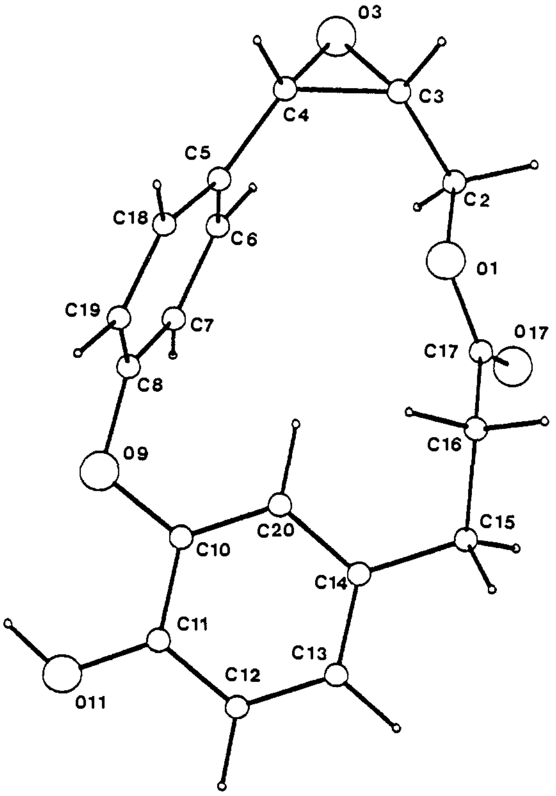
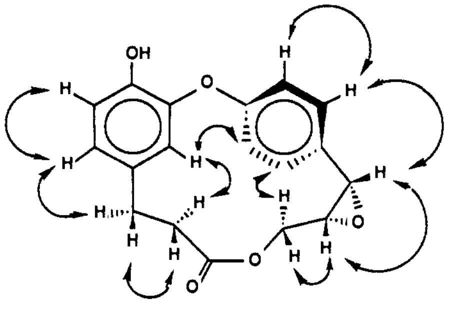


Figure 1. A PLUTO representation of combretastatin D-1 (1).



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Combretastatin D-1 with NOE

Figure 2. Combretastatin D-1 with NOE.

Such exceptional shielding of an aromatic proton was attributed to its entrance into the shielding cone of the other aromatic ring. Support for this assumption and the structure of combretastatin D-1 was obtained by an X-ray crystal structure determination (cf. Figure 1[4]) and examining the Dreiding model of this lactone. Restricted rotation between the two aromatic rings was apparent in the model. NOE experiments suggested that in solution the most stable conformation of the macrocycle also exists as presented in structure **1**, i.e., the carbonyl groups of the lactone must face away from the ring.

Attempts to determine the absolute configuration of combretastatin D-1 (**1**) on the basis of crystallographic data were unsuccessful. However, the absolute configuration of the epoxide ring was assigned (3*R*,4*S*) by comparing the sign of the Cotton effect curves in the CD spectrum[5] of epoxide **1** with the Cotton effect curves of (1*R*,2*R*)-(+)-1-phenylpropylene oxide and (1*S*,2*S*)-(−)-1-phenylpropylene oxide.

Combretastatin D-1 may originate biosynthetically from two units of tyrosine or equivalent *via ortho* phenol coupling, deamination, partial reduction, epoxidation, and lactonization. The significance of this new biosynthetic product in respect to antineoplastic and other biological properties is presently under study.

Acknowledgment. Necessary financial assistance was provided by Grant CA-30311-01-03 awarded by the National Cancer Institute, DHHS, the Arizona Disease Control Research Commission, the Robert B. Dalton Endowment Fund, the Fannie E. Rippel Foundation, Eleanor W. Libby, and the Waddell Foundation (Donald Ware). M.L.N. is pleased to thank the Research Grants Committee, UCT, and the CSIR for financial assistance.

Supplementary Material Available: Tables of bond distances and angles and positional parameters for combretastatin D-1 (6 pages); table of observed and calculated structure factors (14 pages). Ordering information is given on any current masthead page.

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[5] CD spectra (CH_3OH): **1**, ε (nm) 0 (308), +13.4 (285), 0 (275), +5.9 (267), −34.2 (247), 0 (240); (1*R*,2*R*)-(+)-1-phenylpropylene oxide, ε (nm) 0 (278), +0.15 (271), +0.07 (267), +0.16 (263), +0.09 (259), +0.11 (257), 0 (235); (1*S*,2*S*)-(−)-1-phenylpropylene oxide, ε (nm) 0 (278), −0.15 (271), −0.07 (267), −0.16 (263), −0.09 (259), −0.11 (257), 0 (235).

Epoxidation of Olefins on Silver: Conversion of Norbornene to Norbornene Oxide by Atomic Oxygen on Ag(110)

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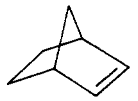
Received August 11, 1988

The nature of the reactive oxygen in olefin epoxidation is a subject of much debate.[1] We wish to report the epoxidation of an olefin by atomic oxygen on silver under ultrahigh vacuum. Norbornene (**1**) reacts with atomic oxygen on Ag(110) to form norbornene oxide (**2**) at 310 K during temperature-programmed reaction. The importance of this observation is 3-fold. First, the role of atomic oxygen in the epoxidation of olefins is a subject of substantial controversy.[1] In this work, atomic oxygen is proved to easily epoxidize an olefin on a silver surface. Second, ethylene and atomic oxygen do not react when coadsorbed on silver under ultrahigh vacuum.[2] As a consequence of the present work, this fact is attributed to an activation energy for ethylene desorption that is lower than that for reaction between ethylene and atomic oxygen. Finally, the epoxidation of olefins on silver is shown to be facilitated by the absence of an acidic hydrogen on the olefin.



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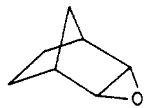

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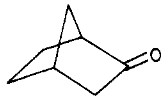

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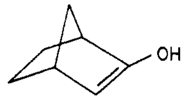

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We chose norbornene as a candidate for epoxidation on Ag(110) for two reasons. The high molecular weight of norbornene compared to ethylene leads to a greater binding energy between norbornene and the surface and, consequently, to a higher desorption temperature. Thus norbornene and atomic oxygen remain coadsorbed to nearly 300 K, making it possible to observe reactions with activation energies up to approximately 15 kcal/mol.

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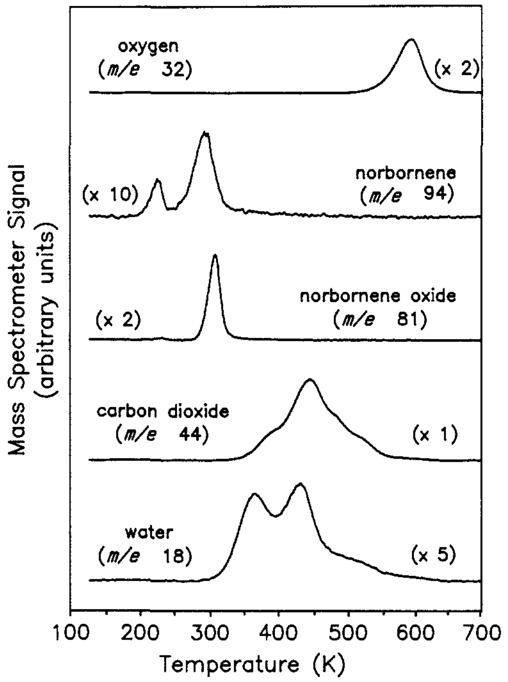

Figure 1. Temperature-programmed reaction of norbornene in the presence of excess surface oxygen atoms on Ag(110). The oxygen coverage was approximately 0.2 monolayers. The heating rate was 12 K/s. Multiplication factors are referenced to the carbon dioxide spectrum and are corrected for degree of fragmentation in the mass spectrometer.

Furthermore, the location of the norbornene allylic hydrogens at bridgehead sites results in a gas-phase acidity that is low compared to other alkyl-substituted olefins (ΔH_{acid} = 401 kcal/mol for norbornene[3] versus 391 kcal/mol for propylene[4]). Since facile activation of acidic C–H bonds by atomic oxygen on Ag(110) is well documented,[5] the absence of acidic hydrogens was anticipated to be important in preventing reactions leading to products other than epoxides.

Figure 1 shows that norbornene oxide is formed at 310 K when coadsorbed norbornene and atomic oxygen are heated from 120 to 700 K on Ag(110). When norbornene oxide is adsorbed on either clean or oxygen-covered Ag(110), desorption occurs below 300 K.[6] Since norbornene oxide is formed above its characteristic desorption temperature, we infer that the rate-limiting step for norbornene oxide evolution is reaction between norbornene and oxygen. Unreacted norbornene desorbs at 230 and 300 K. Water and carbon dioxide are also produced. Water evolves in two peaks at 380 and 435 K, with a shoulder at 520 K. Carbon dioxide appears as a broad peak at 450 K, with shoulders at 390, 475, and 525 K. The origin of these products will be discussed elsewhere.[6] Finally, oxygen, from the recombination of excess surface oxygen atoms, desorbs at 600 K. For these coverages of norbornene and oxygen, the surface is clean after reaction.

Norbornene oxide was identified based on mass spectral data. All ions up to *m/e* 200 were examined, and none higher than *m/e* 110 were present in the 310 K product peak. Thus, *m/e* 110 is identified as the product parent ion, corresponding to a stoichiometry of $C_7H_{10}O$. Also, reaction of norbornene and ^{18}O on Ag(110) shows formation of *m/e* 112 but not of *m/e* 114, demonstrating that the 310 K product contains exactly one oxygen atom. The 310 K product was unequivocally assigned as norbornene oxide by comparison of its mass spectral cracking pattern to that of norbornene oxide, as summarized in Table I. Analysis was complicated by the fact that norbornene oxide and norbornene have many common cracking fractions. However, for the ions shown in Table I, the contribution of norbornene cracking was negligible. Of particular note is the ratio of the molecular ion, *m/e* 110, to *m/e* 81. For the oxidized norbornene product we measured a ratio of 6.1:100; for the norbornene oxide sample we measured 5.8:100. The measured *m/e* 110:*m/e* 81 ratio of norcamphor (**3**) is 200:100. Norbornene-1-ol (**4**), the only other possible product from reaction at the norbornene double bond without subsequent rearrangement of the hydrocarbon skeleton, was excluded as a product due to its instability with respect to rearrangement to norcamphor. If norbornene-1-ol were formed, then fast rearrangement to norcamphor would be expected, especially upon electron impact in the mass spectrometer. The mass spectrum of the oxidized product can therefore not be attributed to norcamphor or norbornen-1-ol. The mass spectra of possible rearranged products were not measured, but according to standard mass spectral references, the measured *m/e* 81:*m/e* 110 and *m/e* 81:*m/e* 82 ratios are most consistent with norbornene oxide.[7] In particular, on the basis of published spectra, we were able to exclude the formation of the following molecules: norbornene-derived alcohols, alkyl-substituted furans, methyl-substituted cyclohexenones, cycloheptenones, and alkenyl-substituted six-membered oxygen-containing rings.[7] The formation of other products may also be eliminated based on the fact that evolution of the norbornene oxidation product occurs in the presence of a large excess of surface oxygen (Figure 1). It is known that atomic oxygen reacts on Ag(110) with alcohols, C_3 and larger alkenes, and alkynes,[5] eliminating the possible formation of these molecules in the presence of surface oxygen.

Table I. Relative Yields of the Ions Used for Determination of the Norbornene Oxide Product

m/e	norbornene oxide product	pure norbornene oxide sample	pure norcamphor sample
81	100.0	100.0	100.0
82	30.6	30.5	33.8
95	23.8	20.6	35.4
105	1.6	1.2	0.0
106	1.5	1.1	0.0
109	3.7	4.0	23.1
110	6.1	5.8	200.1

The epoxidation of norbornene by atomic oxygen on Ag(110) is important for the following reasons. The reaction unambiguously demonstrates that atomic oxygen can epoxidize an olefin on a silver surface. The result is therefore pertinent to the continuing controversy over whether atomic or molecular oxygen epoxidizes ethylene on silver catalysts.[1] Second, the fact that norbornene epoxidation occurs under ultrahigh vacuum suggests that the lack of ethylene epoxidation under similar conditions[2] is due to an activation energy for desorption that is low compared to that for epoxidation. For norbornene, the binding energy with silver is sufficiently high that epoxidation competes with desorption. Finally, silver is shown to be active for the epoxidation of norbornene, an olefin of low gas-phase acidity.[3] We attribute the low epoxidation yields from propylene[8] and butene[9] to their high gas-phase acidity[4] relative to norbornene. The reaction of olefins with nonacidic allyl hydrogens, such as norbornene, results in the suppression of undesireable C–H bond activation processes that ultimately lead to combustion.

Acknowledgment. We gratefully acknowledge the support of the National Science Foundation (NSF CBT 8701342) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. **1**, 498-66-8; **2**, 278-74-0; Ag(110), 14391-76-5; oxygen, 7782-44-7; water, 7732-18-5; carbon dioxide, 124-38-9.

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