substituent (X) must be a reasonably good leaving group in order for the rearrangement to occur. Involvement of a nitrile ylide intermediate (**65**) in these reactions was demonstrated by trapping experiments. The quantum efficiency and rate of reaction were shown to be directly related to the leaving group ability.

Conclusion

The photocycloaddition reaction of 2*H*-azirines is an extremely versatile and important process. The range of synthetic possibilities which it opens for the construction of five-membered heterocyclic rings is extremely large. Significant progress has been made toward understanding the factors which determine the photochemical behavior in a given system. Since it is evident that nitrile ylides are very important species for the synthesis of a wide variety of nitrogen-containing compounds, we are continuing our efforts to develop new and useful applications of 2*H*-azirine photochemistry.

It is a pleasure to acknowledge the vital contribution of my collaborators, whose names are to be found in the references. Together, we thank the National Science Foundation and the National Institutes of Health for financial support of our research.

Solution Chemistry of Arene Oxides

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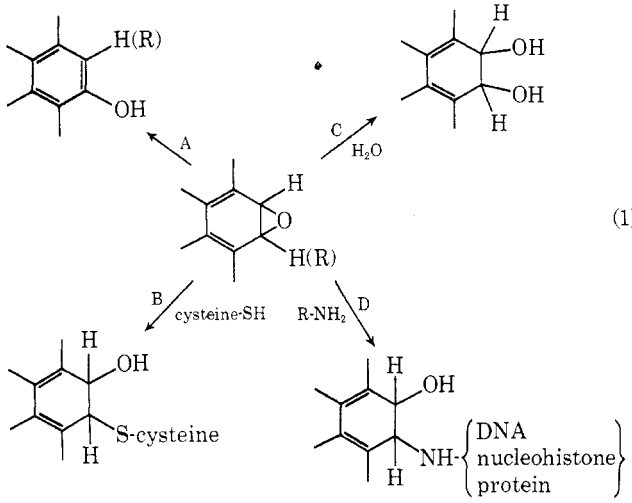
The inherent chemical interest in the chemistry of the epoxides of aromatic hydrocarbons (arene oxides) is heightened by their importance in biochemistry and toxicology (eq 1). Thus, arene oxides are: (1) proven or proposed intermediates in the biosynthesis (path A) of various metabolically important phenols (i.e., phenylalanine → tyrosine, tryptophan → 5-hydroxytryptophan → seretonin, 4-hydroxyphenylpyruvic acid → homogentisic acid, etc.);[1] (2) intermediates in aromatic compound detoxification via the biosynthesis of mercapturic acids[2] (path B) and dihydro diols (path C);[3] and (3) proven causative agents of necrosis,[4] mutagenesis,[5] and carcinogenesis[6,7] as a result of covalent binding to cellular macromolecules (path D). Recent reviews have dealt with the biochemical and toxicological aspects of aromatic epoxides and their chemical synthesis.[1,3,8]



(1)

Examination of eq 1 reveals that the biologically important reactions of arene oxides may be divided into the categories of epoxide rearrangement (A) and nucleophilic addition (B–D). This Account is limited to our investigations of the mechanism of arene oxide rearrangement to phenols, the susceptibility of arene oxides to nucleophilic addition, and the differences in the chemistry of K-region and non-K-region epoxides. The K region of aromatic hydrocarbons does not possess full aromatic character, and its excision from a molecule does not greatly alter the resonance energy.[9] Historically, those polycyclic hydrocarbons possessing K regions have been associated with carcinogenesis.

General Acid Catalysis and the Stepwise Conversion of Arene Oxides via Carbocations to Phe-

After dropping out of high school to serve in the military, Thomas C. Bruice attended the University of Southern California (B.S.,1950, Ph.D.,1954) and received his postdoctoral training at UCLA. Prior to moving to University of California, Santa Barbara, in 1964, Professor Bruice held faculty positions in biochemistry at Yale University Medical School and the Johns Hopkins School of Medicine and in chemistry at Cornell University. In 1974 he was elected a member of the National Academy of Sciences. His research has involved the study of the mechanisms of reactions of biochemical interest.

Paula Yurkanis Bruice received her A.B. from Mount Holyoke College in 1963 and her Ph.D. from the University of Virginia in 1968. After postdoctoral training in the Department of Biochemistry at the University of Virginia Medical School and in the Department of Pharmacology at Yale Medical School, she was appointed Assistant Professor at Connecticut College. In 1971 her marriage to Thomas C. Bruice brought her to California. She is a lecturer in the Department of Chemistry and in the College of Creative Studies at the University of California, Santa Barbara. Her research interests largely concern mechanisms of reactions of organic compounds of biological interest.

(1) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, **28**, 1129 (1972).
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(4) B. B. Brodie, W. D. Peid, A. K. Cho, G. Sipeo, G. Krishna, and J. R. Gillette, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 160 (1971).
(5) B. N. Ames, P. Sims, and P. L. Grover, *Science*, **176**, 47 (1972).
(6) P. L. Grover, P. Sims, E. Huberman, H. Marquardt, T. Kuroki, and C. Heidelberger, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1098 (1971).
(7) W. Levin, A. W. Wood, H. Yagi, P. M. Dansette, D. M. Jerina and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 243 (1976).
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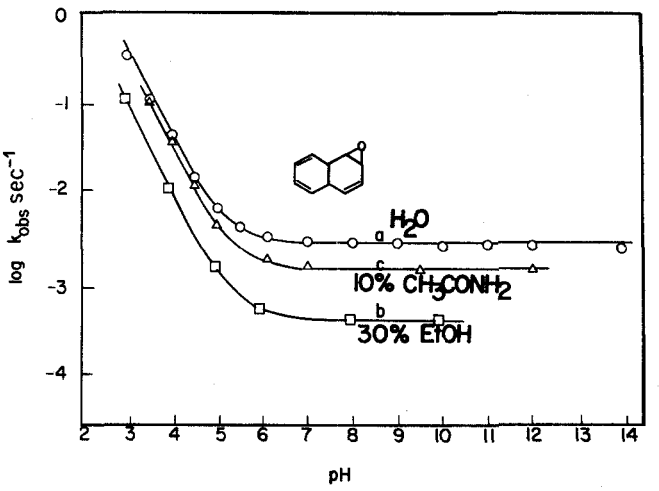
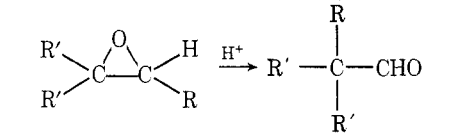
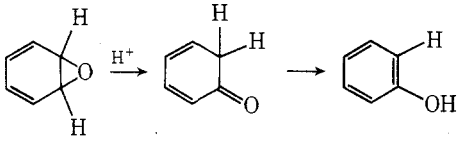


Figure 1. The pH dependence of the aromatization of naphthalene oxide (2),[14] 30 °C, μ = 1.0

nols. One might anticipate that some common chemistry should be shared by aliphatic epoxides and arene oxides. One common feature is the acid-catalyzed rearrangement of aliphatic oxides (eq 2)[10] and aromatic oxides (NIH shift,[11-13] eq 3). The mechanism for the



(2)



(3)

reaction of eq 3 was suggested to involve *concerted* ring opening and hydrogen transfer, followed by a dienone–phenol rearrangement to yield phenol.[6,11-13] However, these arene oxide rearrangements had not been thoroughly investigated.

The pH dependence of the aromatization of naphthalene 1,2-oxide (2) is provided in Figure 1;[14] aromatization is both acid catalyzed and spontaneous or water catalyzed (eq 4). Equation 4 also pertains to the rearrangement of benzene oxide (1) and most other non-K-region oxides (see inset to Figure 4). A lowering of the dielectric constant of the solvent decreases the values of both k_H and k_0 for all the arene oxides we have investigated and establishes that the transition states for the rate-determining steps are of greater polarity than are the ground states. Substituent effects on k_H and k_0 support this conclusion. The large negative ρ^+ values evidenced in Figure 2 clearly indicate that the transition

$$k_{obsd} = k_H a_H + k_0 \quad (4)$$

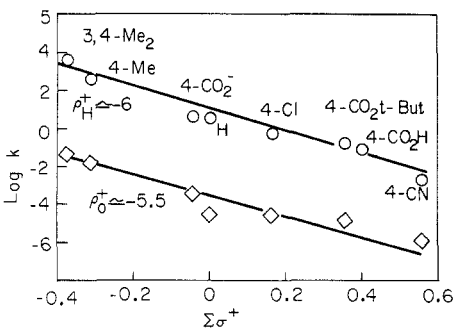
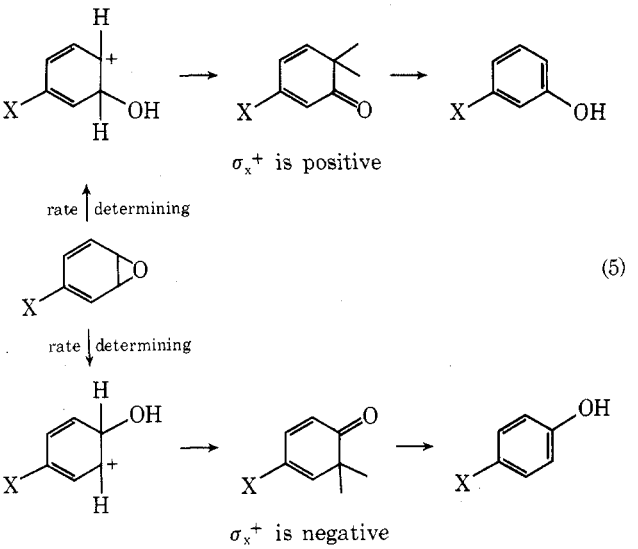


Figure 2. $\rho^+\sigma^+$ plots for the H_3O^+ catalyzed (○) and H_2O catalyzed (◇) aromatization of substituted benzene oxides (H_2O, μ = 1.0, 30 °C). Data for 3,4-dimethyl-, 4-methyl-, and 4-chlorobenzene oxides, from ref 15; 3,4-epoxybenzenecarboxylic acid and -carboxylate from ref 16; benzene oxide, ref 14; *tert*-butyl 3,4-epoxybenzenecarboxylate, ref 17; 4-cyanobenzene oxide, ref 18. Suitable values of σ^+ have been taken from ref 19 and 20.

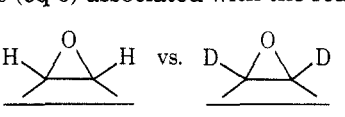
states are of carbocation character.

The formation of a carbocation via epoxide ring opening for both the k_H and k_0 pathways is also supported by the finding that the predominant phenolic product is that predicted to be formed upon rearrangement of the most stable carbocation; i.e., 4-substituted benzene oxides with electron-donating substituents give primarily para-substituted phenols while those with electron-withdrawing substituents aromatize primarily to meta-substituted phenols (eq 5). This



(5)

feature is seen for all oxide rearrangements involving hydrogen migration. Rate-limiting carbonium ion formation is further supported by the primary deuterium isotope effects (eq 6) associated with the rearrangement



(6)

of 1, 2, and phenanthrene 9,10-oxide (3), which range from 1.00 to 1.05 for both water (k_0) and hydronium ion (k_H) catalysis.[21,22] Rapid carbonium ion formation

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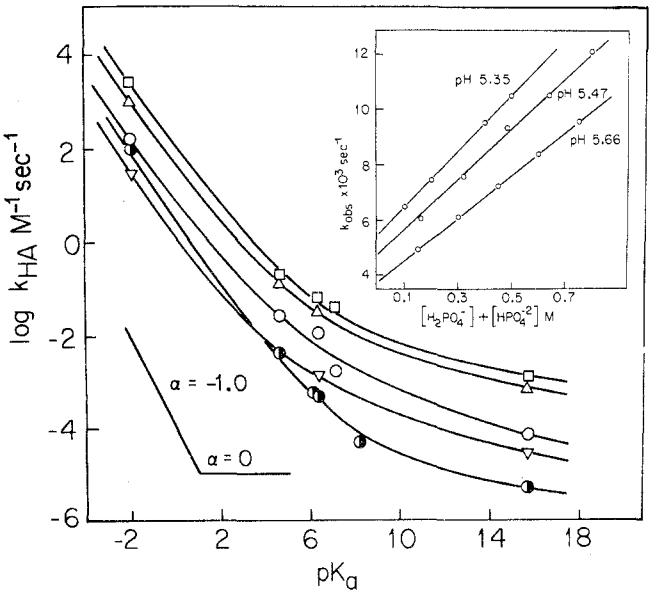


Figure 3. Brønsted plots for general acid catalyzed rearrangement of 1 (▽), 2 (○), 3 (◑), 4 (△), and 5 (□).[26] Inset to figure: phosphate buffer dilution plots for aromatization of naphthalene 1,2-oxide (2). (For the experiments in both plots: H_2O, μ = 1.0, 30 °C.)

followed by rate-limiting hydride transfer, or a cyclic mechanism in which ring opening and hydride transfer are concerted, would both be expected to exhibit values of $k^H/k^D > 2$.[23]

In the epoxide ring-opening step, the role of H_3O^+ may be that of a specific acid catalyst, while H_2O may possess no catalytic function and act only as a polar solvent. Alternatively, the mechanisms associated with the $k_H[H_3O^+]$ and $k_0[H_2O]$ terms may represent general acid catalyzed reactions in which a proton from either H_3O^+ or H_2O is transferred to the epoxide oxygen in the course of carbonium ion formation. General acid catalysis is not observed with saturated aliphatic epoxides, although it has been reported for 1,3-cyclohexadiene oxide[24] and, not surprisingly, for epoxy ether hydrolysis.[25] In the pH range of spontaneous rearrangement, the entropies of activation and the kinetic deuterium solvent isotope effects (Table I[14,15,26]) for arene oxide rearrangement clearly suggest that a water molecule is structured into the transition state and that the HO–H bond has been stretched to some small extent on reaching the transition state.[27] A careful search for catalysis by other acid species revealed that it could be discerned only from pH 5.5 to 7.5, the pH range where both H_3O^+ and H_2O catalysis compete. In Figure 3 are presented Brønsted plots for the acid species catalysis of aromatization of oxides **1–5**.[22,26] The inescapable conclusion is that oxide ring opening involves general acid catalysis.

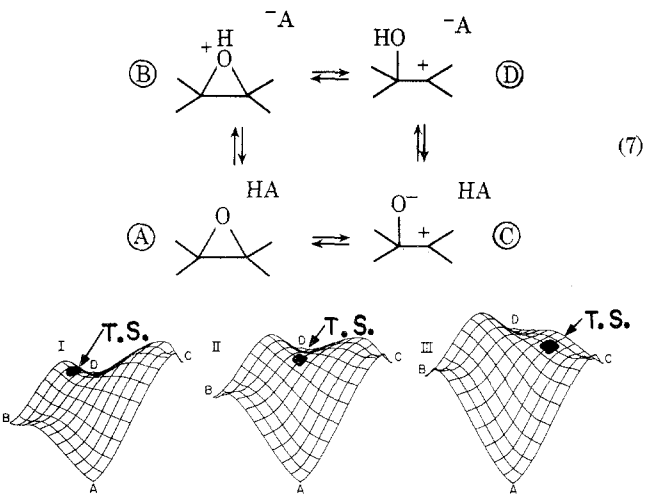
The libido rule[28] requires that a general acid should have a pK_a between that of protonated substrate and

Table I
Entropies of Activation and Solvent Isotope Effects for Spontaneous Rearrangement

Oxide	$\Delta S^{\ddagger}$, eu	$k_0^{H_2O}/k_0^{D_2O}$
Benzene oxide (1)	−25.3,[a] −15.4[b]	1.33,[a] 1.32[b]
Naphthalene 1,2-oxide (2)	−25.7[b]	1.26[b]
Phenanthrene 1,2-oxide (4)	−20.1[b]	1.26[b]
Phenanthrene 3,4-oxide (5)	−23.8[b]	1.26[b]
1,4-Dimethylbenzene oxide (6)	−28.2[c]	1.34[c]

[a] Reference 14. [b] Reference 26. [c] Reference 15.

product. Since the pK_a of H_3O^+ approaches that of oxide$^+$–H and the pK_a of H_2O is close to that of the product alcohol >C$^+$–C(OH)<, it is entirely reasonable to suppose that H_3O^+ and H_2O catalysis represents borderline specific acid–general acid and general acid–spectator catalysis,[29] respectively. These features can be seen in the alternate route (MAR) contour maps[30] for the rate-determining conversion of arene oxide to carbocation (eq 7). The free-energy contours of I, II, and



(7)

III pertain to pH 0, 6, and 11, respectively. Thus within the limits of the MAR computation the mechanism for k_H borders on specific acid–general acid catalysis, while that for k_0 borders on general acid catalyzed ring opening and spontaneous ring opening followed by a partially rate-determining diffusion-controlled protonation of $-O^-$ by H_2O. Inspection of II reveals that near pH 6.0 the $\Delta G^{\ddagger}_{B\rightarrow D}$ and $\Delta G^{\ddagger}_{C\rightarrow D}$ values for the rate-controlling steps of H_3O^+ and H_2O catalysis, respectively, are nearly identical, and a free-energy minimum between A and D provides for concerted general acid catalysis. The Brønsted plots of Figure 3 vary in slope from $-\alpha \simeq 0.8$ for H_3O^+ catalysis to $-\alpha \simeq 0.1$ for H_2O catalysis.[26] This marks the first experimental observation of the complete range of general acid catalysis (from almost complete to very little proton transfer).

Investigation[22] of the solvolysis of phenanthrene 9,10-oxide (3) has served to further illuminate the general catalytic nature of the oxide ring-opening reaction and, most importantly, has provided an understanding of the differences in the chemistry of K-region and non-K-region oxides. The pH–rate profile for reaction of **3** is provided in Figure 4. The points on the plot

(21) G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Chem. Commun.*, 784 (1972).
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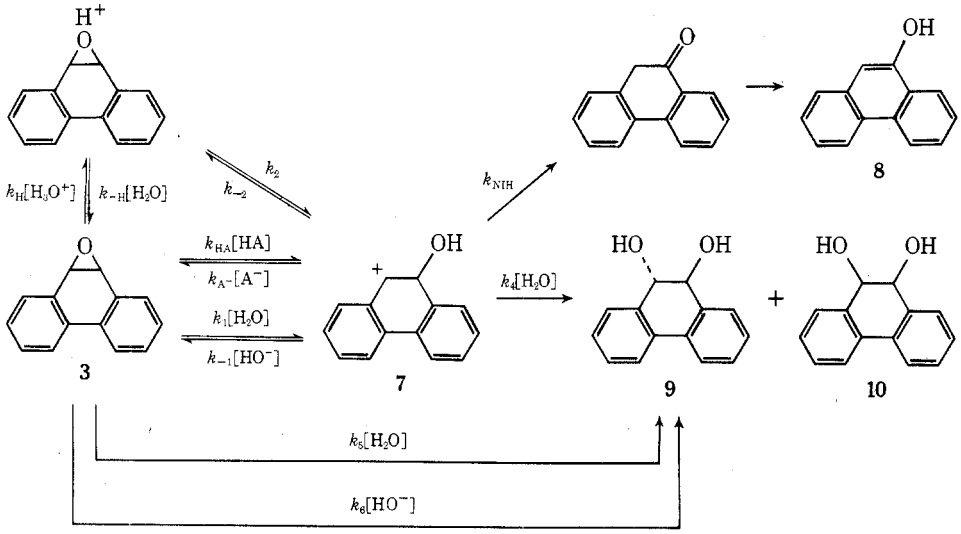
Scheme I



indicated by arrows represent rate constants determined for 9,10-dideuteriophenanthrene 9,10-oxide; no primary deuterium isotope effect is observed. For convenience of discussion, Figure 4 has been divided into regions A to E. Regions A and B are attributed respectively to H_3O^+ (k_2) and H_2O (k_1) catalyzed opening of the arene oxide to the carbonium ion (**7**) (Scheme I). The carbonium ion can undergo rearrangement (k_{NIH}) to form 9-phenanthrol (**8**) or be trapped by H_2O (k_4) resulting in the formation of the trans and cis diols, **9** and **10**. In regions B and C the disappearance of oxide was found to be subject to general acid catalysis by buffer acids (Figure 3). Since H_2O is acting as a general acid catalyst to form carbonium ion (k_1), microscopic reversibility requires that the ring closure of carbonium ion to oxide be catalyzed by hydroxide ion ($k_{-1}[HO^-]$). As $[HO^-]$ increases, $k_{-1}[HO^-]$ begins to compete with k_{NIH} and $k_4[H_2O]$, accounting for the observed decrease in rate with increasing pH in region C. Since **7** is formed in regions A, B, and C, the ratio of the final products from pH 1 to 8 should be identical. This is found to be the case (i.e., 75% **8**, 18% **9**, and 7% **10**). That the general acid catalyzed reaction of **3** provides 9-phenanthrol and 9,10-dihydro diols in a constant ratio from pH 1 to 8 provides convincing support for a common carbocation intermediate. Regions D and E are ascribed to direct nucleophilic attack on the arene oxide by water and hydroxide ion, respectively; this mechanism is supported by the fact that the product obtained in this pH region consists of ≥98% trans diol (**9**). The nucleophilic susceptibility of arene oxides will be considered later. However, the formation of stable dihydro diols appears to be a feature of K-region oxides and very electron-deficient non-K-region oxides. For the K-region oxide (**3**) dihydro diols are formed both by carbocation trapping and by direct attack of H_2O and HO^-, whereas for electron-deficient oxides their formation results only from attack of HO^-.

Additional Evidence for Carbocation Formation When an Alkyl Group Is the Migrating Species, and the Oxygen Walk. Isomerization of 1,4-dimethylbenzene oxide (**6**) was known to proceed with varying degrees of methyl migration to yield 2,5- and 2,4-dimethylphenols.[31] At high pH the product consists of 13% **11** and 87% **12**, and the rate of product formation

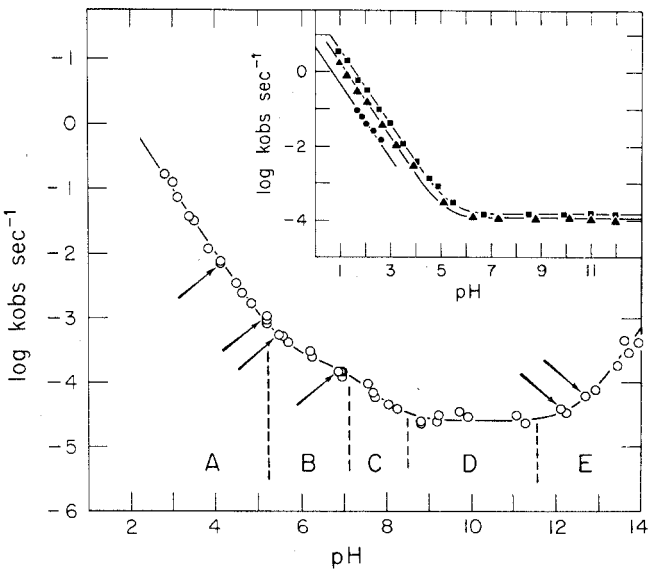
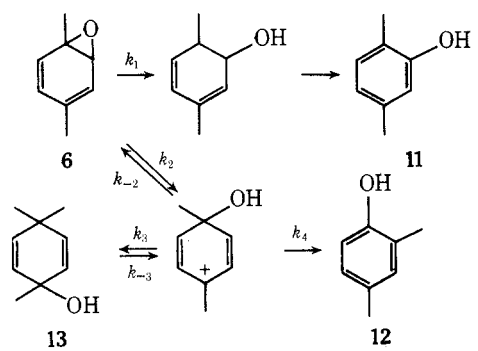


Figure 4. Log k_{obsd} vs. pH profile for the disappearance of phenanthrene 9,10-oxide (**3**) (H_2O, 30 °C, μ = 1.0). The arrows denote values of log k_{obsd} determined for 9,10-dideuteriophenanthrene 9,10-oxide.[22] Inset to figure: pH–rate profiles (50% dioxane:H_2O, v/v, μ = 0.1, 30 °C) for aromatization of phenanthrene 3,4- (■), 1,2- (▲), and 9,10-oxides (●).

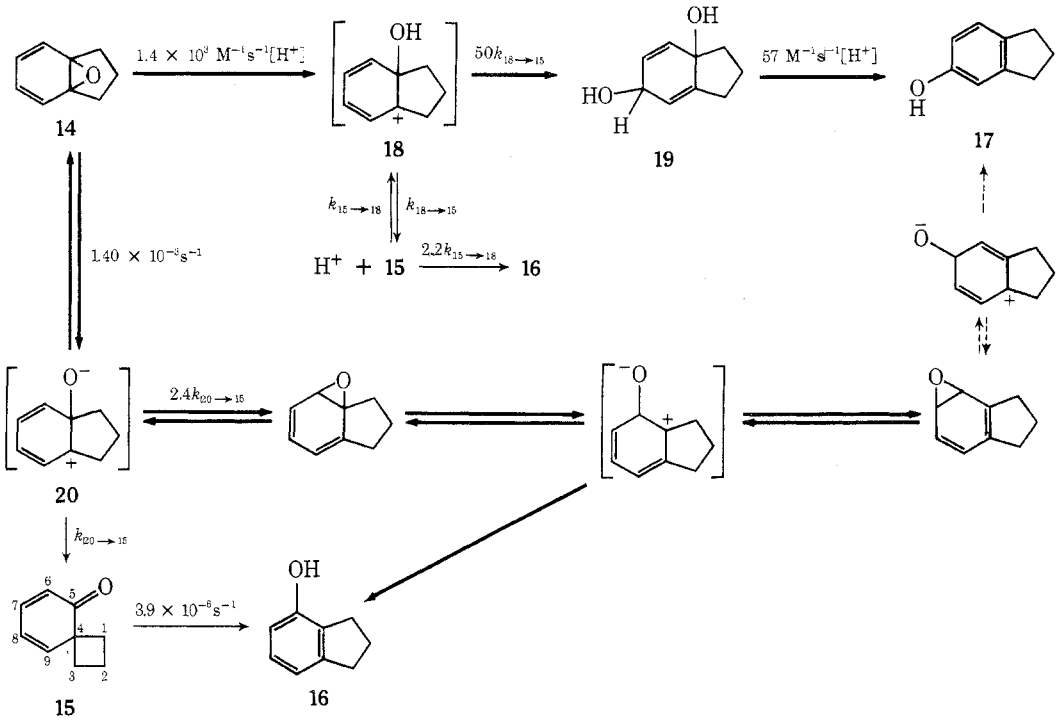
is the same as that for oxide disappearance. Under acidic conditions, when the reaction of the oxide is complete, the product consists of 54% **11** and 46% **12**. Phenol formation continues, however, after all of the



(8)

(31) (a) N. Kaubisch, J. W. Daly and D. M. Jerina, *Biochemistry*, 11, 3080 (1972); (b) E. A. Fehnel, *J. Am. Chem. Soc.*, **94**, 3961 (1972).

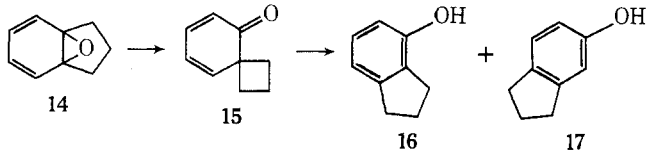
Scheme II[a]



[a] Heavy arrows, major pathway; light arrows, minor pathway; dashed arrows, trace pathway.

starting oxide (**6**) has disappeared. Clearly in the acid pH range, but not in the pH-independent range, an intermediate (**13**) accumulates. Kinetic studies plus spectrally determined product ratios from both oxide and intermediate are in accord with the mechanism of eq 8.[15] The $\Delta G^{\ddagger}$ values associated with all transition states, with the exception of that for formation of **11** from its precursor cation, are within 1.5 kcal M^{-1} in free-energy content. Consequently, the methyl migration associated with the k_4 step is partially rate limiting, whereas the corresponding hydrogen migration is not.

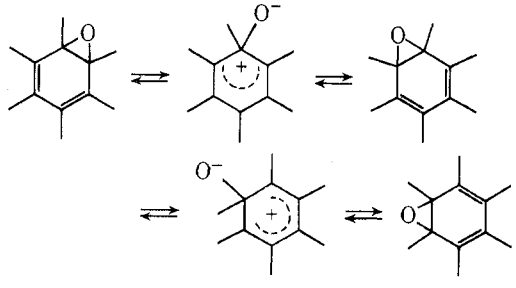
The isomerization of 8,9-indan oxide (**14**) had previously been investigated,[32,33] and it was reported that 5-indanol (**17**) accompanied the formation of 4-indanol (**16**) from **14** via **15** (eq 9). Formation of **17**, unlike **16**,



(9)

cannot arise directly from **15**. It occurred to us that formation of **17** may be the result of solvent trapping of carbocation as seen with **6**, or, alternately, may arise from an "oxygen walk" [34] since the carbocation once formed may collapse to provide an isomer of the starting oxide (eq 10). Subsequent investigation revealed that both possibilities were operative.[35]

The pH dependence of the disappearance of 8,9-



(10)

indan oxide (**14**) resembles that found for oxides **1**, **2**, **4**, **5**, and **6**. However, at all pH's the rate of disappearance of oxide is not proportional to the rate of appearance of phenolic products, thus requiring the formation of stable intermediates. From kinetic intermediate trapping and product studies the mechanism of Scheme II is obtained. The appearance of **17** in the basic pH region is attributed to an oxygen-walk mechanism (eq 10). The percent formation of **17** (originating from the oxygen walk) increases on going from 50% (v/v) dioxane–H_2O to H_2O.[36]

Reaction of Arene Oxides with Nucleophiles. The ability to experimentally detect nucleophilic addition to an arene oxide is dependent upon the nucleophile and the structure of the oxide. Examination of the pH–rate profiles for rearrangement of **1**, **2**,[14] **4**,[26] **6**,[15] and **16**[35] (Figure 1 and inset to Figure 4) establishes that increasing [HO^-] by 10^5- to 10^7-fold does not bring about an increase in the rate of disappearance of oxide. In aqueous solution, polarizable nucleophiles (such as N_3^-, RS^-) add in a 1,2 or 1,6 trans fashion to benzene oxide (**1**), but no addition is seen with hard nucleophiles of comparable or greater basicity.[37] This discrimination is not due to the fact that oxides such as **1** are not sus-

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(33) J. W. Daly, D. M. Jerina, H. Ziffer, B. Witkop, F. G. Klärner, and E. Vogel, *J. Am. Chem. Soc.*, **92**, 702 (1970).
(34) P. Y. Bruice, G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, **95**, 1673 (1973).
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(37) For a most pertinent study and additional references, see: A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, *J. Am. Chem. Soc.*, **96**, 6929 (1974).

ceptible to attack by nitrogen and oxygen nucleophiles but is the result of competition between the second-order nucleophilic addition reaction and the water-catalyzed aromatization reaction.[38] Thus, nucleophilic attack by amines and oxygen nucleophiles on **1** occurs too slowly to compete with the aromatization reaction, while attack by sulfur nucleophiles is sufficiently rapid that it effectively competes with aromatization.[39] As anticipated, on the basis of the greater importance of polarizability as compared to basicity (Edwards relationship),[40] the basicity of the thiolate species has little influence upon its rate of reaction with benzene oxide (Brønsted β value of 0.2).[39] The reaction of arene oxides with glutathione 5-epoxide transferase appears to be highly specific for glutathione.[41] The lack of sensitivity that arene oxides exhibit to thiol basicity suggests that the apparent requirement of the enzyme for glutathione must reside in its specificity as a cosubstrate for the enzyme and not in its intrinsic nucleophilicity. The low Brønsted β value suggests that it should be possible for high concentrations of any thiol to sequester arene oxides in vivo.

Although the non-K-region oxides of phenanthrene (**4** and **5**), like benzene and naphthalene oxide, are not susceptible to nucleophilic attack by HO^- (see inset to Figure 4), the isomeric K-region oxide undergoes nucleophilic addition of HO^-, CO_3^{2-}, H_2O, amines, and, of course, mercaptans.[22,38] The second-order rate constants for reaction of HO^-, H_2O, and primary and secondary amines with **3** (30 °C) and with ethylene oxide (25 °C)[42] are related by eq 11, which shows that the

$$\log k_{n(3)} = 1.3 \log k_{n(\text{ethylene oxide})} + 1.7 \qquad (11)$$

sensitivity of the two oxides to the nature of the nucleophile is similar and that the arene oxide is the more reactive. For thiolate anion addition, ethylene oxide[43] exhibits the greater sensitivity to the pK_a of the thiol (eq 12).

$$\log k_{n(3)} = 0.35 \log k_{n(\text{ethylene oxide})} + 0.96 \qquad (12)$$

Phenanthrene 9,10-oxide is only slightly more reactive toward nucleophilic attack by thiolate anions than are the isomeric non-K-region oxides **4** and **5**; the second-order rate constants for reaction with 2-mercaptoethanol are 3.38, 1.58, and 2.04 M^{-1} s^{-1}, respectively. Thus the K region does not make the oxide necessarily a better alkylating agent! This is little appreciated and is a most important point since it is significant to an understanding of carcinogenesis. It is the repression of both the rate of pH-independent ring opening and the rate of the NIH shift at the K region that allows **3** to exist longer in solution, so that it survives to be an alkylating agent. Values of $k_1[H_2O]$ are 3.10×10^{-2}, 5.55×10^{-2}, and 2.1×10^{-4} s^{-1} for phenanthrene 1,2-, 3,4-, and 9,10-oxides, respectively. Thus, the lifetime of the K-region oxide (**3**) is almost 100 times greater (region B) and 1000 times greater (region D, Figure 4) than that of the other oxides. Once formed, the carbonium ions obtained from the 1,2- and 3,4-oxides go on to phenol as a result of intramolecular hydride transfer and proton elimination. In the case of the carbonium ion formed from the 9,10-oxide, phenol formation must be sufficiently repressed to allow both solvent trapping which results in the formation of dihydro diols and HO^- catalyzed reclosure to oxide (Scheme I). The depression of the spontaneous or water-catalyzed rate constants for aromatization is particularly marked for the K-region oxides benz[*a*]anthracene 5,6-oxide (**21**), pyrene 4,5-oxide, and benzo[*a*]pyrene 4,5-oxide.[22] Keller and Heidelberger recently reported a kinetic study of the solvolysis of four K-region arene oxides in 50% dioxane:water: **3**, **21**, dibenz[*a*,*h*]anthracene 5,6-oxide (**22**), and 3-methylcholanthrene 11,12-oxide (**23**).[44] Except in the case of **23**, these studies were carried out only in the acid pH region. As a consequence of examining these oxides only under acidic conditions where nucleophilic addition is not expected,[22] Keller and Heidelberger observed only carbonium ion formation (Scheme I). Consequently, they were led to propose that the attachment of cell macromolecules to arene oxides occurs via a carbonium ion trapping mechanism, at odds with our finding that a wide variety of nucleophiles can become attached to arene oxides by a direct nucleophilic displacement mechanism.[22,38] The K-region oxide **23** was investigated up to pH 12, and its rate of rearrangement was reported to be described by eq 4, the kinetic expression we have found to be applicable to non-K-region arene oxides. This compound may be more closely analogous to the non-K-region oxides since the rate of the acid-catalyzed ring-opening reaction is 50- to 120-fold greater than those of the other K-region oxides, and the rate of the pH-independent ring-opening reaction is of about the same magnitude as those of non-K-region oxides in the same solvent.[22] However, the rate constant obtained for the reaction of **23** at pH 12, as well as the reported pH-dependent product distribution, suggests that solvolysis does not simply follow eq 4, as suggested by Keller and Heidelberger, but that there is some contribution from direct nucleophilic attack of hydroxide ion at high values of pH.

In order to visualize the importance of the rate of the ring-opening reaction in determining the susceptibility of an oxide to nucleophilic attack we have employed a "nucleophilic susceptibility index", defined as the relative rate of attack by 2-mercaptoethanol divided by the relative rate of water-catalyzed epoxide ring opening. A tabulation of the nucleophilic susceptibility indices for a number of arene oxides is included in Table II. The K-region oxide (**3**) can be seen to be the arene oxide that most closely resembles ethylene oxide, which is also an effective alkylating agent.

The foregoing discussion suggests that repression of the ring-opening reaction should allow the observation of nucleophilic addition to benzene and other simple non-K-region arene oxides. Since the rate constant for ring opening is rather drastically repressed by electron-withdrawing substituents (Figure 2) while that for nucleophilic addition should be enhanced, one would expect that substitution of benzene oxide by electron-withdrawing substituents should lead to nucleophilic

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(39) D. M. E. Reuben and T. C. Bruice, *J. Chem. Soc., Chem. Commun.*, 113 (1974); *J. Am. Chem. Soc.*, **98**, 114 (1976).
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Table II
Relative Rates of Spontaneous Ring Opening (A) and Thiolate Anion Nucleophilic Attack (B)

Compound	A^a	B^b	B/A = nucleophilic susceptibility index
Ethylene oxide	1[c]	1[e]	1
Benzene oxide (1)	2 000[d]	4[f]	0.002
Naphthalene 1,2-oxide (**2**)	5 000[d]	41	0.008
Phenanthrene 1,2-oxide (**4**)	50 000[d]	39	0.0008
Phenanthrene 3,4-oxide (**5**)	88 000[d]	50	0.0006
Phenanthrene 9,10-oxide (**3**)	300[d]	82	0.3

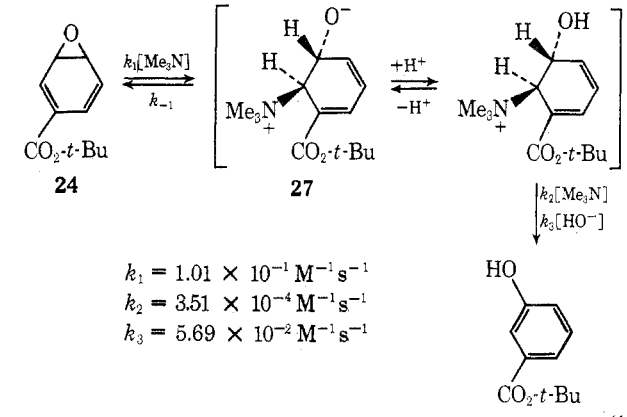
[a] Ethylene oxide measured at 25 °C, all others at 30 °C. [b] Attack on ethylene oxide measured at 20 °C, others at 30 °C. [c] Reference 42. [d] Reference 22. [e] Reference 43. [f] Reference 39.

addition of nonpolarizable nucleophiles. Berchtold and co-workers[45] found that reaction of 4-carbo-*tert*-butoxybenzene oxide (**24**) with LiOH in aqueous dioxane yielded as a product *tert*-butyl *trans*-2,3-dihydroxy-2,3-dihydrobenzoate (**25**). In our hands[17] the kinetics of the reaction of **24** in aqueous solution exhibited, in addition to pronounced H_3O^+ and H_2O catalyzed aromatization, a term dependent upon $[HO^-]$. Reaction with HO^- became evident above pH 11, where the diol **25** could be shown to be formed. With the more electron-deficient 4-cyanobenzene oxide (**26**), disappearance of oxide becomes first order in $[HO^-]$ above pH 9. Indeed, HO^- attack is found to be more facile than the H_3O^+ catalyzed reaction of this oxide (eq 13).[18]

$$\frac{d[\mathbf{26}]}{dt} = [\mathbf{26}](2.5 \times 10^{-3})a_H + 1.33 \times 10^{-6} + (2.1 \times 10^{-2})[HO^-] \quad (13)$$

Facile nucleophilic addition could be an important aspect in necrosis, mutagenesis, etc., brought about by certain electron-deficient benzene oxides. These results suggest a chilling possibility. Drug molecules possessing phenyl groups with electron-deficient substituents could undergo enzymatic epoxidation in vivo and thus become potential health hazards since, when transformed to arene oxides, they could be potent alkylating agents.

Nucleophilic Catalysis of the Aromatization of Arene Oxides. Of considerable interest is our finding that reaction of **24** with amines results in metastable adducts that yield phenol via a base-catalyzed reaction. For trimethylamine the sequence of events given in eq 14 has been established.[17] This route could be of particular importance in biochemistry since it provides a means for nucleophilic catalysis of the aromatization of arene oxides (other than the NIH shift) at an active site. Evidence has recently been presented that a mechanistic alternative to the NIH shift is prevalent in the hydroxylation reaction of benzenoid compounds by hepatic monoxygenases.[46] Furthermore, the monoxygenase reaction is characterized by a C–H(D) isotope effect which could originate from the general base catalyzed elimination step of eq 14.



(14)

Although once proposed as being reactive toward amides and proteins in general, simple arene oxides undergo aromatization too rapidly to allow attack by nonpolarizable nitrogen and oxygen nucleophiles.[47] The findings that (a) the rate of the aromatization reaction is depressed for K-region arene oxides and simple arene oxides with electron-withdrawing substituents and (b) these arene oxides are particularly susceptible to attack by thiols suggest that they may find utility as alkylating agents for protein sulfhydryl groups. Incubation of glyceraldehyde-3-phosphate dehydrogenase, an SH-dependent enzyme, for 2 h with 1×10^{-3} M **3**, 4-carboxybenzene oxide (**28**), or **24** results in the loss of 89, 86, and 99% of the initial activity, respectively. Under like conditions, incubation of yeast alcohol dehydrogenase with **24** results in a loss of >99% of the initial reactivity.[48]

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