

Comparison of the Reactions of Lewis and Brønsted Acids with Amines. It seems interesting to compare the addition of an amine to a kind of Lewis acid studied here with the analogous Brønsted acid-base reaction. Superficially proton transfer between phenols and amines seems to have little in common with reaction 1a. When we consider, however, that the ion pairs formed do hardly dissociate in media of low dielectric constant such as in chlorobenzene, which was used in this study, we observe a very similar sequence of reaction steps:^{24,25}



Again a highly polar complex, here an ion pair, is formed by a primary addition step and reordering of the encounter complex. For comparison we give the reaction and activation quantities of an example of this type of reaction, the complex formation between 2,4-dinitrophenol and tri-*n*-octylamine, in Table VI.²⁵ Similar to our example large negative values for reaction and activation entropies are reported.

So far we have treated reaction 1a as a single elementary step, not controlled by diffusion, which is consistent with the kinetic data (see section II) and the positive value of ΔH^\ddagger_{12} or E_{a1}^\ddagger , respectively. Complex formation between phenols and amines studied in chlorobenzene behaves somewhat differently^{24,25} (Table VI): in this case formally negative values of ΔH^\ddagger_{12} and E_{a1}^\ddagger were obtained which demand a mechanism of at least two steps in order to explain the negative sign by a preequilibrium.

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References and Notes

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Comparative Chemistry of the Bay- and Non-Bay-Region Tetrahydro Epoxides of Phenanthrene

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Abstract: It has been previously proposed that the great mutagenic and carcinogenic activity of the tetrahydro epoxides of a number of polycyclic aromatic hydrocarbons, in which the epoxide moiety resides at a "bay region", is due to the greater stability of the bay region benzylic carbonium ion formed upon oxirane ring opening. The rate constants for specific-acid-, general-acid-, and water-catalyzed oxirane ring opening of the bay (I) and nonbay (II) epoxides of 1,2,3,4-tetrahydrophenanthrene are compared. Also compared are the second-order rate constants for nucleophilic attack upon I and II. With few notable exceptions the various second-order rate constants for the various reactions of I and II were found to be quite similar with the rate constants for I exceeding those of II by an approximate average of threefold. Similar rate ratios are seen in the reactions of the bay and nonbay phenanthrene arene oxides wherein the bay benzylic carbonium ion stability cannot be a factor. A notable exception is the general-acid-catalyzed oxirane ring opening by H_3PO_4 , where the second-order rate constant for I exceeds that for II by 40-fold. Brønsted α (-0.7) and β_{nuc} (+0.25) values obtained with I and II are indistinguishable. Also similar are the values of ΔS^\ddagger and kinetic solvent isotope effects ($k^{\text{H}_2\text{O}}/k^{\text{D}_2\text{O}}$) for H_2O - and H_3O^+ -catalyzed oxirane ring opening. The values of ΔS^\ddagger and $k^{\text{H}_2\text{O}}/k^{\text{D}_2\text{O}}$ for H_3O^+ -mediated solvolysis are as expected for a specific acid mechanism. Nevertheless, the values of the log $k_{\text{H}_3\text{O}^+}$ fit accurately to the Brønsted plots for general acid catalysis. Product studies show a mixture of cis and trans diols to be formed at low and intermediate pHs, while only trans diols are formed at high pH. These results are discussed.

Introduction

There is presently strong evidence that the ultimate carcinogenic metabolites of benzo[*a*]pyrene and benz[*a*]anthracene are dihydrodiol epoxides in which the epoxide function is in the bay region¹ of the saturated angular benzo ring.^{2a-b} On the basis of perturbational molecular orbital calculations it has been suggested that bay-region epoxides should be more re-

active than corresponding non-bay-region epoxides owing to the greater calculated stability of the benzylic bay region carbonium ion.³ Studies have confirmed that the bay-region dihydrodiol epoxides of benzo[*a*]pyrene,^{2g} benz[*a*]anthracene,^{2a,4} and chrysene⁵ are more highly mutagenic than are the corresponding non-bay-region dihydrodiol epoxides. However, it has not been shown that bay and nonbay epoxides

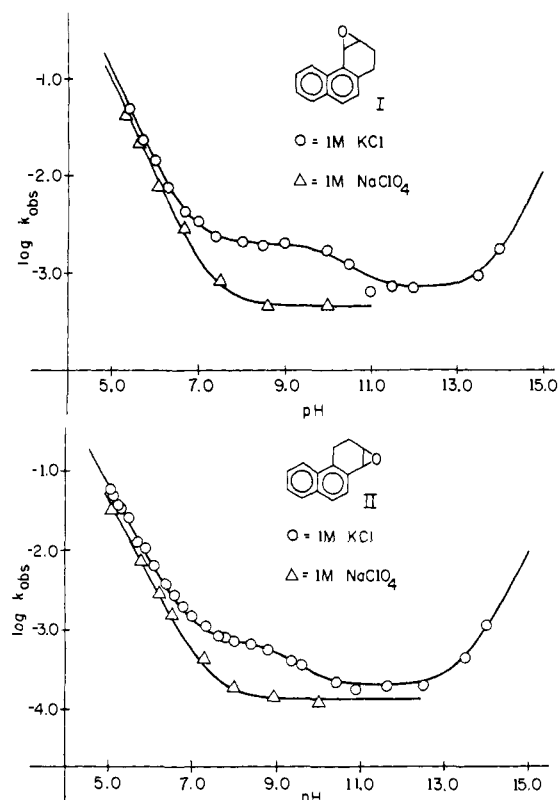
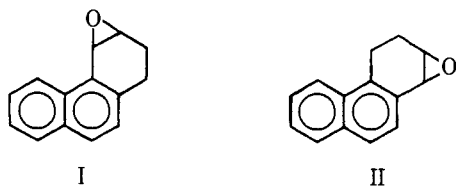


Figure 1. pH-rate profile for the solvolysis of 1,2,3,4-tetrahydrophenanthrene 3,4-oxide (I) and 1,2,3,4-tetrahydrophenanthrene 1,2-oxide (II) in aqueous solution, $\mu = 1.0$, at 30 °C. The theoretical lines were derived from eq 1 and 2.

differ significantly in their *chemical* reactivity as would be predicted by the bay-region theory.³

Accordingly we have synthesized the bay (I) and nonbay (II) epoxides of 1,2,3,4-tetrahydrophenanthrene, the simplest



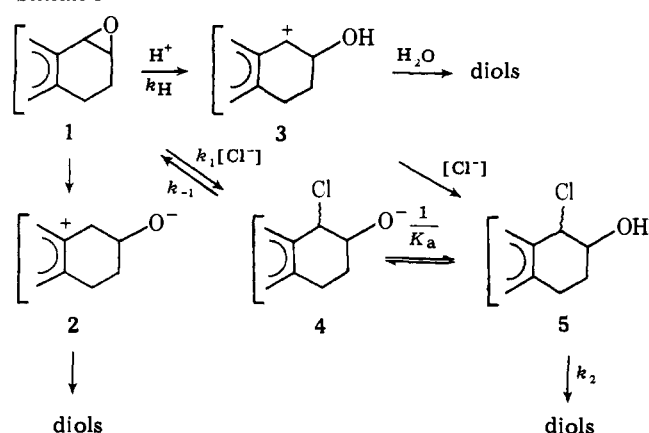
system containing a bay region. Their rates of hydrolysis, reactions with general acids, amines, and thiols, and hydrolysis products have been studied in order to determine their relative chemical reactivities.

Experimental Section

I. Materials. 1,2,3,4-Tetrahydrophenanthrene 3,4-oxide (I) and 1,2,3,4-tetrahydrophenanthrene 1,2-oxide (II) were prepared from the corresponding bromohydrins.⁶ The bromohydrins were recrystallized to constant melting point; the epoxides were used without further purification. Epoxide II had mp 92–93 °C (lit.⁶ mp 90–91 °C). Epoxide I (mp 62–63 °C; NMR δ 3.75 (H₃, 1 H), 4.6 (d, H₄, 1 H)) contained a small amount (<5%) of the 3-keto compound which did not affect the kinetics of the reactions. The epoxides were stored as solutions in ethanol at –20 °C and were used within 2 weeks. Authentic samples of the tetrahydrophenanthrene *cis*-1,2- (mp 157–158 °C, ethyl acetate) and *cis*-3,4-diols (mp 170–171 °C, ethyl acetate) were obtained via the reaction of osmium tetroxide with the corresponding dihydrophenanthrene. (These diols had acceptable NMR spectra and showed one peak by TLC and reverse phase LC.) The *trans*-1,2- and *trans*-3,4-diols of tetrahydrophenanthrene were obtained via the Prevost reaction on the appropriate dihydrophenanthrene.¹⁹ All other materials were purchased from the best available source and used as received.

II. Kinetic Determinations. The hydrolyses of I and II were carried

Scheme 1



out in doubly glass distilled water with the ionic strength maintained at 1.0 with KCl or NaClO₄. Salt solutions were extracted with 0.01% dithizone in CCl₄ to remove any heavy metal contamination. Rates were determined by following the disappearance of I at 232 nm and II at 237 nm; the concentration of epoxide employed was about 1×10^{-4} M. The pH-dependent solvolyses of I and II, the determination of the temperature dependence of the solvolytic constants, and the reactions of I and II with β -mercaptoethanol were carried out in a Radiometer pH-stat assembly specifically designed for a Cary 15 spectrophotometer.^{7a} In order to prevent leakage of Cl[–] from the calomel electrode in reactions where NaClO₄ was employed to maintain μ , a flowing liquid junction was used.^{7b} Reactions in formate buffers were monitored at 299 nm with a Durrum stopped-flow spectrophotometer. All other investigations of buffer catalysis were monitored at 299 nm with a Cary 16 or 118 spectrophotometer employing buffers to maintain pH. All spectrophotometers were thermostated at 30 °C. Between pH 7.5 and 11, reactions on the Cary 15 pH-stat assembly were conducted under nitrogen. When buffers were used, generally five serial dilutions were employed at each pH with the pHs of the serial dilutions agreeing within 0.02 pH unit. Readings of pH were determined on a Radiometer Type PMH 26 pH meter. Calculation of pseudo-first-order rate constants, least-square slopes and intercepts, and generation of theoretical pH-rate profiles and pH-product profiles were done using a Hewlett-Packard Model 9825A computer.

III. Product Determinations. Hydrolysis products in 1 M KCl or 1 M NaClO₄ were determined by LC using a Spectraphysics RP-8 reverse phase C-18 column in a solvent of 50:50 water-methanol. The effluent was monitored at 280 nm with a Schoeffel Spectroflow detector and the data collected with a Varian CDS-101 integrator.

Results

The pH-rate profiles for the hydrolysis of I and II in 1 M KCl and 1 M NaClO₄ are shown in Figure 1. The profiles observed in 1 M NaClO₄ may be fit to the usual^{8a} equation²⁷

$$k_{\text{obsd}} = k_{\text{HAH}} + k_0 \quad (1)$$

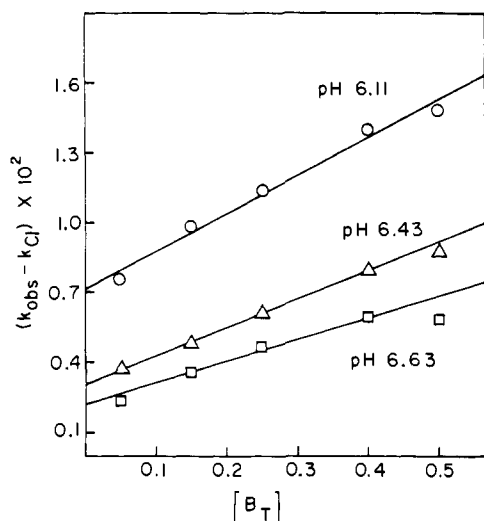
for acid (k_{HAH}) and spontaneous or water catalysis (k_0). The more complicated profiles observed in 1 M KCl are due to the occurrence of a specific effect of chloride ion as proposed by Whalen (Scheme 1).^{8b,9} Steady state for the intermediates 4 and 5 of Scheme 1 provide the rate law^{8d}

$$k_{\text{obsd}} = k_{\text{HAH}} + \frac{k_1[\text{Cl}^-]}{1 + \frac{k_{-1}K_a}{k_2a_{\text{H}}}} + k_0 + k_{\text{OH}}[\text{OH}^-] \quad (2)$$

Similar specific chloride effects have been observed in the cases of indene oxide,^{8b} phenanthrene 9,10-oxide,⁹ and 1,2,3,4-tetrahydronaphthalene 1,2-oxide,^{10a} but to our knowledge have not been observed for any non-K-region arene oxide^{9a} or any arene dihydrodiol oxide.^{10b} The bump between pHs 6 and 10 in the profiles of I and II in 1 M KCl is well accounted for by

Table I. Rate Constants for Hydrolysis of 1,2,3,4-Tetrahydrophenanthrene 1,2-Oxide (I) and 3,4-Oxide (II)

epoxide	electrolyte	$k_H, M^{-1} s^{-1}$	k_0, s^{-1}	k_{OH^-}, s^{-1}	$k_1, M^{-1} s^{-1}$	$k_1 K_a / k_2$
I	1 M KCl	1.4×10^4	8.0×10^{-4}	1.3×10^{-3}	1.5×10^{-4}	5.0×10^{-11}
I	1 M NaClO ₄	1.1×10^4	5.2×10^{-4}	<i>a</i>		
II	1 M KCl	5.5×10^3	1.7×10^{-4}	8.1×10^{-4}	4.2×10^{-4}	6.3×10^{-10}
II	1 M NaClO ₄	3.5×10^3	1.2×10^{-4}	<i>a</i>		

^a Not determined.**Figure 2.** Plots of k_{obsd} (corrected for chloride contribution to rate) vs. total cacodylate buffer concentration for the general-acid-catalyzed solvolysis of 1,2,3,4-tetrahydrophenanthrene 1,2-oxide at three pH values.

the second term in eq 2. At intermediate pHs addition of chloride ion to I becomes competitive with the acid and spontaneous rates. At high pH the equilibrium between I and 5 shifts to the epoxide, and the pH-independent spontaneous rate (k_0) predominates, while above pH 13.5 direct attack of HO⁻ becomes significant. Values of the rate constants k_H , k_0 , and k_1 for I and II are shown in Table I.

Reaction with General Acids and Bases (Nucleophiles). A variety of general acids catalyze the hydrolysis of epoxides I and II with the rate constants shown in Table II. In each case rates were measured at a minimum of three different pHs, employing five buffer dilutions at each pH. Rate constants were obtained by dividing the slope of plots such as those shown in Figure 2 by $a_H / (K_a + a_H)$ where K_a is the acid dissociation constant of the general acid. As has been noted,^{9b} for epoxides exhibiting a chloride effect, the contribution of the chloride term to the observed rate must be accounted for when KCl is used to maintain constant ionic strength. Tris, imidazole, and glycine buffers were made from the amine hydrochloride and diluted with 1 N KCl, giving serial dilutions with a constant chloride concentration of 1 M. Phosphate buffers were held to constant ionic strength with sodium perchlorate. Observed rates for the cacodylic acid buffer were corrected before plotting by subtraction of the chloride contribution (calculated from eq 2). For the acetate and formate buffers, contributions to the observed rate by chloride attack were negligible in the pH range studied.

The free amine base of glycineamide as well as its conjugate acid react with both I and II. The reaction obeyed the rate law given in the equation

$$k_{obsd} = k_{1y} + \left[\frac{k_{ga} a_H}{(K_a + a_H)} + \frac{k_n K_a}{(K_a + a_H)} \right] [B_T] \quad (3)$$

$$\text{where } k_{1y} = k_H a_H + \frac{k_1 [Cl^-]}{1 + \frac{k_{-1} K_a}{k_2 a_H}} + k_0 \quad (3a)$$

Table II. Rate Constants for General-Acid-Catalyzed Hydrolysis of I and II

general acid	pK _a	elec-trolyte ^e	$k_{ga}, M^{-1} s^{-1}$	
			I	II
H ₃ O ⁺	-1.75	KCl	1.4×10^4	5.5×10^3
D ₃ O ⁺	-2.1 ^f	KCl	3.1×10^4	1.9×10^4
H ₃ PO ₄	1.6 ^a	NaClO ₄	9.4×10^3	2.2×10^2
H ₂ PO ₄ ⁻	6.42 ^b	NaClO ₄	2.3×10^{-1}	3.4×10^{-2}
(HOCH ₂) ₃ -CNH ₃ ⁺	8.25 ^c	KCl	1.7×10^{-3}	0
imidazolium	7.14 ^c	KCl	2.2×10^{-2}	0
H ₃ N ⁺ CH ₂ -COHN ₂	8.13 ^c	KCl	4.0×10^{-3}	4.4×10^{-4}
cacodylic acid	6.12 ^d	KCl	2.3×10^{-1}	3.4×10^{-2}
acetic acid	4.62 ^d	KCl	1.6	2.6×10^{-1}
formic acid	3.45 ^d	KCl	4.4	0

^a G. M. Loudon and D. E. Ryons, *J. Org. Chem.*, **40**, 3574 (1975).^b P. Y. Bruce and T. C. Bruce, *J. Am. Chem. Soc.*, **98**, 2023 (1976).^c P. Y. Bruce, T. C. Bruce, H. Yagi, and D. M. Jerina, *ibid.*, **98**, 2973 (1976). ^d Determined by half-neutralization. ^e Ionic strength 1.0.^f Approximate pK_a.

where K_a is the dissociation constant for protonated glycineamide. A plot of k_{obsd} vs. $[B_T]$ gives a line with an intercept k_{1y} and a slope given by the equation

$$\text{slope} = \frac{k_{ga} a_H + k_n K_a}{(K_a + a_H)} \quad (4)$$

A secondary plot of slope/ $(K_a / (a_H + K_a))$ vs. a_H as shown in Figure 3 provides a line whose slope is k_{ga} / K_a and whose intercept is the second-order rate constant for reaction of epoxide with amine free base. Similar behavior is observed in the hydrolysis of the 3,4-oxide (I) in Tris buffer; no reaction of Tris with II was observed.

In contrast, the disappearance of epoxides I and II from Na₂HPO₄/NaH₂PO₄ buffers over the pH range 5.5–6.5 are described by the expression

$$k_{obsd} = k_{1y} + k_{ga1} a_H [H_2PO_4^-] + k_{ga2} [H_2PO_4^-] \quad (5)$$

A plot of k_{obsd} vs. total phosphate concentration $[P_T]$ will have an intercept of k_{1y} and a slope as given in the equation

$$\text{slope} = \frac{k_{ga1} (a_H)^2 + k_{ga2} K_{a1} a_H}{(a_H)^2 + K_{a1} a_H + K_{a1} K_{a2}} \quad (6)$$

where K_{a1} is the dissociation constant for H₃PO₄ ($10^{-1.6}$)¹¹ and K_{a2} is the dissociation constant for H₂PO₄⁻ ($10^{-6.42}$). Over the pH range in question $(a_H)^2$ may be neglected. A secondary plot of slope/ $[a_H / (a_H + K_{a2})]$ vs. a_H has an intercept of k_{ga2} (the second-order rate constant for general-acid-catalyzed hydrolysis by H₂PO₄⁻) and a slope of k_{ga1} / K_{a1} . The term $a_H [H_2PO_4^-]$ can be interpreted as general acid catalysis by H₃PO₄ at four pH units above its pK_a, or as preequilibrium protonation of the epoxide followed by nucleophilic attack by H₂PO₄⁻. Either possibility leads to rate constants which do not exceed the diffusion-controlled limit. Unexpectedly large general-acid rate constants for H₃PO₄ are general for phenanthrene and naphthalene tetrahydrooxides. Product studies

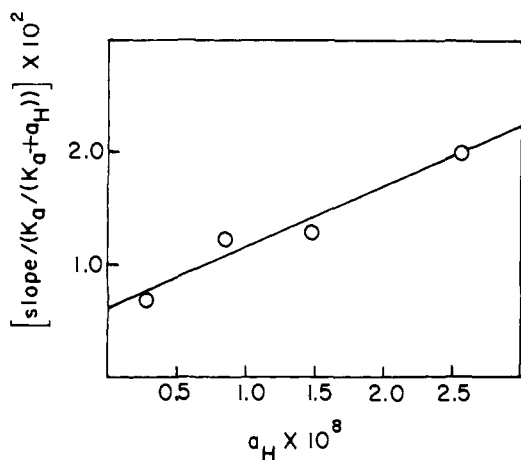


Figure 3. Secondary plot of $\text{slope}/(K_a/(K_a + a_H))$ vs. a_H for the solvolysis of 1,2,3,4-tetrahydrophenanthrene 3,4-oxide in glycine buffer. The theoretical line was computer generated by a least-squares program.

Table III. Rate Constants for the Reaction of Nucleophiles with Epoxides I and II ^a

nucleophile	pK_a^b	$k_n, M^{-1} s^{-1}$	
		I	II
imidazole	7.14	0	0
glycinamide	8.13	6.1×10^{-3}	3.8×10^{-3}
Tris	8.25	1.4×10^{-3}	5.0×10^{-4}
benzylamine	9.50	1.8×10^{-2}	9.6×10^{-3}
allylamine	9.92	1.0×10^{-2}	6.8×10^{-3}
ethylamine	10.73	9.1×10^{-3}	3.6×10^{-3}
methylamine	10.85	2.2×10^{-2}	1.0×10^{-2}
dimethylamine	11.05	4.5×10^{-2}	3.7×10^{-2}
CO_3^{2-}	9.68	0	0
2-mercaptoethanol	9.45	5.1	2.45
hydroxide ion	15.75	1.3×10^{-3}	8.1×10^{-4}

^a All reactions at 30 °C with an ionic strength of 1 maintained by KCl. The concentration of Cl^- was constant in each dilution. ^b P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, **98**, 2973 (1976).

on the hydrolysis of 1,2,3,4-tetrahydrophenanthrene 1,2-oxide in phosphate buffers have shown that there is no significant amount of attack on protonated epoxide by $H_2PO_4^-$.^{10b} Large general acid rate constants have been reported for the hydrolysis of vinyl ethers in phosphate buffers and have been interpreted as H_3PO_4 catalysis at pHs 4–5 units higher than the pK_a of H_3PO_4 .¹¹ The logarithms of the second-order rate constants for the general-acid-catalyzed hydrolysis of I and II are plotted in Figure 4 as a function of the pK_a of the general acid. Statistical correction of the rate constants does not result in any significant change in the Brønsted plots. The claim by Whalen^{9b} that general acid catalytic rate constants differ depending on the presence of KCl or $NaClO_4$ to hold constant ionic strength has not been substantiated in our laboratory,¹² provided that the concentration of chloride ion is constant throughout the experiment.

A variety of nucleophilic species (amines, β -mercaptoethanol anion, and hydroxide ion) react with I and II in aqueous solution. The second-order rate constants were determined by dividing the slope of a plot of k_{obsd} vs. $[B_T]$ by $K_a/(a_H + K_a)$, where K_a is the dissociation constant of the conjugate acid. These rate constants are shown in Table III. No rate enhancement was observed in HCO_3^-/CO_3^{2-} buffers for either I or II. In these reactions the buffers could be acting as general bases, assisting in the removal of a proton from an attacking water molecule, or as nucleophiles. It is almost certain that the amines and the β -mercaptoethanol anion are

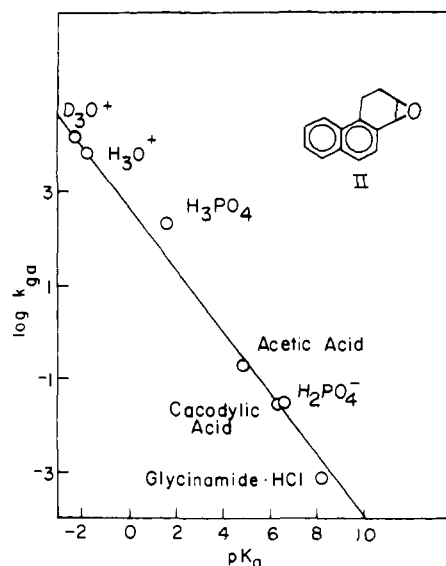
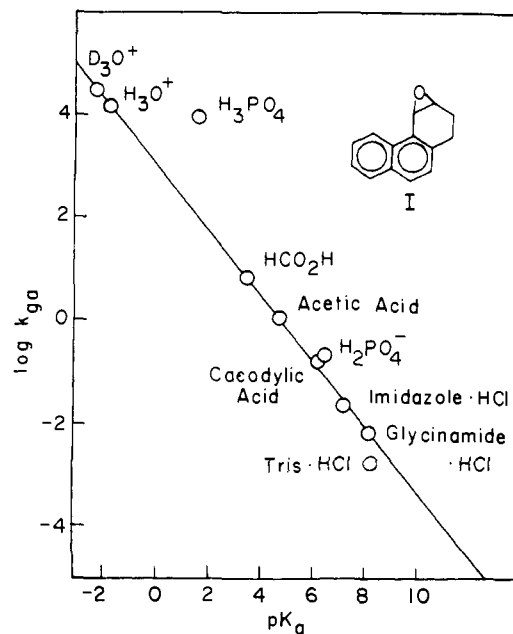


Figure 4. Brønsted plot of the logarithm of the second-order catalytic constants for general-acid-catalyzed solvolysis of 1,2,3,4-tetrahydrophenanthrene 3,4-oxide (I) and 1,2,3,4-tetrahydrophenanthrene 1,2-oxide (II) vs. the pK_a of the general acid. The pK_a of D_3O^+ was estimated to be -2.1 .²⁶

acting as nucleophiles and not as general bases, since carbonate ion gives no catalysis, although its pK_a is higher than those of some of the amines which do show catalysis.¹³ The logarithms of the second-order rate constants for attack of amines on I and II are plotted in Figure 5 as functions of amine pK_a . The negative deviation of Tris can be accounted for by its sterically hindered nature.¹⁴ Ethylamine also gave rate constants lower than would be predicted from its pK_a . Similar negative deviations of ethylamine have been observed in its reaction with phenanthrene 9,10-oxide¹⁵ and ethylene oxide.¹⁶ The value of β_{nuc} is 0.25 for attack of amines on both epoxides I and II.

The activation parameters for hydrolysis of epoxides I and II in acidic and basic media are shown in Table IV. The values of ΔS^\ddagger under acidic conditions argue for an A1 mechanism for the acid-catalyzed reaction path, but are not conclusive. A ΔS^\ddagger of -1.6 eu has been found for acid-catalyzed hydrolysis of tetramethylethylene oxide, but product studies indicate an A2 mechanism,¹⁷ although acidic hydrolysis of ethylene oxide has a $\Delta S^\ddagger = -6.1$, the evidence is contradictory as to whether an A1 or A2 mechanism is involved.¹⁸

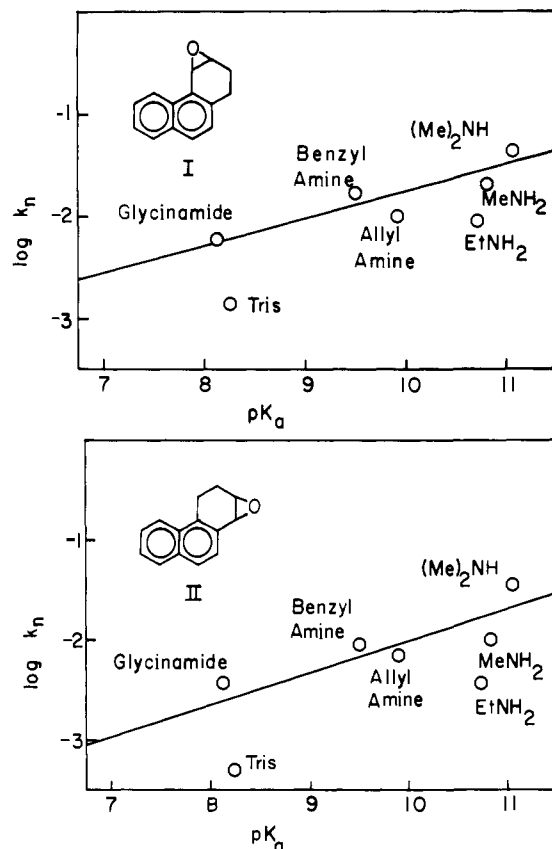


Figure 5. Brønsted plot of the logarithm of the second-order rate constants for the reaction of amine nucleophiles with 1,2,3,4-tetrahydrophenanthrene 3,4-oxide (I) and 1,2,3,4-tetrahydrophenanthrene 1,2-oxide (II) vs. pK_a of the amine.

Table IV. Activation Parameters for Hydrolysis of Epoxides I and II

epoxide	pH	ΔH^\ddagger ^a	ΔS^\ddagger ^b
I	5	10.0	-7
I	10	14.1	-26
II	5	13.5	+3
II	10	16.5	-21

^a In kcal/mol. ^b In eu.

The solvent primary deuterium isotope effects in the spontaneous and acid-catalyzed portions of the pH-rate profiles of I and II are given in Table V.

Product Studies. The hydrolysis products of epoxides I and II (Figure 6) in 1 M KCl and 1 M NaClO₄ solution were determined by LC analysis, using authentic cis and trans diols. At all pHs cis and trans diols were the only products. Other possible products would have been detected in the analysis or in the UV spectrum of the product mixture. At high pH, the UV spectrum of the crude reaction mixture was identical with that of authentic trans diol. No ketonic products were observed at any pH. However, the hydrolysis of the bay-region oxide I in 0.1 M NaClO₄ solution has been previously reported²⁵ to give substantial amounts of cis diol and ketones at alkaline pHs. We have no explanation for the disagreement of our results.

The product mixtures in the presence of chloride ion arise in part via the formation of chlorohydrins, which can either react via an S_N2 process or by solvolysis to give a benzylic carbonium ion, as in Scheme II, which was derived from Whalen's scheme for the kinetic rate expression.^{8b,9} It is clear that in the acidic range attack of chloride on the protonated epoxide (or carbonium ion) must be significant since more cis

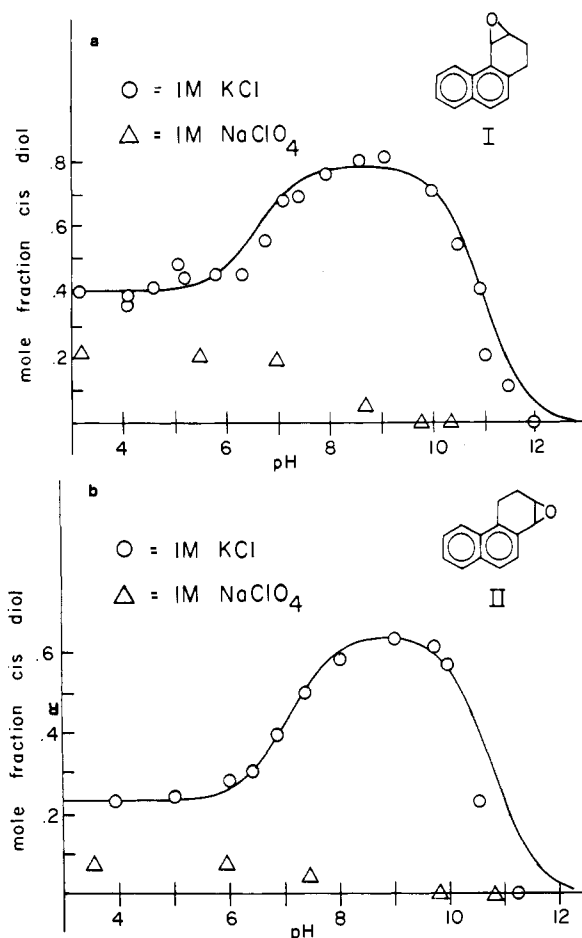


Figure 6. (a) Mole fraction after normalization of cis diol observed from the hydrolysis of 1,2,3,4-tetrahydrophenanthrene 3,4-oxide (I) in 1 M KCl and 1 M NaClO₄. The solid line is theoretical and was generated as described in text. (b) Mole fraction after normalization of cis diol observed from the hydrolysis of 1,2,3,4-tetrahydrophenanthrene 1,2-oxide (II) in 1 M KCl and 1 M NaClO₄. The solid line is theoretical and was generated as described in text.

Table V. Solvent Isotope Effects in the Hydrolysis of I and II

epoxide	$k_H^H^3O^+/k_D^D^3O^+$	$k_H^H^2O/k_D^D^2O$
I	0.5	0.8
II	0.3	0.75

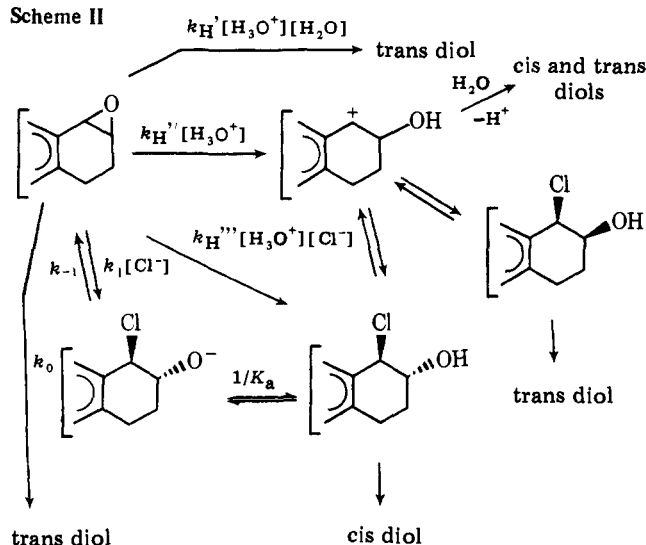
diol is formed in the presence of chloride than in its absence. At intermediate pHs attack of chloride on the unprotonated epoxide to give initially the trans chlorohydrin predominates. At very basic pH, the equilibrium between chlorohydrin and epoxide shifts in favor of epoxide formation, and the spontaneous pathway is favored, giving only trans diol.

A good approximation of the actual fraction of cis diol formed can be obtained from the equation

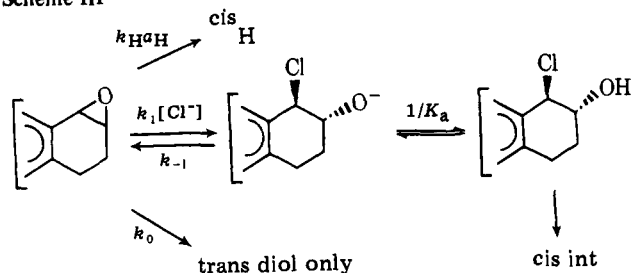
$$\text{fraction cis diol} = \frac{(\text{cis}_H)k_{HAH} + \frac{(\text{cis}_{int})K_1}{1 + \frac{k_{-1}K_a}{k_2a_H}}}{k_{HAH} + \frac{k_1}{1 + \frac{k_{-1}K_a}{k_2a_H}} + k_0} \quad (7)$$

which is derived from Scheme III. The cis_H and cis_{int} are the mole fractions of cis diol which would be observed if only the acid pathway (or intermediate pathway, respectively) were operating as derived from the theoretical fit. These theoretical

Scheme II



Scheme III



fits are shown in Figure 6. The values of the rate constants, k_{H} , and cis_{int} employed to fit the experimental product analyses to pH profiles are given in Table VI.

The k_1 and $k_{-1}K_a/k_2$ constants derived from product analysis do not fit the $\log k_{\text{obsd}}$ vs. pH rate profiles as well as the kinetically derived constants given in Table I. The assumption that the three pathways are independent is to some extent incorrect. That cis_{int} equals 1.0 for both epoxides indicates that solvolysis of the chlorohydrin to give the benzylic carbonium ion is at best a minor pathway. The cis diol arising from reaction of epoxide with Cl^- must be formed mainly by nucleophilic displacement of Cl^- by H_2O from the intermediate trans chlorohydrin.

Discussion

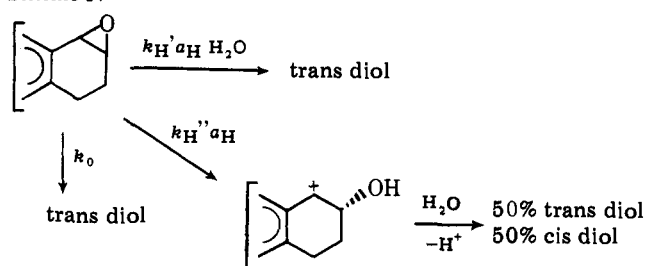
The pH-rate profiles (Figure 1) for solvolysis of 1,2,3,4-tetrahydrophenanthrene 3,4-oxide (I) and 1,2-oxide (II) are very similar to those observed for phenanthrene 9,10-oxide^{9a} and indene oxide.⁸ A mechanism consistent with the rate laws for the hydrolysis of I and II in the presence of Cl^- is given in Scheme I. Under acid conditions (slope of -1 in the pH-rate profile), the epoxides undergo acid-catalyzed opening of the epoxide ring to provide a carbocation. The entropies of activation and the solvent kinetic isotope effects in this region are compatible with either specific acid catalysis or general acid catalysis. However, since $\log k_{\text{H}}$ falls on the Brønsted plot ($\alpha \approx 0.7$) with other general acids (Figure 4), the H_3O^+ -catalyzed reactions appear to be of a general acid nature.

At intermediate pHs, attack of Cl^- on the epoxide to yield chloroalkoxide becomes competitive with acid- and water-mediated solvolysis;¹⁹ protonation of the intermediate chloroalkoxide followed by solvolysis provides diol products. At pH 11–12 spontaneous ring opening to give a zwitterion followed by addition of water is the predominant pathway. The very negative values of ΔS^\ddagger for spontaneous solvolysis of I and II are similar in size to those observed for phenanthrene 1,2- and 3,4-oxide²¹ and require water structuring in the transition state.

Table VI. Product Derived Constants for Hydrolysis of Epoxides I and II in KCl

	I	II
$k_{\text{H}}, \text{M}^{-1} \text{s}^{-1}$	1.4×10^4	5.5×10^3
$k_1, \text{M}^{-1} \text{s}^{-1}$	2.8×10^{-3}	3.0×10^{-4}
$k_{-1}K_a/k_2$	4.5×10^{-11}	5.0×10^{-11}
k_0, s^{-1}	8.0×10^{-4}	1.7×10^{-4}
cis_{H}	0.4	0.23
cis_{int}	1.0	1.0

Scheme IV



However, the solvent kinetic isotope effects ($k_0^{\text{H}_2\text{O}}/k_0^{\text{D}_2\text{O}}$) for spontaneous solvolysis of I and II are significantly smaller than those determined previously for phenanthrene 1,2- and 3,4-oxides (0.75 and 0.8 compared to 1.24 and 1.36). This is due to the water molecule acting more as a nucleophile with the incipient carbonium ion in the case of the tetrahydro epoxides I and II, while in the arene oxides the greater stability of the carbonium ion allows the water molecules to serve as proton donors. (Because the NIH shift to give phenols predominates with the phenanthrene 1,2- and 3,4-oxides, water cannot be involved as a nucleophile.) Even greater values of $k_0^{\text{H}_2\text{O}}/k_0^{\text{D}_2\text{O}}$ ($=1.8$) have been recently reported for the spontaneous ring opening of tetramethylethylene oxide.¹⁷ The role (nucleophile vs. proton source) of the water molecule(s) frozen into the transition states for spontaneous hydrolysis of epoxides is clearly dependent upon the structure of the epoxide. Above pH 13 direct attack of hydroxide ion on the epoxide becomes significant.²⁰ For epoxides I and II, the chloride term remains significant up to pH 11, while in phenanthrene 9,10-oxide and indene oxide the k_0 rate exceeds the rate due to chloride attack at ca. pH 9.5.

The amounts of cis diol formed in the hydrolysis of I and II are shown in Figure 6 as a function of pH. In 1 M NaClO_4 solution the electrolyte does not interfere in the reaction, and the product distribution arises from reaction with lyate species (Scheme IV). The amount of cis diol formed depends on the rate constants for A2 ($k_{\text{H}}/a_{\text{H}}[\text{H}_2\text{O}]$) and A1 hydrolysis which in turn has some dependence on the free energy of formation of the benzylic carbonium ion. The greater fraction of cis diol formed from the bay-region epoxide I indicates that the bay-region benzylic carbonium ion is more stable than is the non-bay-region benzylic carbonium ion. At higher pHs the k_0 rate predominates and only trans diol is formed.

It has been previously shown in this laboratory that the Brønsted line for acid-catalyzed solvolysis of arene oxides changes from -1 for H_3O^+ (specific acid catalysis) to ca. zero for H_2O catalysis (encounter controlled protonation of the intermediate zwitterion) so that general acid catalysis was observed in the pH region of 5–7.²¹ Both I and II exhibit general acid catalysis with α values of 0.7. For the bay-region epoxide I the value of $k_{\text{H}_3\text{PO}_4}$ exhibits a positive deviation of 50-fold from the Brønsted line provided by nine other general acid species (Figure 4), including H_2PO_4^- . For both I and II the logarithm of the second-order rate constant for H_3O^+ catalysis (k_{H}) fits accurately to the Brønsted plot for general acids. These constants are associated with $\Delta S^\ddagger \sim 0$ and solvent

kinetic isotope effects ($k_{\text{H}}^{\text{H}_3\text{O}^+}/k_{\text{D}}^{\text{D}_3\text{O}^+}$) of 0.5 and 0.3 for I and II, respectively. These values are compatible with either specific or general acid catalysis. It must be concluded that the catalysis of the solvolysis of I and II is general acid in nature.

The values of k_{ga} (with the exception of $k_{\text{H}_3\text{PO}_4}$) were between 0.6- and 9-fold greater for I than for II. For H_3PO_4 , k_{ga} for the bay-region epoxide (I) was ~ 40 times greater than for II. Also, no rate enhancement for hydrolysis of II was observed in formate buffer, though HCO_2H -catalyzed solvolysis of I was determined. These data indicate that the bay-region epoxide is more sensitive to catalysis of solvolysis by very acidic general acids. General-acid-catalyzed hydrolysis of both K-region and non-K-region arene oxides has been reported.^{9a,21} General-acid-catalyzed hydrolysis of a non-arene oxide has been reported in only four cases: 1,3-cyclohexadiene monoxide,^{22a} cyclopentadiene monoxide,^{22b} tetramethylethylene oxide,¹⁷ and 1-methoxy-1-phenyl-2-methyl-1,2-epoxypropane.²³

The slopes of the Brønsted plots (β_{nuc}) for the reaction of I and II with amine nucleophiles (Figure 5) are identical just as are the α values for general-acid-catalyzed oxirane ring opening. The values of the second-order rate constants for I are but ca. three times greater than are those for II. The value of β_{nuc} for I and II (0.25) is similar to the value of β_{nuc} for reaction of primary and secondary amines with phenanthrene 9,10-oxide (0.4) and with ethylene oxide (0.3).¹⁵ In contrast, arene oxides such as phenanthrene 1,2-oxide and 3,4-oxide are not attacked by hard, nonpolarizable nucleophiles such as amines, owing to their higher rates for spontaneous ring opening and concomitant aromatization.^{13,15}

The second-order rate constants for attack of β -mercaptoethanol on I and II can be used to determine their relative susceptibility to nucleophilic attack. A "nucleophilic susceptibility index" (NSI) has been defined^{15,24} as the ratio (A/B) of the second-order rate constant for attack by β -mercaptoethanol anion (A) to the first-order rate constant for solvolysis with water (B), all divided by the same ratio for ethylene oxide. When an epoxide has an NSI > 1 , it has a "lasting ability in water" combined with an electrophilicity that makes it a better alkylating agent (in water) than ethylene oxide. Epoxides I and II were found to have NSIs of 0.1 and 0.2, respectively. In comparison, phenanthrene 9,10-oxide has an NSI of 2.0, while non-K-region arene oxides have values ranging from 10^{-2} to 10^{-4} .²⁴

In general the reactions of epoxides I and II are seen to be remarkably similar. Rate constants for the 3,4-oxide (I) are greater than those for the 1,2-oxide (II) by about threefold. The bay-region oxide I differed from oxide II in that its hydrolysis was catalyzed by formic acid and in the much greater value of its general acid rate constant with H_3PO_4 . The average rate difference of threefold for all the other reactions corresponds to a difference in energy of less than 1 kcal mol⁻¹ and is too small to attribute to any particular cause. Approximately the same relative reactivity is seen for phenanthrene 3,4- and 1,2-oxides; hydrolysis of the bay-region arene oxide is two to three times faster than that of the non-bay-region arene oxide, even though in the case of the arene oxides the intermediate is an allylic, and not a benzylic, carbonium ion.¹⁵ Clearly the approximately threefold greater rate of hydrolysis of the tetrahydro epoxide I as compared to II is not necessarily attributable to the greater stability of the bay-region benzylic carbonium ion since the same ratio is seen for the arene oxides where formation of the bay-region benzylic carbonium ion is not involved. However, the product studies indicate a somewhat lower energy for the bay-region benzylic carbonium ion than

for the nonbay (7% cis diol for II vs. 20% cis diol for I).

It should be noted that the results in the phenanthrene system may not be strictly applicable to the corresponding benz[a]pyrene derivatives. The difference in energy between the bay and nonbay benzylic carbonium ions has been predicted to be greater for benz[a]pyrene than for phenanthrene.³ Therefore the difference in reactivity of the bay- and nonbay-region epoxides of benz[a]pyrene may be much larger than in the phenanthrene systems. However, the bay-region epoxide (I) has been reported²⁵ to have 10–15% of the mutagenic activity of 7,8,9,10-tetrahydrobenzo[a]pyrene 9,10-oxide in *S. typhimurium* strain TA 100.

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