Acknowledgment. Partial support of this work by Grant CA37054 from the National Institutes of Health is gratefully appreciated. We thank Dr. S. Ōmura for samples of **1** and **2** and helpful information and the NIH-supported (Grant DRR00480) mass spectrometry facility at Michigan State University for high resolution mass spectra.

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(23) Mp's (°C) of crystalline solids: (±)-**2**, 279-284 °C dec [lit.[1] for (-)-**2**, dec >290 °C]; **6**, 260 °C dec; **7**, 172-173 °C; **13**, 82-84 °C; **15**, 81-82 °C; **16**, 115-116 °C. ^{1}H NMR spectra ($CDCl_3$) of key intermediates: **7**, δ 3.58 (3 H, s), 3.79 (3 H, s), 3.96 (3 H, s), 4.00 (3 H, s), 5.26 (2 H, s), 5.32 (2 H, s), 6.84 (1 H, s), 7.45 (1 H, s), 7.60 (1 H, s); **15**, δ 1.36 (3 H, s), 3.09 (2 H, br s), 3.66 (1 H, dt, J = 6.6, 11.3 Hz), 3.98 (1 H, m), 4.22 (2 H, t, J = 6.6 Hz), 5.37 (1 H, d, J = 10.9 Hz), 5.83 (1 H, d, J = 17.5 Hz), 6.63 (1 H, dd, J = 17.5, 10.9 Hz), 6.76 (1 H, s), 6.87 (1 H, s), 11.85 (1 H, s); *trans*-**19**, δ 1.40 (3 H, s), 3.14 (2 H, s), 3.61 (3 H, s), 3.66 (2 H, m), 3.71 (3 H, s), 3.97 (3 H, s), 4.01 (3 H, s), 4.10 (2 H, m), 4.25 (2 H, t, J = 7.5 Hz), 5.26 (2 H, s), 5.40 (2 H, s), 6.88 (1 H, s), 6.91 (1 H, s), 7.07 (1 H, s), 7.14 (1 H, d, J = 15.0 Hz), 7.26 (1 H, s), 7.62 (1 H, d, J = 15.0 Hz), 7.64 (1 H, s), 11.95 (1 H, s). The structures assigned to **7**, **15**, and **19** as well as those of other compounds are supported by combustion analysis or exact mass determinations.

Hydrolysis Kinetics of the Ultimate Hepatacarcinogen *N*-(Sulfonatooxy)-2-(acetylamino)fluorene: Detection of Long-Lived Hydrolysis Intermediates

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N-(Sulfonatooxy)-2-(acetylamino)fluorene (**1**) is a putative ultimate hepatacarcinogen derived from metabolism of 2-(acetylamino)fluorene.[1] We report herein preliminary results of an investigation of the hydrolysis kinetics of **1**[2] and the discovery of several labile intermediates which may play a role in the in vivo chemistry of **1**.

Kinetics were monitored by UV spectroscopy in 5 vol % CH_3CN-H_2O (μ = 0.5 M (KCl)) at pH 1.0-9.5 and 20 °C.[3] Absorbance data were fit well by eq 1 (n varied from 1 to 4, depending on pH). Buffer independent rate constants, k_i, and experimental details are collected in Table I in the Supplementary Material. One rate constant, k_2, is dependent on $[\text{phosphate}]_T$ and $[\text{tris}]_T$. Much of this dependence in phosphate buffers is due

$$A_t = A_\infty + \sum_{i=1}^{n} A_i e^{-k_i (B_T) t} \qquad (1)$$

to nucleophilic catalysis (see below), but general acid catalysis also occurs in both buffers. Figure 1 shows that five pseudo-first-order processes occur. The rate constant k_1 is pH and buffer independent as are rate constants for hydrolysis of the more reactive *N*-(sulfonatooxy)acetanilides.[3] A plot of log k_1 for **1** (extrapolated to 40 °C from data at 5-25 °C) and six ring-substituted *N*-(sulfonatooxy)acetanilides[3a] vs σ^+ gives a ρ of -5.7 ± 0.6 (r = 0.97), which is in the range expected for heterolysis of the N-O bond.[3,4] Three of the other processes are pH dependent

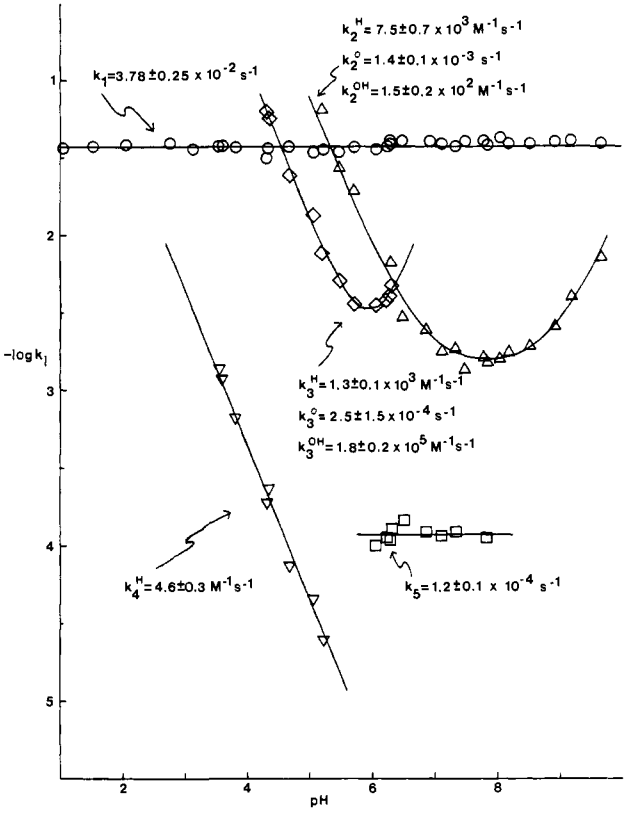
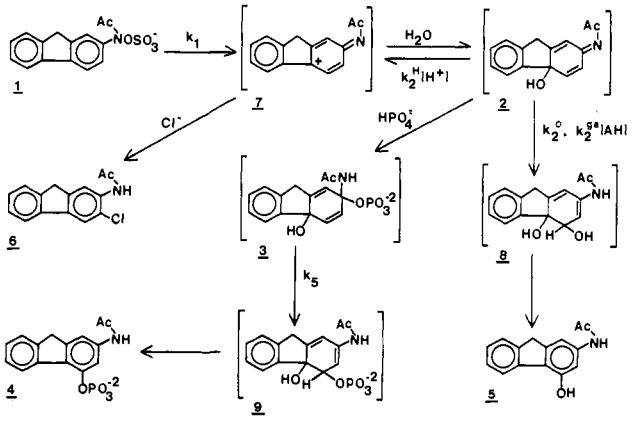


Figure 1. pH-rate profile for the hydrolysis of **1** at 20 °C in 5 vol% CH_3CN-H_2O (μ = 0.5 M (KCl)). The k_i were obtained by fits to eq 1. Rate constants shown in the figure were obtained by least-squares fits to appropriate rate equations.

Scheme I



(Figure 1). The rate constant k_5 is observed only in phosphate buffers, but its magnitude is independent of $[\text{phosphate}]_T$ and pH.

At pD 7.8 and 5 °C in 0.02-0.04 M KD_2PO_4/K_2DPO_4 (no KCl) **1** (ca. 2.8 mM) decomposes with a half-life of ca. 1 min into a longer lived species **2**, detected by 500 MHz ^{1}H NMR[5] (Scheme I), which also decomposes with a $[\text{phosphate}]_T$ dependent half-life of 3-7 min (consistent with k_2 at 5 °C) into **3**.[6] This species decomposes into **4**[7] with a half-life at 5 °C of 15-20 h

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(5) ^{1}H NMR for **2**: (500 MHz, D_2O) δ 2.32 (3 H, s), 3.64 (1 H, d, J = 18 Hz), 4.10 (1 H, d, J = 18 Hz), 6.1-6.35 obscured by **3**, 6.43 (1 H, d, J = 10 Hz), aromatic region obscured by **3**. The chemical shift of the acyl methyl group of **2** is consistent with that of other *N*-acylimines (ref 3b, 8, and 15).

(6) ^{1}H NMR for **3**: (500 MHz, D_2O) δ 2.07 (3 H, s), 3.28 (1 H, d, J = 17.5 Hz), 3.62 (1 H, d, J = 17.5 Hz), 6.10 (1 H, d, J = 10.1 Hz), 6.29 (1 H, d, J = 10.1 Hz), 6.35 (1 H, s), 7.41 (3 H, s, br), 7.58 (1 H, s); ^{31}P NMR (121.5 MHz, D_2O) δ 11.4 (relative to trimethyl phosphate). **3** rearranges into **4** and other unidentified materials upon attempted isolation. Only one diasteriomer appears to be present.

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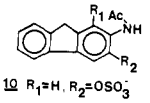
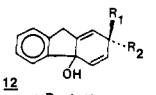
(consistent with k_5 at 5 °C of 1.2×10^{-5} s^{-1}). Intermediates similar to **2** have been detected in the solvolysis of monocyclic analogues of **1**,[3b,8] but no phosphate adduct similar to **3** has been detected in such reactions.

In basic phosphate buffers (pH > 6.8) the major hydrolysis products of **1** (with yields in 0.025 M phosphate at pH 7.8, μ = 0.5 M (KCl)) are **4** (11.1 ± 0.2%), **5**[9] (51 ± 1%), and **6**[10] (8.9 ± 0.3%).[11] Since **4** is stable to the reaction conditions, **5** is not produced by its hydrolysis. HPLC experiments confirm that **5** is formed by the decomposition of **2** at pH 7.8, while **6** is formed more rapidly from the decomposition of **1**. A minimum hydrolysis mechanism in accord with our results under these conditions is shown in Scheme I. The yields of **5** and **6** become 5.7 ± 0.2% and 65 ± 3%, respectiveiy, at pH 4.7 and 1.1 ± 0.2% and 83 ± 4%, respectively, at pH 3.6. The product yield variation with pH indicates that most of k_2^H involves acid-catalyzed reversion of **2** to the nitrenium ion **7**. Table II in the Supplementary Material provides yields for **5** and **6** under various pH conditions. Product studies indicate that **2** is converted into **5** by uncatalyzed (k_2^0) and general acid catalyzed (k_2^{ga}) paths in phosphate buffers (k_2^{ga} for $H_2PO_4^-$ is 0.22 ± 0.01 M^{-1} s^{-1}). There is precedent for the addition-elimination path involving **8** in monocyclic systems,[3b,8] but other possibilities cannot be ruled out at this time. The conversion of **3** into **4** probably occurs via an allylic rearrangement of a tight ion pair to produce **9**,[12] with subsequent elimination of H_2O. The lack of dependence of k_5 on $[phosphate]_T$ is consistent with this proposal. The minor products **10** and **11**, detected in pH invariant yields of ca. 2.0% and 1.0%, respectively,[13] are likely formed via internal return from an intimate ion pair (not shown in Scheme I).[3,4]



10 R_1=H, R_2=OSO_3^-

11 R_1=OSO_3^-, R_2=H



12 **a** R_1=AcNH, R_2=OH

b R_1=OH, R_2=AcNH

At pD 5.8 in 0.03 M KD_2PO_4/K_2DPO_4 and pD 4.8 in 0.03 M AcOD-d_4/KOAc (no KCl) at 5 °C two species, tentatively identified as the diastereomeric carbinolamides **12a** and **12b**, which decompose at rates consistent with k_3 and k_4 at 5 °C, are detected by NMR.[14] The pH dependence exhibited by k_3 is consistent with that observed for other carbinolamides.[15] Since at pH < 5.0 **6** is the predominant reaction product, it appears that k_3^H and k_4^H largely involve return to **7** via **2**. The products derived from the k_3^0 and k_3^{OH} processes have not yet been identified.

The half-life of **1** at physiological temperatures is ca. 4.0 s from extrapolation of our kinetic data. Since the sulfotransferase system which generates **1** in vivo appears to be located in the cytosol,[1] a long-lived intermediate such as **2** (half-life ca. 2.0 min at 37 °C and pH 7) may play a role in the biological effects attributed to **1**. We have demonstrated that **2** is subject to direct nucleophilic attack by H_2O and phosphate and also decomposes to **7** via k_2^H at pH > 6.0. Either of these routes may serve as a means for **2** to react with nucleophilic sites on cellular macromolecules. We are currently investigating the reactions of **2** with other nucleophilic species.

Acknowledgment. This work is supported by a grant from the American Cancer Society (BC-348). The 500 MHz NMR spectra were obtained with the assistance of Dr. C. E. Cottrell at the Ohio State University Chemical Instrument Center using Equipment funded in part by NIH Grant No. 1 S10 RR01458-01A1.

Supplementary Material Available: Table I containing buffer independent pseudo-first-order rate constants for the hydrolysis of **1** at 20 °C, and Table II containing buffer independent yields of **5** and **6** produced during the hydrolysis of **1** (3 pages). Ordering information is given on any current masthead page.

Intermolecular Addition of Epoxides to Activated Olefins: A New Reaction

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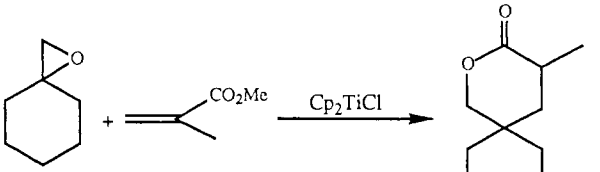
Epoxides play an increasingly pivotal role in organic synthesis. This reflects both their ready availability and their ability to undergo selective substitution reactions with nucleophiles. It occurred to us that the utility of epoxides as synthetic intermediates would be further enhanced by the availability of methods for their selective elaboration by electrophiles. We now report such a reaction, the addition of epoxides to activated olefins.

Our strategy utilizes a transition-metal-centered radical to effect the homolysis of an epoxide C–O bond.[1] Thus dropwise addition of a green THF solution (2 equiv) of Cp_2TiCl[2] to a solution of the epoxide of methylenecyclohexane (1 equiv) and excess methyl methacrylate (10 equiv) in THF results in the formation of the spirolactone **1** in 81% yield (eq 1). The carbon-centered radical



(1)

1

formed by the homolysis of the C–O bond (presumably via the cyclopropylcarbinyl-like intermediate **2**[1b]) adds to methyl methacrylate (MMA), and the resulting radical **3** is efficiently scavenged by a second equivalent of Ti(III) rather than undergo further additions (Scheme I). Under these conditions, no ole-

(7) ^1H NMR for **4**: (500 MHz, D_2O) δ 2.19 (3 H, s), 3.96 (2 H, s), 7.28–7.61 (5 H, m), 8.29 (1 H, s); ^{31}P NMR (121.5 MHz, D_2O) δ −3.2 (relative to trimethyl phosphate). Treatment of **4** with *E. coli* alkaline phosphatase yields **5** (ref 10).

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(2) Most of these studies were carried out with isolated $[Cp_2TiCl]_2$ prepared according to the procedure of Manzer.[2a] In a typical reaction, Cp_2TiCl (430 mg, 2 mmol) dissolved in 10 mL of THF was added to a mixture of the epoxide and 10 equiv of the olefin in 10 mL of THF over 5 min, and the mixture was stirred for 10 min. The reaction was quenched with cold 10% H_2SO_4 and extracted into ether. The ether extract was dried after being washed with $NaHCO_3$, and the products were isolated by chromatography. The reaction can also be done with in situ generated reagent prepared by reduction of the commercially available Cp_2TiCl_2 with activated zinc[2b] (and containing an equivalent of $ZnCl_2$) giving somewhat lower yields. In the in situ preparation, excess zinc was removed by cannula transfer of the supernatant liquid into a mixture of the epoxide and the acceptor. (a) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 84. (b) Green, M. L. H.; Lucas, C. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000.

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