at a slower rate directly to (*R*)-γ-nonanolide and retains throughout the hydrogen atom originally present on the hydroxyl-substituted carbon atom.

Possible intermediates in the degradation of **3** to **6** are shown in Scheme II. It is possible that the C_{11} species **17**, which possesses *Z*,*E* stereochemistry, could undergo isomerization, by way of **18**, to **19**, which incorporates the α-*E*-configured double bond that apparently is required for further β-oxidation.[19] It may be that a satisfactory explanation for the loss of deuterium is to be found in knowledge of mechanisms of the conversion of (*S*)-**17** into (*R*)-**19** and in the conformational changes, which accompany that conversion.

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Registry No. 1, 10219-69-9; 2, 115511-53-0; 3, 135106-69-3; 4, 59285-67-5; 5, 69830-92-8; 6, 104-61-0; 9, 135106-70-6; 10, 135106-71-7; 11, 135106-72-8; 12, 135106-73-9; (±)-16-14*d*, 135106-74-0.

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Production of 2-Octenyl Radicals from the Fe(III)•Bleomycin-Mediated Fragmentation of 10-Hydroperoxy-8,12-octadecadienoic Acid

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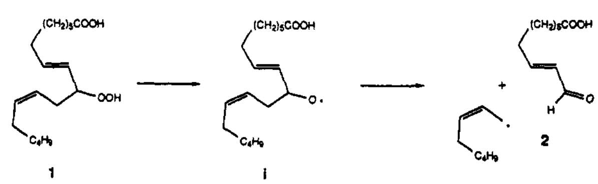
Summary: The Fe(III)·BLM-mediated fragmentation of 10-hydroperoxy-8,12-octadecadienoic acid was demonstrated unambiguously to occur via homolytic O–O bond scission.

The bleomycins (BLMs) are a family of glycopeptide-derived antibiotics with clinically useful antitumor activity.[1] In the presence of metal ions such as Fe^{2+}, bleomycin forms a binary complex [Fe(II)·BLM] that can reductively activate molecular oxygen.[2] The resulting unstable and reactive species termed "activated bleomycin" is believed to be an oxygenated metallobleomycin.[3] Activated bleomycin degrades DNA[2,3] and RNA[4] and also oxidizes and oxygenates low molecular weight substrates such as styrene and naphthalene.[5] Burger et al. have shown that the same activated bleomycin is accessible from either Fe(II)·BLM + O_2 or Fe(III)·BLM + H_2O_2;[3f] the latter reaction is analogous to the "peroxide shunt" pathway in cytochrome P-450 activation by various oxygen transfer agents.[6]

Scheme I. Decomposition of 10-Hydroperoxy-8,12-octadecadienoic Acid (1) to 10-Oxo-8-decenoic Acid (2) via Homolytic O–O Bond Scission



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Titration of activated bleomycin with I^- and thio-NADH also showed that activated bleomycin has two more oxidizing equivalents than Fe(III)·BLM;[7] the accumulated evidence suggests that activated bleomycin is probably best represented as a high valent metal–oxo [Fe(V)=O] species.

The formation of a perferryl species from Fe(II)·BLM + O_2 or Fe(III)·BLM + H_2O_2 requires heterolysis of the O–O bond in O_2 and H_2O_2. Heterolytic cleavage would be required for formation of the putative perferryl species, but a less oxidized [Fe(IV)=O] species could also be produced by homolytic cleavage of the O–O bond. In fact, Bruice and his co-workers have demonstrated that the analogous activation of metalloporphyrins could occur either heterolytically or homolytically, depending on the nature of the peroxide employed.[8]

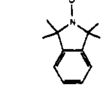
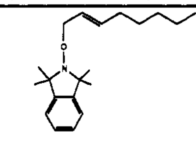
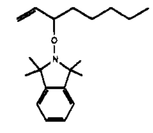
Two laboratories have recently described the Fe(III)·BLM-catalyzed decomposition of 10-hydroperoxy-8,12-octadecadienoic acid (1)[9] and the concomitant formation of 10-oxo-8-decenoic acid (2) as the predominant product.[7b,10] The appearance of 10-oxo-8-decenoic acid was presumed to result from β-scission of alkoxyl radical **i**, the latter of which would logically have arisen by homolytic scission of the peroxide O–O bond (Scheme I). In fact incubation of Fe(III)·BLM with alkyl hydroperoxide 1 afforded an activated Fe·BLM that could demethylate *N,N*-dimethylaniline (35% yield, based on consumed 1), but did so less well than the activated BLM produced from Fe(III)·BLM + H_2O_2 (90%, based on H_2O_2).[7b] Likewise, while the activated BLM produced from Fe(III)·BLM + H_2O_2 readily effected the epoxidation of styrene and hydroxylation of naphthalene, as well as DNA degradation, the species resulting from admixture of Fe(III)·BLM + 1 could only effect styrene epoxidation and did so inefficiently. Accordingly, it was suggested that the two methods of activation had produced different activated species.

One potential problem with the foregoing mechanistic rationale is that it is based entirely on the observed formation of 10-oxo-8-decenoic acid; no direct evidence has been provided for the concomitant formation of 2-octenyl radicals, and at least two types of processes could potentially result in the conversion of 1 → 2 via *heterolytic* cleavage of the O–O bond.[11] Neither of these would result in the formation of an activated bleomycin, an observation at least superficially consistent with the paucity of chemistry observed for this "activated bleomycin".

In order to distinguish between the homolytic mechanism in Scheme I and the heterolytic mechanisms of the type discussed by Labeque and Marnett,[11] we sought to determine whether 2-octenyl radicals were, indeed, produced as a consequence of the degradation of 10-hydroperoxy-8,12-octadecadienoic acid (1) by Fe(III)·BLM. Accordingly, bleomycin-mediated degradation of the alkyl hydroperoxide was carried out in the presence of the radical trapping agent 1,1,3,3-tetramethylisoindoline-*N*-oxyl[12,13] under conditions shown previously[7b,10] to lead to complete degradation of hydroperoxide 1. Degradation reactions carried out in the presence of the nitroxide contained two products; these were isolated and identified by ^{1}H NMR as 2-(2-octenyloxy)-1,1,3,3-tetramethylisoindoline and 2-(octenyl-3-oxy)-1,1,3,3-tetramethylisoindoline.[14] The formation of these products, which presumably arose from trapping of the allylic radical produced during the degradation of 1, was quantified by HPLC (Table I).[15] As shown in Table I, the use of a large excess of 1,1,3,3-tetramethylisoindoline-*N*-oxyl permitted the trapping of the isomeric alkoxyamines in 87% yield, based on decomposed hydroperoxide 1.

The heterolytic mechanisms predict the formation of 2-octenol (and possibly octen-3-ol, if an allylic carbonium ion were generated during the rearrangement). These two alcohols could not be detected in reaction mixtures containing hydroperoxide 1 + Fe(III)·BLM or Fe(II).[16]

Table I. Yields of Alkoxyamines Resulting from Fragmentation of 10-Hydroperoxy-8,12-octadecadienoic Acid in the Presence of 1,1,3,3-Tetramethylisoindoline-*N*-oxyl[a,b]

	 (mM)	 (mM)	 (mM)
Fe(II)[c]	50	0.54	0.53
Fe(II)[c]	100	0.85	0.81
Fe(III)·BLM	50	0.43	0.42
Fe(III)·BLM	100	0.88	0.86

[a] Carried out at room temperature for 1 h in 4:1 $CH_3OH–H_2O$ using 2 mM 10-hydroperoxy-8,12-octadecadienoic acid (1), and either 3 mM Fe(II) or 2 mM Fe(III)·BLM, essentially as described.[7b] The product were analyzed by HPLC;[15] quantification was effected by calculating the response factor for isolated samples of each product.[14] [b] Admixture of 2 mM 10-hydroperoxy-8,12-octadecadienoic acid and 100 mM 1,1,3,3-tetramethylisoindoline-*N*-oxyl afforded no reaction. [c] Degradation of 1 by Fe^{2+} in a Fenton-type reaction[9] provided authentic homolytic scission products.

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(9) Prepared by the photooxygenation of linoleic acid. See: Labeque, R.; Marnett, L. J. *J. Am. Chem. Soc.* **1987**, *109*, 2828.

(10) Padbury, G.; Sligar, S. G.; Labeque, R.; Marnett, L. J. *Biochemistry* **1988**, *27*, 7846.

(11) While Labeque et al. have argued against an ionic mechanism in the hematin-induced decomposition of 10-hydroperoxy-8,12-octadecadienoic acid, they did not directly demonstrate the intermediacy of 2-octenyl radicals. Labeque, R.; Marnett, L. J. *Biochemistry* **1988**, *27*, 7060.

(12) The use of stable nitroxides as trapping agents for carbon-centered radicals has been described previously. The rate constants for carbon radical trapping are large and approach rates of diffusion-controlled reactions; the trapped alkoxyamine products are stable and amenable to facile isolation and characterization. Nitroxides have also been used to calibrate a number of "radical clock" reactions. See: (a) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 1629. (b) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1988**, *53*, 1632.

(13) Prepared in three steps from *N*-benzylphthalimide as described. See: Griffiths, P. G.; Moad, G.; Rizzardo, E.; Solomon, D. H. *Aust. J. Chem.* **1983**, *36*, 397.

(14) A solution of 10-hydroperoxy-8,12-octadecadienoic acid (5 mg, 16 μmol) and 1,1,3,3-tetramethylisoindoline-*N*-oxyl (30 mg, 160 μmol) in methanol (8 mL) and H_2O (2 mL) was deoxygenated and was then treated with either Fe(III)·BLM (2.4 mg of ferric ammonium sulfate + 8 mg of bleomycin; 5.5 μmol) or ferrous ammonium sulfate (6.7 mg, 17 μmol). The alkoxyamines were isolated by chromatography on silica gel (hexane) to afford 1 mg of each of the isomeric alkoxyamines. 2-(2-Octenyloxy)-1,1,3,3-tetramethylisoindoline was isolated as an off-white wax, R_f 0.20 (silica gel TLC, hexane); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3, J = 6.9 Hz), 1.45 (br s, 12), 1.54 (s, 6), 2.11 (q, 2), 4.48 (d, 2, J = 6.0 Hz), 5.64 (m, 2), 7.12 (m, 2), and 7.22 (m, 2). The coupling constant of the olefinic H's (δ 5.64) was determined as 12 Hz by decoupling studies. 2-(Octenyl-3-oxy)-1,1,3,3-tetramethylisoindoline was isolated as an off-white wax, R_f 0.26 (silica gel TLC, hexane): ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 3), 1.31–1.43 (3 s, 12), 1.53 (m, 6), 1.78 (m, 2), 4.14 (q, 1), 5.10–5.15 (m, 2), 5.84 (m, 1), 7.07 (m, 2), and 7.20 (m, 2).

(15) HPLC analysis (Alltech econosphere C_{18} column, 4.6 mm × 10 cm, 3 μm) was carried out, using 4:1 $CH_3CN–H_2O$ as eluant, at a flow rate of 1.0 mL/min (UV detection, 270 nm). 2-(2-Octenyloxy)-1,1,3,3-tetramethylisoindoline eluted at 11.8 min, 2-(octenyl-3-oxy)-1,1,3,3-tetramethylisoindole at 12.9 min.

The present data demonstrate unambiguously that the decomposition of 10-hydroperoxy-8,12-octadecadienoic acid (1) by Fe(III)·BLM proceeds by homolytic cleavage of the peroxide O–O bond, as outlined in Scheme I, which should result in concomitant formation of an activated Fe·BLM. As noted previously,[7b] both the mechanisms of formation and chemical behavior of this species seem consistent with its representation of a high valent metal–oxo [Fe(IV)=O] species less oxidized than the species resulting from admixture of Fe(III)·BLM + H_2O_2 or Fe(II)·BLM + O_2.

It may be noted that the techniques employed here to control and analyze the oxidation states of activated BLM are potentially of more general utility in analyzing the mechanistic course of metal-centered oxygenation/oxidation reactions.

Acknowledgment. We thank Prof. Jack Baldwin, Oxford University, for a helpful discussion during the course of this work. This work was supported by PHS Research Grant CA-38544, awarded by the National Cancer Institute.

(16) Solvolsis of the *p*-toluenesulfonate of octen-3-ol in aqueous acetone, in the presence or absence of 1,1,3,3-tetramethylisoindoline-*N*-oxyl, led to the formation of the isomeric allylic alcohols in a 1:1 ratio. No alkoxyamines could be detected when 1,1,3,3-tetramethylisoindoline-*N*-oxyl was present, thereby demonstrating that 2-octenyl carbonium ions do not react with the nitroxide to give alkoxyamines.

Telomers of Bent Arenes. Acid-Catalyzed Dimerization and Trimerization of the 1,4-Hexamethylene-Bridged Arenes [6]Paracyclophane, [6](1,4)Naphthalenophane, and [6](1,4)Anthracenophane

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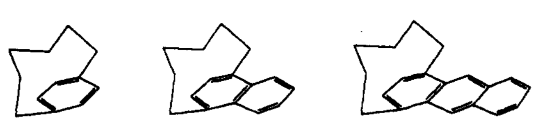
Summary: Whereas treatment of 1,4-hexamethylene-bridged benzene [6]paracyclophane (1) with a catalytic amount of H_2SO_4 gave, as a minor product, dimer 6, along with isomers 4 and 5, similar treatment of 1,4-hexamethylene-bridged naphthalene [6](1,4)naphthalenophane (2) afforded predominantly dimers 7 and 8, together with trimers 9 and 10. The 1,4-hexamethylene-bridged anthracene [6](1,4)anthracenophane (3) yielded only trimers 13 and 14.

It is well-known that alkyl-substituted arenes undergo acid-catalyzed isomerization.[1] Only under extremely drastic conditions, however, does dehydrogenative dimerization, i.e., the Scholl reaction,[2] take place, usually with low efficiency to give low yields of products. On the other hand, short-bridged cyclophanes undergo facile acid-catalyzed isomerization to more stable isomers because a large amount of strain is released thereby.[3] One notable exception is the $AlCl_3$/HCl-promoted skeletal rearrangement of [2.2.2](1,3,5)cyclophane, wherein the formation of intramolecular carbon–carbon bonds between the two aromatic rings leads, at least initially, to a less stable isomer.[4] Here, we report *the first examples of the acid-catalyzed dimerization and trimerization of 1,4-hexamethylene-bridged arenes* which possess severely deformed aromatic nuclei, i.e., [6]paracyclophane (1),[3c,5] [6](1,4)naphthalenophane (2),[6] and [6](1,4)anthracenophane (3).[6]



1 2 3

Earlier, we reported[3c,7] that the treatment of 1 (5×10^{-2} M CH_2Cl_2 solution) with a catalytic amount of acid (TfH or TFA) at room temperature yielded the corresponding meta and ortho isomers 4 and 5. However, when a more concentrated solution (1.5×10^{-1} M) of 1 was treated with a catalytic amount of H_2SO_4, the dimer 6[8] was also formed as a minor product (21%), together with a 1:1 mixture of 4 and 5 (59%). Similar treatment of the naphthalene 2 produced dimers 7[8] and 8,[8] which possess meta- and ortho-bridged naphthalenophane units, respectively, as major products (72%). The relative amount of 8 increased as the reaction time was increased, which indicated that 8 was produced by isomerization of 7. Two minor products, trimers 9[8] and 10[8] (15%), were also isolated. The structures of 9 and 10 were inferred from the similarity between their ^1H NMR spectra and those of anthracene trimers 13 and 14.[9] No monomeric products were detected even after

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(7) Careful reexamination of the products revealed that a small amount of dimer 6 was formed even under these conditions. The treatment of 1–3 with a catalytic amount of TFA resulted in product distributions similar to those obtained on treatment with H_2SO_4.

(8) The spectroscopic characteristics and other analytical data, which are given in the supplementary material, are in accord with the assigned structure.

(9) Characteristic ^1H NMR signals ($CDCl_3$) for the vinyl and methine protons of 9, 10, 13, and 14 are as follows. 9: δ 6.17 (d, *J* = 6.8 Hz), 5.79 (d, *J* = 7.3 Hz), 5.60 (dd, *J* = 8.8, 8.3 Hz), 3.51 (d, *J* = 5.4 Hz), 3.26 (d, *J* = 6.8 Hz), 2.94 (br m), 2.86 (d, *J* = 6.8 Hz). 10: δ 6.06 (d, *J* = 7.0 Hz), 5.66 (d, *J* = 7.3 Hz), 5.61 (dd, *J* = 9.2, 8.1 Hz), 3.48 (br m), 3.45 (d, *J* = 5.9 Hz), 3.19 (d, *J* = 7.0 Hz), 2.91 (d, *J* = 7.3 Hz). 13: 6.46 (d, *J* = 7.0 Hz), 5.95 (d, *J* = 7.3 Hz), 5.66 (t, *J* = 8.0 Hz), 3.71 (d, *J* = 5.8 Hz), 3.49 (d, *J* = 7.0 Hz), 3.39 (br m), 3.04 (d, *J* = 7.0 Hz). 14: 6.31 (d, *J* = 6.8 Hz), 5.84 (d, *J* = 6.8 Hz), 5.65 (dd, *J* = 8.8, 8.3 Hz), 3.82 (br m), 3.64 (d, *J* = 5.9 Hz), 3.43 (d, *J* = 6.3 Hz), 3.13 (d, *J* = 7.3 Hz).

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