alkenes as well as hydrogen atom abstraction.

A mechanistic pathway is suggested in Scheme I. Ni^{IV}–oxo intermediates have been proposed for the cyclam complexes responsible for epoxidation with PhIO,[7,9] and a similar mechanism may be occurring with the salen complex. Because of higher d orbital occupancy however, a Ni^{IV}–oxo complex of salen might not have a structure strictly analogous to the known (salen)-$Cr^{V}{=}O^{+}$ complex[15] or the proposed square pyramidal (TPP)-$Fe^{IV}{=}O^{+}$,[16] although it would be expected to be highly reactive toward olefins. The lack of stereospecificity in the epoxidation pathway is consistent with the subsequent nickel–oxo–olefin intermediate existing as an open chain radical with rapid rotation possible before reductive elimination to yield epoxides. Trapping of this intermediate **5** by OCl^{-} provides an explanation for the appearance of benzaldehyde in the reactions of phenyl-substituted alkenes. Subsequent oxidation of PhCHO to $PhCO_2H$ is well-known with NaOCl. Rigorous degassing of the solutions to remove O_2 prior to the reaction had little effect on the composition of the products. However, bubbling O_2 through the reaction mixture markedly increased the amount of PhCHO + $PhCO_2H$ formed. This further suggests that intermediate **5** may be trapped by dissolved O_2. Further work in this area is in progress to determine more precisely the structure of the proposed intermediates.

In summary, Ni^{II}(salen) complexes are unusually active as catalysts for olefin oxidation in the presence of hypochlorite. In view of nature's ability to use nickel-containing enzymes in redox processes[17] and chemists' ability to create new ligands, the future of nickel complexes in catalysis of hydrocarbon transformations is quite attractive.

Acknowledgment. We gratefully acknowledge a grant from the National Science Foundation (CHE-8706616) in support of this work.

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Observations on the Activation of Bicyclomycin

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The mode of action of the antibiotic, bicyclomycin (**1**), remains enigmatic. Proposals have appeared suggesting that the biological process entails the binding of nucleophilic species (i.e., sulfhydryl proteins) to the exomethylene group in **1**[1-4] within the peptidoglycan assembly of Gram-negative bacterial cell walls.[3,4] Recently, Vasquez[3] and Williams[4] have both proposed that drug activation is initiated by enzymatic cleavage of the C_9–N_{10} bond of the piperazinedione ring in bicylomycin. Adequate support for these hypotheses is lacking. Progress has been hampered by the inability to activate the drug under conditions which approximate the biological process. In all previous cases, use of either highly basic[1a,4,5] or acidic[6] conditions were required to functionalize the exomethylene group in **1**. In this communication, we report the *binding of bicyclomycin to thiols at room temperature at near neutral "pH"*. Evidence is provided that functionalization of the exomethylene group in bicyclomycin is accompanied by an extraordinary mixed-Claisen condensation.

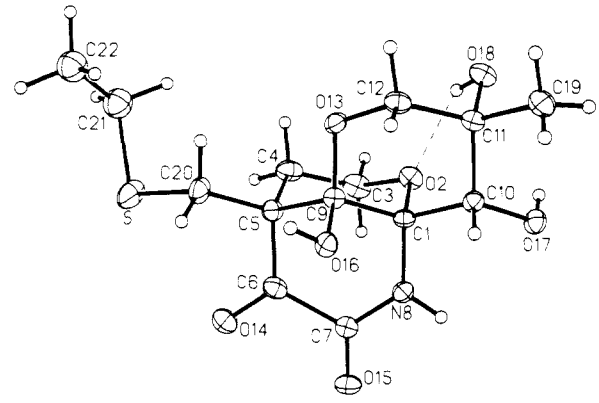

Figure 1. View of compound **2** showing the atom labeling scheme. The thermal ellipsoids are 30% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter.

Treatment of a 3:1 tetrahydrofuran–aqueous Tris-HCl mixture[7] containing bicyclomycin (0.8 mM) and 16 equiv of ethyl mercaptan (room temperature, 20 h, final "pH" 8.1) gave 45% of **2**[8] along with starting material and a trace amount of two additional compounds.[9] High resolution mass spectral analysis of the major product showed a molecular ion at m/e 347.1053 (calcd for $C_{14}H_{21}NO_7S$, 347.1039) compatible with the formation of a 1:1 adduct between **1** and ethyl mercaptan and the loss of ammonia. Inspection of both the ^1H and ^{13}C NMR spectra indicated that a single diastereomer was generated in the reaction. Evidence that the thioethoxy group was bound to the exomethylene group in **1** was furnished by the appearance of an AB quartet at δ 2.96 for the C_{5a} methylene protons.[1a,5] The ^{13}C NMR spectrum for **2** displayed two carbonyl carbon resonances at 160.0 and 195.2 ppm. The latter signal was considerably downfield from the corresponding resonances in **1**[10] and suggested the presence of an α,β-unsaturated carbonyl system.[11] In agreement with this proposal, the IR spectrum exhibited carbonyl absorption bands at 1730 and 1670 cm^{-1}.[12] Verification of these spectral assignments was provided by the X-ray crystallographic analysis of **2** (Figure 1).[13]

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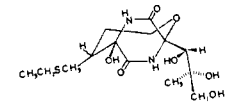
(5) Kohn, H.; Abuzar, S. *J. Am. Chem. Soc.*, in press.
(6) Kohn, H.; Abuzar, S. *J. Org. Chem.*, in press.
(7) The reaction is biphasic at the onset but within a few hours becomes homogeneous.
(8) Select data for compound **2**: mp 216–218 °C; R_f 0.70 (10% methanol–chloroform); $[\alpha]^{25}D$ + 51.7° (c1, CH_3OH); IR 1730, 1670 cm^{-1}; ^1H NMR (CD_3OD) δ 1.15 (s, 3 H), 1.25 (t, 3 H, J = 7.3 Hz), 1.91 (d, 1 H, J = 14.0 Hz), 2.31 (ca. dt, 1 H, J = 6.3, 14.0 Hz), 2.58 (q, 2 H, J = 7.3 Hz), 2.90 (1/2 AB_q, 1 H, J = 13.9 Hz), 3.02 (1/2 AB_q, 1 H, J = 13.9 Hz), 3.63 (d, 1 H, J = 12.3 Hz), 3.76 (ca. dt, 1 H, J = 2.1, 14.0 Hz), 3.92 (s, 1 H), 4.03 (dd, 1 H, J = 6.3, 14.0 Hz), 4.04 (d, 1 H, J = 12.3 Hz); ^{13}C NMR (CD_3OD) 15.1, 21.2, 29.6, 32.4, 33.1, 56.7, 58.7, 70.9, 71.9, 72.4, 85.3, 96.1, 160.0, 195.2 ppm.
(9) One of the two minor products has been tentatively identified as the bicyclomycin–ethyl mercaptan adduct on the basis of the observed ^1H NMR spectra data.[5]



(10) Kohn, H.; Abuzar, S.; Korp, J. D.; Zektzer, A. S.; Martin, G. E. *J. Heterocycl. Chem.*, in press.
(11) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; p 282.
(12) Nakanishi, K.; Solomon, P. M. *Infrared Absorption Spectroscopy*; 2nd ed.; Holden-Day: San Francisco, 1977; p 38.
(13) Crystal data for **2**: $C_{14}H_{21}NO_7S$, M = 347.4, orthorhombic, space group $P2_12_12_1$, a = 6.714 (1) Å, b = 10.379 (2) Å, c = 22.181 (4) Å, V = 1546 Å^3, Z = 4, Nicolet R_{3m}/V diffractometer, Mo Kα (λ = 0.71073 Å), μ = 2.35 cm^{-1}, 2581 reflections $I > 3\sigma(I)$ refined to R = 0.039 (R_w = 0.027).

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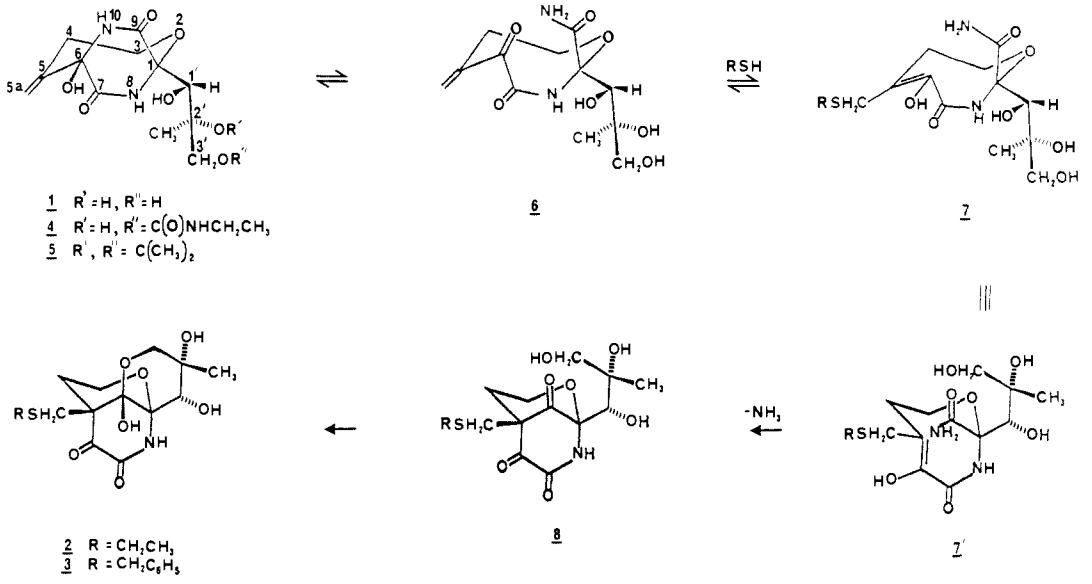
Scheme I. Proposed Pathway for the Generation of Compounds **2** and **3**



Several experiments afforded information concerning this unique transformation. First, no significant consumption of bicyclomycin was observed by using the prescribed experimental conditions in the absence of ethyl mercaptan.[14] Second, treatment of an aqueous solution of **1** with ethyl mercaptan without tetrahydrofuran furnished **2** in lower amounts (TLC analysis). Third, repetition of the initial experiment using benzyl mercaptan gave **3** (53% yield).[16,17] Fourth, addition of ethyl mercaptan to a 3:1 tetrahydrofuran–water solution containing either the 3′-*O*-ethyl carbamate derivative **4**[19] or the acetonide **5**[20] led to no significant reaction after 24 h.[14] At higher "pH" values (10.2–12.5), treatment of **5** with mercaptans furnished the unrearranged C_{5a}-substituted sulfide.[4,5]

These results are in agreement with the pathway depicted in Scheme I.[21] Drug activation is envisioned to occur by initial ring cleavage of the hemiaminal bond to furnish **6**. Subsequent addition of ethyl mercaptan to the α,β-unsaturated carbonyl system generates **7** which is ideally situated to undergo an *intramolecular mixed-Claisen condensation* to produce **8** and ammonia. Cyclization of **8** in the final step yields the observed hemiketal **2**.

The isolation of compounds **2** and **3** and the accompanying experimental observations provide new information concerning the chemical pathway(s) for the activation of bicyclomycin which demand further study. The lack of reactivity of carbamate **4** and acetonide **5** and the enhanced activity of **1** in tetrahydrofuran–water mixtures versus water alone suggest that drug activation is facilitated by intramolecular hydrogen bonding of the triose ring hydroxyl groups with the 2,5-piperazinedione unit in **1**. Significantly, the observed intramolecular mixed-Claisen transformation generates **8** under exceedingly mild conditions. This reactive species[22] may be capable of undergoing further chemical transformations necessary for drug function. The mechanism and implications of this reaction are currently being pursued.

Acknowledgment. We thank the National Institutes of Health (GM37934) and the Robert A. Welch Foundation (E-607) for their support of this research. The National Science Foundation (CHE-8616352) is gratefully acknowledged for providing matching funds for the purchase of a high field NMR spectrometer. Special thanks are given to Dr. James D. Korp for performing the X-ray crystallographic analysis of compound **2** and Dr. Simon Gaskell (Baylor College of Medicine) for obtaining the mass spectral results. We also express our appreciation to Dr. K. Inokuchi and the Fujisawa Pharmaceutical Co., Ltd, Japan, for providing us with a gift of bicyclomycin.

(14) A similar result was observed for dihydrobicyclomycin.[15]

(15) Kamiya, T.; Maeno, S.; Hashimoto, M.; Mine, Y. *J. Antibiot.* **1972**, *25*, 576.

(16) Select data for compound **3**: mp 108–110 °C; R_f 0.75 (10% methanol–chloroform); IR 1730, 1680 cm^{-1}; ^1H NMR (CD_3OD) δ 1.13 (s, 3 H), 1.86 (d, 1 H, J = 14.1 Hz), 2.23 (ca. dt, J = 7.4, 14.1 Hz), 2.80 (1/2 AB_q, 1 H, J = 14.0 Hz), 2.93 (1/2 AB_q, 1 H, J = 14.0 Hz), 3.59 (d, 1 H, J = 11.9 Hz), 3.70–3.80 (m, 3 H), 3.88 (s, 1 H), 3.96 (d, 1 H, J = 11.9 Hz), 3.92–4.05 (m, 1 H), 7.20–7.35 (m, 5 H); M_r 409.1191 (calcd for $C_{19}H_{23}NO_7S$, 409.1195).

(17) Use of select secondary amines (i.e., morpholine, ethyl 1-piperazinecarboxylate) gave a comparable result.[18]

(18) Abuzar, S.; Kohn, H., unpublished results.

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(21) Alternatively, thiol- or hydroxyl-mediated cleavage of the amide bond at carbon-9 may have occurred to generate the corresponding thiol ester or ester, respectively, prior to cleavage of the hemiaminal bond and addition of the mercaptan to the exomethylene group.

(22) Compound **8** can be viewed as a masked derivative of 2,4,5-trioxooctanoic acid.

O–H Bond Dissociation Energies in Para-Substituted Phenols[1]

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Hammett substituent effects in free-radical chemistry have intrigued chemists for some considerable time.[3] Classical studies[4-9] focused on hydrogen abstraction at substituted toluenes,

(1) National Research Council of Canada. Issued as NRCC publication 28927.

(2) University of Leiden.

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