duced within 8 h. The reaction of $(CH_3)_2SO_4$ with water to give methanol does not interfere with the reaction with chloride ion under study. The reaction was conducted in a round-bottom flask sealed with a vacuum stopcock. After the reaction was complete the CH_3Cl was distilled from the flask into a dry ice–acetone bath under vacuum at room temperature, and from the dry ice–acetone bath onto solid KOH at liquid N_2 temperature. The CH_3Cl was then purified as previously described.[2] The reaction was assumed to occur exclusively with $(CH_3)_2SO_4$ with no contribution from reaction of CH_3OSO_3H.[18]

$(CH_3)_2SO_4$ sulfate is known to react with DMF to give an adduct,[19] a reaction that can be conveniently followed by NMR. However, in the presence of 0.15 M LiCl no indication of the formation of this salt could be observed by NMR, and it was therefore assumed that this complication did not arise. Samples of CH_3Cl for mass spectroscopic analysis were collected by trap-to-trap distillation as described above from reaction of 0.1 g of $(CH_3)_2SO_4$ in 50 ml of 0.15 M LiCl for 12 h. The percent reaction of Cl^- was determined from titration of the initial and final concentrations of Cl^-.

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Comparison of the Mechanisms of Solvolysis and Rearrangement of K-Region vs. Non-K-Region Arene Oxides of Phenanthrene. Comparative Solvolytic Rate Constants of K-Region and Non-K-Region Arene Oxides

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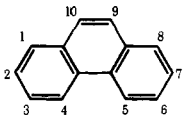
Abstract: The non-K-region arene oxides, phenanthrene 1,2- and 3,4-oxide, rearrange in water to produce only phenanthrols. These unsymmetrical arene oxides open preferentially to the vinylogous benzylic carbonium ion; thus 1-phenanthrol and 4-phenanthrol are the major products obtained from the 1,2-oxide and 3,4-oxide, respectively. Opening of the epoxide ring is rate limiting, is subject to both specific acid and general acid catalysis, and in the absence of buffer follows the rate law $k_{obsd} = k_H a_H + k_{H_2O}$. Phenanthrene 9,10-oxide, the K-region arene oxide, rearranges to ~75% 9-phenanthrol, 18% trans 9,10-dihydro diol, and 7% cis 9,10-dihydro diol below pH 7 and ≥98% trans dihydro diol above pH 9. The rate-limiting opening of the epoxide ring is catalyzed by hydronium ion and general acids. Below pH 7, dihydro diol formation is the result of carbonium ion trapping by water. This reaction effectively competes with the NIH shift. From ~pH 9 to 11, dihydro diol formation results from nucleophilic attack of water on the arene oxide, while at pH's greater than 11 its formation is the result of nucleophilic attack by hydroxide ion. Thus the K-region arene oxide behaves like an ordinary aliphatic epoxide in basic solution. Deuterated analogues of phenanthrene 9,10-oxide were employed to verify carbonium ion formation as the rate-limiting step below pH 7 and the occurrence of the NIH-shift pathway for a K-region arene oxide.

Introduction

The metabolism of aromatic hydrocarbons involves the conversion of the hydrocarbon to an arene oxide by hepatic microsomal oxidation. Arene oxides have been implicated as the agents responsible for the carcinogenic and mutagenic activity displayed by certain polycyclic aromatic hydrocarbons.[2] Those hydrocarbons that exhibit carcinogenic activity have a common structural feature called a K-region[3] which is easily recognized since its excision from the aromatic hydrocarbon leaves only cyclic conjugated aromatic rings; thus, the 9,10 bond of phenanthrene is a K-region. Because of the association of carcinogenic activity with the presence of a K-region, we have undertaken an investigation of I and II (where the oxide is at a non-K-region position) and III (where the oxide is at the K-region position) in order to determine the



I, 1,2-oxide
II, 3,4-oxide
III, 9,10-oxide

differences in solvolytic chemistry exhibited by non-K-region vs. K-region arene oxides. These compounds represent the three primary metabolites of phenanthrene. The rate constants for the H_3O^+catalyzed reaction of the K-region oxides III, X, XI, and XII are compared with those of non-K-region arene oxides.

Experimental Section

Phenanthrols. Reference standards of the isomeric 1-, 2-, 3-, 4-, and 9-hydroxyphenanthrenes were obtained as previously described.[4a]

Phenanthrene Oxides. Preparation of phenanthrene 1,2-oxide (I) and 3,4-oxide (II) was by the halohydrin ester route,[4] while preparation of phenanthrene 9,10-oxide (III) was by the dioxolane route.[5]

[9,10-$^2H_2$]Phenanthrene 9,10-Oxide. Reduction of phenanthrene-9,10-quinone (Aldrich) with $LiAl^2H_4$ by an established procedure[6] provided *trans*-9,10-dihydroxy-9,10-dihydro-[9,10-$^2H_2$]phenanthrene, which was converted to [9,10-$^2H_2$]phenanthrene 9,10-oxide by reaction with the dimethyl acetal of dimethylformamide in refluxing $CHCl_3$ for 36 h.[7] Comparison of the mass spectra of the normal and deuterated dihydro diols indicated that all the molecules contained at least one deuterium, while 96% of the molecules were dideuterated.

[9-^{2}H]Phenanthrene 9,10-Oxide. 9-Phenanthrylmagnesium bromide, prepared from 9-bromophenanthrene (Aldrich), was hydrolyzed with deuterium oxide to provide [9-^{2}H]phenanthrene, which was oxidized to *cis*-9,10-dihydroxy-9,10-dihydro-[9-^{2}H]phenanthrene with osmium tetroxide;[8] the mass spectrum of the diol indicated 86% monodeuteration. The diol was converted to [9-^{2}H]phenanthrene 9,10-oxide via the dioxolane route[5] without loss of deuterium.

3-Bromophenanthrene 9,10-Oxide. 3-Bromophenanthrene (the generous gift of Dr. E. May of NIH) was converted to the desired arene oxide by the dioxolane route[5] in an overall yield of 75% based on the cis dihydro diol. In the course of this study, 3-bromophenanthrene 9,10-oxide was also prepared by an alternative procedure.[9]

Kinetic Determinations. The solvolysis of I and II was carried out in aqueous dioxane (50% v/v), with the ionic strength maintained at 0.1 with KCl. Rates were determined by following the disappearance of I at 240 nm and II at 265 nm and/or the appearance of phenolic products at 275 nm. The solvolysis of III was carried out under the above conditions only from pH 1 to 3. The majority of the kinetic determinations for III (pH 2-14) was carried out at 30 °C in doubly glass-distilled water containing 10^{-4} M EDTA with μ = 1.0 (KCl). Appearance of products was followed at 255 and 267 nm. Stock solutions of arene oxides were prepared in acetonitrile and stored in dry ice. The concentration of arene oxide employed in the kinetic studies was about 1×10^{-5} M. Hydrolytic rates were carried out either in a Radiometer pH-stat assembly specifically designed for a Cary 15 spectrophotometer[10] or with a Cary 16, Cary 118, or Gilford Model 2000 spectrophotometer employing buffers to maintain pH. The second-order rate constants for the reaction of hydrazine and methoxyamine with III were determined using the Cary 15 pH-stat assembly. All spectrophotometers were thermostated at 30 °C. All rate determinations were carried out under a blanket of argon or nitrogen. When buffers were used to maintain pH, generally a minimum of four serially diluted buffer solutions were employed at each pH with the pH's of the serial dilutions agreeing within 0.02 pH units. In those cases where buffer catalysis was observed, the hydrolytic rates were determined from the intercepts of plots of k_{obsd} vs. buffer concentration. Readings of pH were determined on a Radiometer type PMH 26 pH meter. Calculation of the pseudo-first-order rate constants and least-squares slopes and intercepts and generation of theoretical pH-rate profiles were done using a Hewlett-Packard Model 9820A computer.

pK_a Determination. The pK_a's of the phenols were determined by spectrophotometric titration in the equilibrium titration cell of the Cary 15[10] in the same solvent and at the same ionic strength and temperature as the kinetic studies. Spectrophotometric titration data were computer fitted to theoretical titration curves.

Product Analyses. The identity and the percentages of the products obtained on solvolysis of I and II were determined by high-pressure liquid chromatography after concentration of 1.0 ml of the kinetic solutions in vacuum for 2 min at 48 °C to remove dioxane. Aliquots of the resulting solutions (50 μl) were injected onto a 1-m du Pont Permaphase ODS column which was eluted with 40% methanol in water at a flow rate of 0.8 ml/min.[4a] Products were quantitated by comparison of the uv response (254 nm) of the detector with the responses produced by accurately known amounts of the authentic phenanthrols.

Solvolysis products of phenanthrene 9,10-oxide (III) were determined by gas chromatography. Reactions were conducted in 10 ml of deoxygenated 1 M KCl at 30 ± 3 °C. After addition of 0.01 ml of phenanthrene 9,10-oxide in acetone (10 mg of oxide/ml of acetone, final concentration 10 μg/ml), the solution was maintained at constant temperature and pH (under N_2) for 5-8 half-lives. The aqueous solutions were then adjusted to pH 7 or lower, and the products were extracted into 2 ml of ethyl acetate which was dried with $MgSO_4$ and K_2CO_3. Products we analyzed by GLC on a 1.5 m, 3% OV-1 column at 175 °C with 25 ml of N_2/min as carrier gas; retention times were 5.2 min for the cis dihydro diol, 6.2 min for the trans dihydro diol, 7.6 min for 9-phenanthrol, and 8.7 min for phenanthrene-9,10-quinone. Identity of the products was established by retention times of authentic standards and by monitoring the effluent of the chromatograph with a mass spectrometer. Stability of the dihydro diols toward oxidation to the quinone was examined at pH 8 and 11 for 6 days. In each case, less than 4% oxidation had occurred. Neither dihydro diol undergoes significant dehydration under the reaction conditions. Storage of organic solutions or alkaline aqueous solutions of 9-phenanthrol results in rapid autoxidation to the corresponding quinone. For experiments designed to establish the magnitude of the NIH shift for III, solutions of III, [9-^{2}H]-III, and [9,10-$^2H_2$]-III (0.2 mg in each case) in 10 ml of 1 M KCl were allowed to react at pH 2.0 for 10 min or at pH 4.0 for 2 h. The solutions were extracted with ethyl acetate, the extract was dried (Na_2SO_4), and the 9-phenanthrol in the extract was acetylated with acetic anhydride in the presence of pyridine. The resulting 9-phenanthryl acetate was subjected to purification by thin-layer chromatography [petroleum ether; chloroform (1:1), R_f = 0.7] to remove dihydro diol diacetates which eliminate acetic acid on gas chromatography. Combined gas chromatography (1.5-m column of 3% OV-1, 200 °C, 20 ml of N_2/min) -mass spectrometry allowed calculation of deuterium contents by inspection of the molecular ion regions. The sample of III was run to establish a reference spectrum for the unlabeled 9-phenanthryl acetate, while [9,10-$^2H_2$]-III was run to determine the extent of exchange under the reaction conditions.

Isomerization of naphthalene 1,2-oxide has been examined in water at 30 °C (μ = 1.0, KCl). The ratio of naphthols produced was determined by high-pressure liquid chromatography. Kinetic solutions were extracted with methylene chloride. The extract was dried (Na_2SO_4) and concentrated to ~0.1 ml with a stream of nitrogen. Aliquots of the resulting solutions were injected onto a 0.25-m du Pont analytical Zorbax Sil column which was eluted with 60% methylene chloride in hexane at a flow rate of 0.4 ml/min. The percentages of 1- and 2-naphthol were 99 and 1% in the pH range 10.0 to 11.4 and were 90 and 10% in the pH range 1.7 to 3.4, respectively.

Results

The pH-rate profiles for the solvolysis of I and II in dioxane-water are given in Figure 1. Because of its slow rate of reaction, III was investigated in water. In order to determine the relative reactivities of I, II, and III, rate constants for the solvolysis of III in dioxane-water were obtained only in the acid pH region and are included in Figure 1. The pseudo-first-order rate constants for I and II may be described by the rate law

$$k_{obsd} = k_H a_H + k_0 \quad (1)$$

where a_H is the hydrogen ion activity determined at the glass electrode. Values of k_H and k_0 for I and II and k_H for III are given in Table I. For the sake of comparison, catalytic constants obtained for the non-K-region arene oxides benzene oxide, 1,2-naphthalene oxide, and 2-methylnaphthalene 1,2-oxide and the K-region oxides benzo[*a*]anthracene 5,6-

Table I. Hydrolytic Rate Constants for Several Arene Oxides

Arene oxide[a]	k_H, M^{-1} s^{-1} [b]	k_0, s^{-1} [b]	k_H, M^{-1} s^{-1} [c]	k_0, s^{-1} [c]
Benzene oxide	3.9	2.74×10^{-5}	30	1.20×10^{-3}
Naphthalene 1,2-oxide	25	9.0×10^{-6}	140	2.90×10^{-3}
2-Methylnaphthalene 1,2-oxide	10	4.24×10^{-4}		
Phenanthrene 1,2-oxide (I)	17	1.15×10^{-4}	1000	3.10×10^{-2}
Phenanthrene 3,4-oxide (II)	38	1.50×10^{-4}	2700	5.55×10^{-2}
Phenanthrene 9,10-oxide (III)	4.6		100	2.1×10^{-4}
Benzo[*a*]anthracene 5,6-oxide (X)	10			
Pyrene 4,5-oxide (XI)	5			
Benzo[*a*]pyrene 4,5-oxide (XII)	9			

[a] Benzene oxide was followed at 250 nm, naphthalene 1,2-oxide at 235 nm, 2-methylnaphthalene 1,2-oxide at 325 nm, X at 290 nm, XI at 240 nm, and XII at 378 nm. [b] Determined at 30 °C in aqueous dioxane (50% v/v), μ = 0.1. [c] Determined at 30 °C in water, μ = 1.0.

Table II. Products Obtained from the Solvolysis of Phenanthrene 1,2- and 3,4-Oxides (I and II) as Measured by High-Pressure Liquid Chromatography on the Kinetic Solutions

Compd	pH	Product
		% 1-phenanthrol[a]
I	2.02	76
	2.54	79
	2.91	79
	4.35	77
	5.10	89
	6.75	95
	7.29	94
	8.80	96
	10.75	97
	11.98	97
		% 4-phenanthrol[b]
II	2.52	69
	3.49	69
	3.98	72
	4.53	71
	4.86	73
	5.48	75
	6.70	81
	8.50	81
	9.80	82
	12.00	82

[a] Remainder is 2-phenanthrol. [b] Remainder is 3-phenanthrol.

Table III. pK_a's of Phenolic Products

Compd	pK_a	Compd	pK_a
1-Phenanthrol	11.04[a]	4-Phenanthrol	11.82[a]
2-Phenanthrol	11.04[a]	9-Phenanthrol	11.05[a]
3-Phenanthrol	11.00[a]	9-Phenanthrol	9.08[b]

[a] Determined at 30 °C in dioxane–water (50% v/v), μ = 0.1 (KCl). [b] Determined at 30 °C in water, μ = 1.0 (KCl).

oxide, pyrene 4,5-oxide, and benzo[*a*]pyrene 4,5-oxide have been included in Table I. The products obtained from the rearrangement of I and II are given in Table II, together with the pH at which they were produced. The pK_a's of the phenolic products were determined spectrophotometrically and are recorded in Table III.

In Figure 2 is shown the pH–rate profile obtained for the rearrangement of III in aqueous solution. The points represent observed pseudo-first-order rate constants (k_{obsd}); in regions where buffer catalysis is observed, the k_{obsd} values were obtained by extrapolation to zero buffer concentration. The theoretical line passing through the points was computer generated from the empirical equation

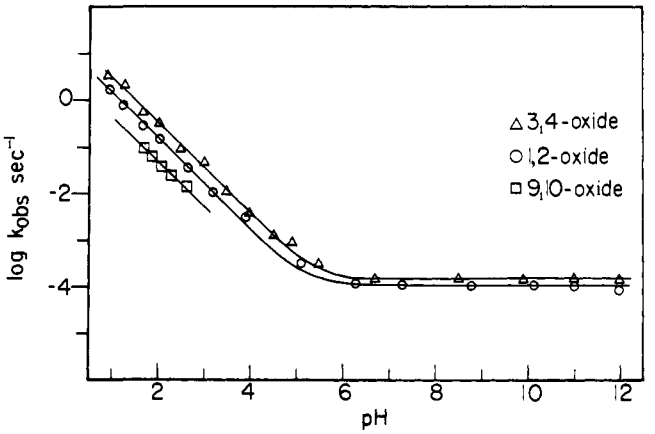


Figure 1. pH–rate profiles for the solvolysis of I, II, and III at 30 °C in dioxane–water (50% v/v), μ = 0.1. The points are experimental and the theoretical lines were derived from the data in Table I.

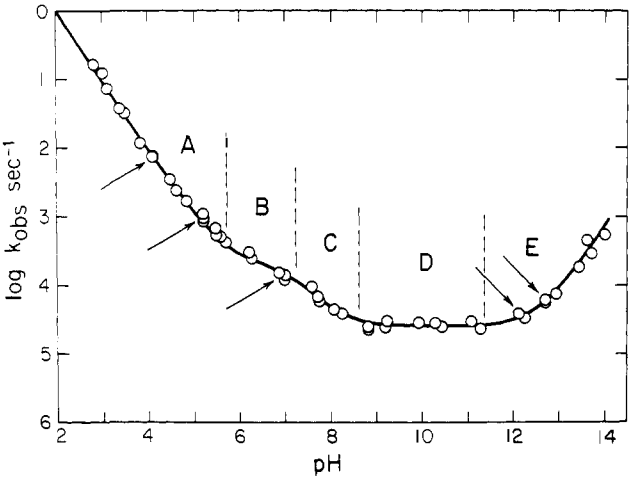


Figure 2. pH–rate profile for the solvolysis of phenanthrene 9,10-oxide in aqueous solution, μ = 1.0, at 30 °C. Arrows point to duplicate determinations for [9,10-$^2H_2$]-phenanthrene 9,10-oxide. The points are experimental. The theoretical line was derived from eq 2.

$$k_{obsd}\ (s^{-1}) = \frac{k_H a_H^2}{K_{app} + a_H} + \frac{k_0 a_H}{K_{app} + a_H} + \frac{k_p K_{app}}{K_{app} + a_H} + \frac{k_b K_{app}}{a_H(K_{app} + a_H)} \quad (2)$$

where k_H = 100, $k_0 = 2.1 \times 10^{-4}$, $k_p = 2.5 \times 10^{-5}$, $k_b = 7.0 \times 10^{-18}$, and pK_{app} = 7.2. The arrows in the figure point to those rate constants obtained for the rearrangement of [9,10-$^2H_2$]phenanthrene 9,10-oxide. Gas chromatography was

Table IV. Ratio of Products Obtained from the Solvolysis of Phenanthrene 9,10-Oxide

pH	9-Phenanthrol[a]	*trans*-9,10-Dihydroxy-9,10-dihydrophenanthrene	*cis*-9,10-Dihydroxy-9,10-dihydrophenanthrene
0	72	17	7
1	74	18	7
2	75	18	7
3[b]	71 (78)	19(18)	10(4)
4	72	18	10
5	74	18	7
6	73	18	5
7[c]	71[d]	28	1-2
8[c]	20[d]	80	<0.5
9	3[d]	97	<0.5
10	8[d]	92	0
11	2	98	0
12	Trace	>98	0
13	Trace	>98	0
14	Trace	>98	0

[a] This entry represents the sum of 9-phenanthrol and its corresponding quinone. The quinone results from autoxidation of phenol on isolation and is not spectrophotometrically detectable in the course of kinetic experiments. In the pH range 0–5 and 11–14, the quinone was not detected. [b] The values in parentheses were obtained with 3-bromophenanthrene 9,10-oxide as substrate. [c] The results at these pH's are somewhat questionable because of the difficulty in maintaining constant $[H^+]$ during the length of time required for completion of reaction. [d] These samples were either mainly or partially quinone when analyzed.

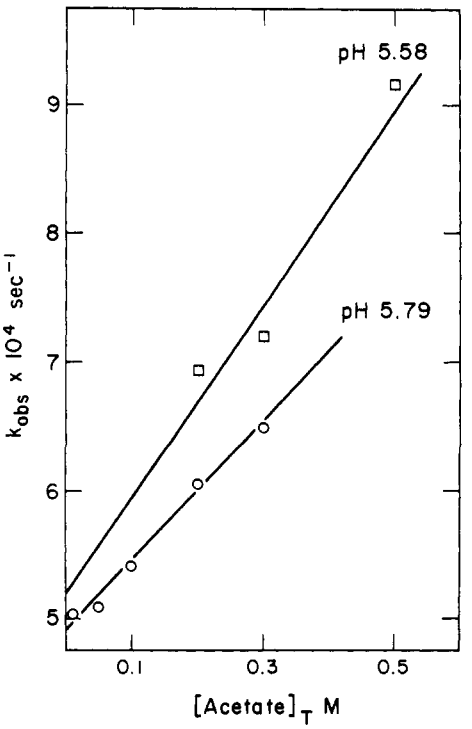


Figure 3. Plots of k_{obsd} vs. total acetate buffer concentration for the general acid catalyzed solvolysis of phenanthrene 9,10-oxide at two pH values.

used to identify the products obtained from the solvolysis of III, and these results are given in Table IV. Approximate product analyses can be determined spectrophotometrically; the phenol has λ_{max} at 251 nm with $\epsilon = 3.5 \times 10^4$ M^{-1} cm^{-1}, and the trans diol has λ_{max} at 267 nm and $\epsilon = 1.9 \times 10^4$ M^{-1} cm^{-1}. The trans diol, obtained by allowing III to rearrange at

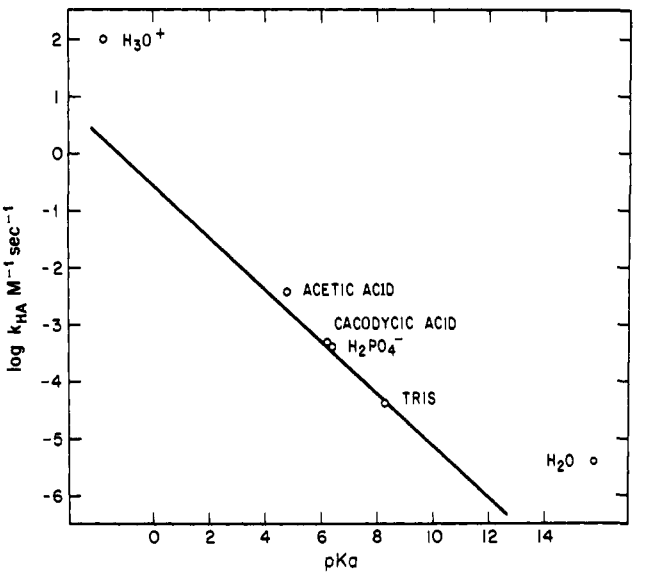


Figure 4. Bronsted plot of the log of second-order catalytic constants for the general acid catalyzed solvolysis of phenanthrene 9,10-oxide vs. the pK_a of the general acid.

pH 11, when acidified with HCl and heated is dehydrated to 9-phenanthrol ($k_{obsd} = 6.0 \times 10^{-4}$ s^{-1} at $H_0 \sim 0.4$ and 70 °C). That the product obtained is the phenol was confirmed by its ultraviolet spectrum and pK_a of 9.0 in water (Table III).

Electronic effects on product distribution were examined by comparing the relative amounts of products obtained from phenanthrene 9,10-oxide with those obtained from 3-bromophenanthrene 9,10-oxide (Table IV). The effect of temperature on the distribution of products was investigated by determining the relative amounts of products formed at pH 3 at five different temperatures (Table V).

Deuterium retention upon solvolysis of [9-^{2}H]phenanthrene 9,10-oxide was examined in the acidic pH region where 9-phenanthrol was formed in order to establish the extent of the NIH shift at the K-region. In this study the term "NIH shift" is employed to designate conversion of carbocation to dienone with group migration as in "k_{NIH}" of Schemes I and II. The solvolysis of [9,10-$^2H_2$]phenanthrene 9,10-oxide (100% $^2H_1$, 96% $^2H_2$) was examined as a standard to determine the amount of exchange under the reaction conditions employed. The latter produced 9-phenanthrol with 95% enrichment by deuterium at C-10 after 5 min of reaction at pH 2 and 90% enrichment after 1 h of reaction at pH 4. For reaction of [9-^{2}H]-III (86% $^2H_1$), enrichments of 67% and 56% were observed, respectively.

General acid catalysis is observed in the solvolysis of I, II, and III. The second-order rate constants for general acid catalysis were obtained by dividing the slopes of plots such as those shown in Figure 3 by $a_H/(K_a + a_H)$ where K_a is the acid ionization constant of the general acid. The second-order rate constants for catalysis by $H_2PO_4^-$ are 3.0×10^{-2} M^{-1} s^{-1}, 5.8×10^{-2} M^{-1} s^{-1}, and 4.0×10^{-4} M^{-1} s^{-1} for I, II, and III, respectively. The logs of the second-rder catalytic constants for the general acid catalyzed solvolysis of III are plotted in Figure 4 as a function of the pK_a of the general acid. The method by which the general acid catalytic constant for Tris was obtained is given in the following paper.[11]

The second-order rate constants (k_n) for the attack of hydrazine and methoxyamine on III were calculated from the equation

$$k_n = \frac{(k_{obsd} - k_{1y})}{\frac{K_a}{K_a + a_H}[N]_T} \quad (3)$$

Scheme I

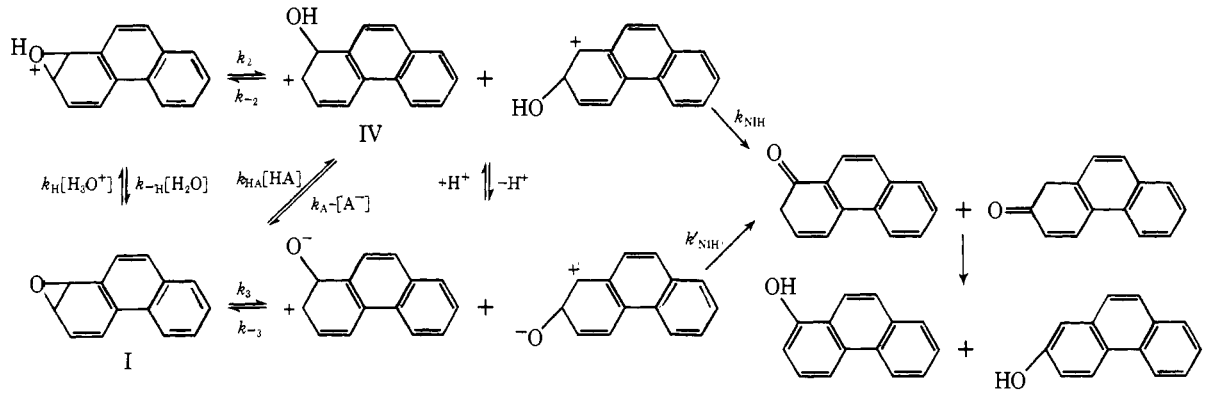


Table V. Effect of Temperature on the Ratio of Products Obtained from the Solvolysis of Phenanthrene 9,10-Oxide at pH 3.0[a]

Temp,[b,c] °C	9-Phenanthrol	Trans dihydro diol	Cis dihydro diol
0	65	27	8
30	72	20	8
45	75	17	8
60	77	15	8
80	80	12	8

[a] Products were analyzed by gas chromatography as in Table IV. [b] Reactions were run for 5–7 half-lives in 1.0 M KCl which had been adjusted to pH 3.00 at 25 °C. [c] Plots of R ln [A]/[B] derived from the above data vs. $1/T$ where A = cis diol and B = trans diol, and A = phenol and B = total diol provided the following relative activation parameters: $\Delta H^{\ddagger}_{cis} - \Delta H^{\ddagger}_{trans} = 2.05$ kcal/mol, $\Delta S^{\ddagger}_{cis} - \Delta S^{\ddagger}_{trans} = 5.0$ cal/(deg mol), $\Delta H^{\ddagger}_{phenol} - \Delta H^{\ddagger}_{diol} = 1.8$ kcal/mol, and $\Delta S^{\ddagger}_{phenol} - \Delta S^{\ddagger}_{diol} = 8.0$ cal/(deg mol), all with correlation coefficients >0.997.

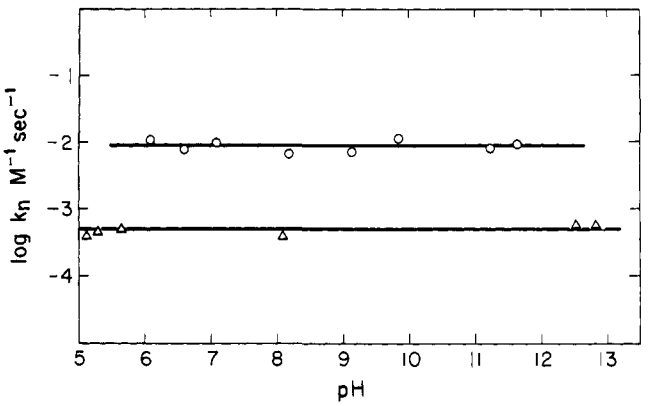


Figure 5. Plots of the log of the second-order rate constants for the reaction of hydrazine (○) and methoxyamine (△) with phenanthrene 9,10-oxide vs. the pH at which they were determined.

where k_{ly} is the rate constant for the reaction of III with lyate species at the pH at which the nucleophilic reaction is carried out, K_a is the acid ionization constant of the amine, and $[N]_T$ the total amine concentration. The log k_n values are plotted in Figure 5 as a function of the pH at which they were obtained.

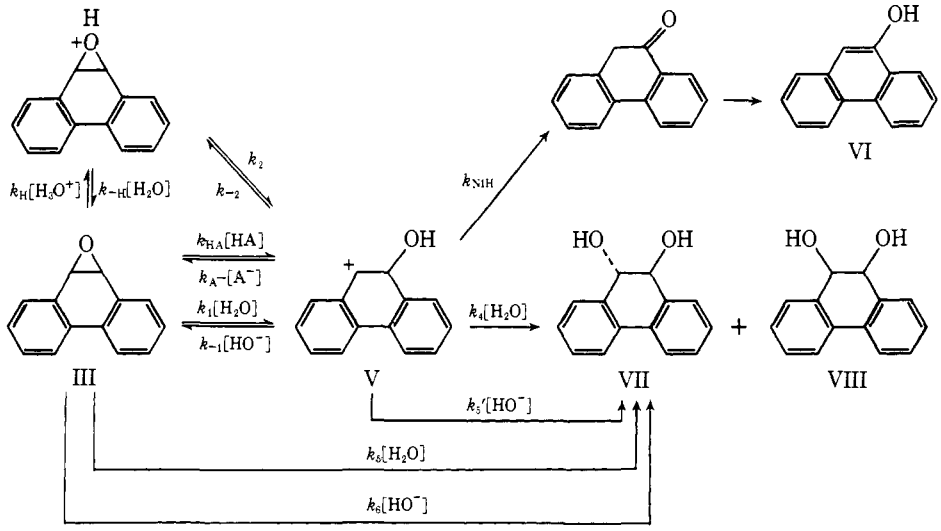
Discussion

The pH–rate profiles (Figure 1) for the rearrangement of the non-K-region phenanthrene oxides (I and II) are identical with those that have been obtained previously for other non-K-region arene oxides such as benzene oxide,[12] 1,4-dimethylbenzene oxide,[13] naphthalene 1,2-oxide,[12] 2-methylnaphthalene 1,2-oxide,[14] and indan 8,9-oxide.[15] As has been found in the previous studies, only phenols are obtained as the final products of the solvolysis of I and II.

A mechanism consistent with the rate laws for the rearrangement of phenanthrene 1,2-oxide (I) is given in Scheme I. Under acid conditions (slope of −1 in the pH–rate profile), the phenanthrene oxide undergoes preequilibrium protonation, followed by rate-limiting opening of the epoxide ring. As the pH–rate profile flattens out from a slope of −1 to a slope of 0, ring opening concerted with general acid catalysis is observed. General acid catalysis is not detected at lower pH values because it is swamped out by the hydronium ion catalysis. In the hydrolysis of aliphatic epoxides, general acid catalysis does not usually occur. To date, it has been detected only in the hydrolysis of 1,3-cyclohexadiene oxide whose intermediate cation is allylic and thus subject to some resonance stabilization.[16] Since the epoxide ring can open in either direction, two carbonium ions are formed which may rapidly undergo the NIH shift[1a,17,18] to yield 1- and 2-phenanthrol (Table II). Under neutral and basic conditions (slope of 0 in the pH–rate profile), the arene oxide opens spontaneously to the zwitterions or, alternatively, opens with general acid catalysis by water to carbonium ions. Ring opening again is the slow step of the reaction, and the two zwitterions (or carbonium ions) formed rearrange rapidly to the two possible phenols. Thus the NIH shift may occur entirely through the carbonium ion (k_{NIH}) or through both the carbonium ion and the zwitterion (k'_{NIH}). The greater resonance stability of the vinylogous benzylic cation (IV) leads to preferential ring opening in the direction of 1-phenanthrol (Table II). This preferred direction of ring opening is even more marked in the nonspecific acid-catalyzed pathway. A similar preference for the vinylogous benzylic cation is also evidenced in the aromatization of naphthalene oxide to 90% 1-naphthol under acidic conditions and 99% of that isomer in neutral and basic solutions. That the rate-limiting step at all pH's is the opening of the epoxide ring has been substantiated in a detailed study of the aromatization of benzene oxide and naphthalene oxide and their deuterated analogues. No primary deuterium kinetic isotope effect was found at any pH, and plots of log k_H and log k_0 (eq 1) vs. σ^* resulted in large ρ values (−7.6 and −7.3, respectively), indicating substantial positive charge and no concurrent hydride transfer in the transition state.[19]

Phenanthrene 3,4-oxide opens somewhat more readily than does the 1,2 isomer (Table I). Its mechanism of rearrangement is identical with that given in Scheme I for the 1,2-oxide, and the preferred formation of 4-phenanthrol (Table II) is as would be anticipated as a result of the greater stability of the vinylogous benzylic cation. Values of the rate constants for aromatization of I and II are given in Table I. The k_H term of the Table corresponds to the k_2K_H term of Scheme I and the k_0

Scheme II



term of the Table to either the k_3 or $k_{H_2O}[H_2O]$ term of the Scheme.

The pH–rate profile for phenanthrene 9,10-oxide (Figure 2) is obviously quite different from those obtained for non-K-region arene oxides. In order to simplify the discussion of mechanism the pH–rate profile of Figure 2 has been divided into five regions labeled A, B, C, D, and E. The general appearance of the profile in regions A and B is similar to the profiles obtained for non-K-region arene oxides (Figure 1).[12-14] Above pH 7, the pH–rate profile for phenanthrene 9,10-oxide is totally unlike those obtained for the non-K-region arene oxides. The products of solvolysis in this pH region are also different for the two classes of arene oxides; phenanthrene 9,10-oxide has the trans 9,10-diol as the sole or predominant product, while non-K-region oxides give only phenolic products. A mechanism that is in agreement with the pH–rate profile of Figure 2 and that can account for the pH-dependent product distribution (Table IV) and the observed absence of a deuterium kinetic isotope effect at all pH's is given in Scheme II.

Region A involves preequilibrium protonation of the arene oxide, followed by rate-limiting opening of the epoxide ring to a carbonium ion (V). General acid catalysis concerted with epoxide ring opening is observed in region B (Figure 3); it is not observed below about pH 5.5 because of the predominance of hydronium ion catalysis. In the absence of buffers, region B is attributed to the same mechanism with water acting as the general acid. The Bronsted plot for general acid catalysis is shown in Figure 4. If the points for hydronium ion and water are neglected, the best least-squares slope results in an α value of -0.5. Substantial positive deviations for these species have also been noted in Bronsted plots for general acid catalysis of the acetyl transfer reaction of *S*-acetylmercaptoethylamine and *S*-chloroacetylmercaptoethylamine.[20]

From the product analyses given in Table IV, it is evident that even in regions A and B where the pH–rate profiles for the K-region and non-K-region arene oxides appear similar, there are differences in mechanism. Solvolysis of the non-K-region arene oxides (I and II) result in exclusive formation of phenanthrols (Table II). However, only about 72% of the product of solvolysis of the K-region oxide (III) is the phenanthrol (VI); the remainder of the product consists of the trans and cis dihydro diols (VII and VIII). Although trans diols have been observed as products in the enzymatic hydration of arene oxides,[21] from data presently available it would appear that diols are not produced in the nonenzymatic hydrolysis of non-K-region arene oxides with the exception of the case of 4-carbo-*tert*-butoxybenzene oxide.[22] It would be fair to surmise that arene oxides containing other electron-deficient groups will be shown to form diols.

Formation of the dihydro diol products indicates that trapping of the carbonium ion by water has become competitive with the NIH shift (Scheme II). The product distribution of Table IV implies that the rate of phenol formation is about threefold greater than the rate of solvent trapping. This competition may occur either as the result of increased stability of the carbonium ion (i.e., it exists in solution long enough to be trapped by water) or a decrease in the rate of the NIH shift. Comparison of the canonical forms of the carbonium ions obtained from I, II, and III predicts that the carbonium ion generated from III is the least stable. This decreased stability is reflected in the greater than 100-fold decrease in its rate of formation (2.1×10^{-4} s^{-1}, Table I) compared with the rate of ring opening of I and II (3.10×10^{-2} and 5.55×10^{-2} s^{-1}, respectively). Thus formation of the dihydro diol products must be the result of the decrease in rate of the NIH shift for the carbonium ion (V) generated from the K-region arene oxide. This would suggest that the free-energy difference between the carbonium ion and the transition state for hydride transfer is greater in the 9,10-oxide than in the non-K-region oxides, whereas the free-energy barrier for hydration of the carbonium ions from K-region and non-K-region arene oxides may be comparable. This is a reasonable supposition since K-region oxides somewhat resemble epoxides.[11] The dihydro diol produced is a mixture of the trans and cis isomers in about a 2:1 ratio. Preference for the trans isomer suggests that the approach of water to the carbonium ion (V) is somewhat shielded by the departing oxygen atom.

The data of Table V indicate that as the reaction temperature is increased, the percentage of the phenolic product increases with a concomitant decrease in the amount of trans-dihydro diol produced. Insertion of a bromo substituent at the 3 position of phenanthrene 9,10-oxide results in increased phenanthrol formation, apparently at the expense of the cis dihydro diol (Table IV). These results suggest that the NIH shift from carbocation has a larger $\Delta H^{\ddagger}$ value and a greater $+\rho$ value than does solvent trapping of this species. The overall conversion of oxide to phenol is known to be associated with a large $-\rho$ since carbocation formation is rate determining.

Since water acts as a general acid to catalyze formation of the carbonium ion, microscopic reversibility requires that the ring closure reaction (k_{-1}) be catalyzed by hydroxide ion. As the concentration of hydroxide ion increases, k_{-1} can compete with k_{NIH} and k_4 with the resulting observed decrease in rate

with increasing pH in region C. Assumption of a steady state in carbonium ion provides the rate expression

$$\nu = \frac{k_1[H_2O](k_{NIH} + k_4[H_2O])}{k_{-1}[HO^-] + k_{NIH} + k_4[H_2O]}[\text{oxide}] \quad (4)$$

for regions B and C. For region B, $(k_{NIH} + k_4[H_2O]) > k_{-1}[HO^-]$ and the equation

$$\nu = k_1[H_2O][\text{oxide}] \quad (5)$$

results which predicts the lack of dependence of rate on pH in this region. In the case of region C, $k_{-1}[HO^-] > (k_{NIH} + k_4[H_2O])$ and eq 4 reduces to

$$\nu = \frac{K_1[H_2O](k_{NIH} + k_4[H_2O])a_H}{K_w}[\text{oxide}] \quad (6)$$

Equation 6 requires the slope of −1 that is observed in this pH region.

The rate of solvolysis levels off to a second plateau region at about pH 9 (region D). The pH independence in this region may be accounted for by three kinetically equivalent mechanisms: (a) nucleophilic attack by water on the arene oxide (k_5), which would result in the rate expression

$$\nu = k_5[H_2O][\text{oxide}] \quad (7)$$

(b) trapping of the carbonium ion by hydroxide ion (k'_5)—rather than by water in this more basic pH range—which would give rise to the pH-independent rate expression

$$\nu = \frac{k_1k'_5[H_2O]}{k_{-1} + k'_5}[\text{oxide}] \quad (8)$$

or (c) rate-limiting spontaneous opening of the arene oxide to a zwitterion which is then trapped by water. The following would suggest that nucleophilic attack of water on the arene oxide is the most reasonable of the mechanisms. The log of the second-order rate constant (k_5) for nucleophilic attack by water falls precisely on a Bronsted plot with the log of the second-order rate constants for attack by carbonate and hydroxide ion (k_6), giving a Bronsted β of 0.2 and a correlation coefficient of 1.00.[11] It also falls on a plot of the log of the second-order rate constant for nucleophilic attack on phenanthrene 9,10-oxide vs. the same value for nucleophilic attack on ethylene oxide.[11] A comparison of the rate constants for trapping of the carbonium ion by hydroxide ion (k'_5) and trapping by water (k_4) gives rise to a Bronsted β of ~0.5 which is larger than anticipated from the work of Ritchie on cation–nucleophile combination reactions.[23] The apparent lack of formation of any cis dihydro diol above pH 9 (Table IV) is also more in keeping with the nucleophilic mechanism of eq 7 than the trapping mechanisms.

Region E represents direct nucleophilic attack of hydroxide ion on the arene oxide (k_6) which results in the first-order dependence on hydroxide ion observed in this pH region.

$$\nu = (k_6a_H/K_e)[\text{oxide}] \quad (9)$$

It should be noted that non-K-region arene oxides are not usually subject to direct attack by hydroxide ion even at pH 14. Values of the individual rate constants of Scheme II are given in Table VI. From the ratio of the rate constant for base-catalyzed closure of the carbonium ion back to arene oxide vs. the rate constants for product formation $k_{-1}/(k_{NIH} + k_4[H_2O])$, it can be calculated that the forward and reverse rates will be equal when the concentration of hydroxide ion is 2.37×10^{-7} M. This corresponds to a pH of 7.2 which is the value of pK_{app} of eq 2.

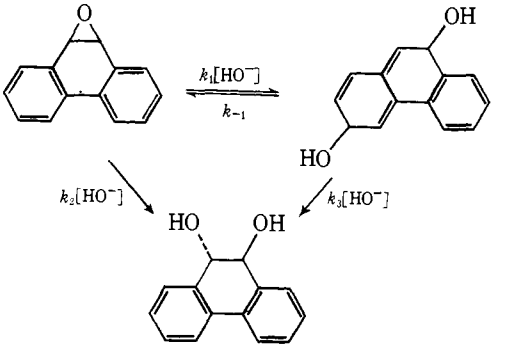
The products obtained from the solvolysis of the 9,10-oxide at various pH's (Table IV) are in agreement with the mechanism of Scheme II. This mechanism would require that the product ratios be identical in regions A, B, and C and would predict the observed increase in the concentration of diol produced at the expense of phenol at higher pH values. Direct nucleophilic attack of water and hydroxide ion on the arene oxide in regions D and E, respectively, predictably gives only the trans diol.

Table VI. Values of the Kinetic Constants of Scheme II

$k_{H_3O^+} = 1.0 \times 10^2\ M^{-1}\ s^{-1}$	$k_5[H_2O] = 2.5 \times 10^{-5}\ s^{-1}$
$k_1[H_2O] = 2.1 \times 10^{-4}\ s^{-1}$	$k_6 = 4.73 \times 10^{-4}\ M^{-1}\ s^{-1}$
$k_{NIH} \simeq 3\ k_4[H_2O]$	$K_w = 1.48 \times 10^{-14}$
$\frac{k_{-1}}{k_{NIH} + k_4[H_2O]} = 4.22 \times 10^6$	$\frac{k'_5}{k_{-1}} = 1.2 \times 10^{-1}$

The ratios of cis and trans adducts in epoxide hydrolysis are known to vary with reagent, solvent,[24] temperature, and electronic effects of substituents.[25] For simple phenyl-substituted oxiranes, the presence of electron-withdrawing groups has been demonstrated to result in a decrease in the cis:trans diol ratio.[25] The products obtained from the solvolysis of 3-bromophenanthrene 9,10-oxide (Table IV) suggest that this electronic effect is operative for the K-region arene oxide as well; while III gave a cis:trans dihydro diol ratio of 0.53, the ratio for the bromo analogue of III was 0.22. This trend when observed in the solvolysis of aryloxiranes was interpreted as being due to a higher degree of carbonium ion character in the transition state leading to the cis isomer.[25] Calculation of transition state enthalpies and entropies from product ratios obtained for phenanthrene 9,10-oxide as a function of temperature (Table V) indicates that the relative activation parameters for the reaction of the arene oxide are comparable with those of the aryl-substituted oxiranes[25b] where the ratios of cis to trans diol also increase with increasing temperature. Battistini and co-workers[25b] have attempted to employ the relative activation parameters in the assignment of transition state structures for aryl oxirane acid-catalyzed solvolysis.

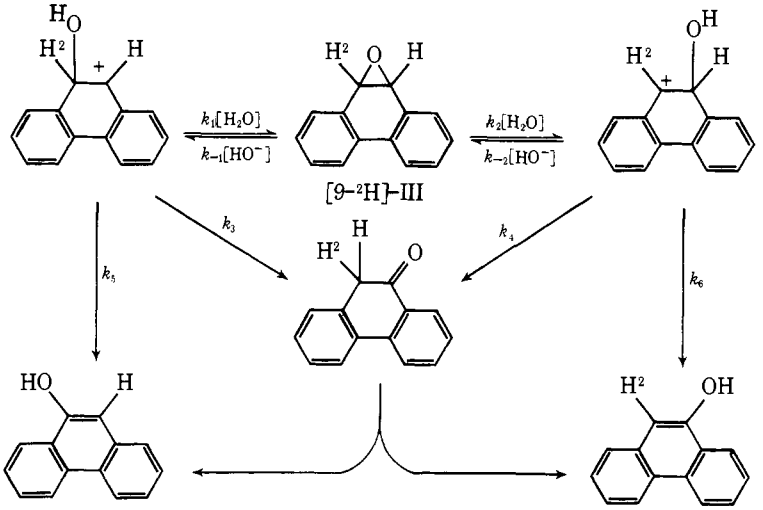
An alternate mechanism which would account for the pH–rate profile of Figure 2 and the pH-dependent product distribution of Table IV would be identical with Scheme II in regions A and B but would attribute the decrease in rate observed with increasing pH in region C to hydroxide ion attack on the arene oxide to form a stable intermediate such as the para dihydro diol of eq 10.[26] The plateau of region D would



(10)

then be the result of expulsion of hydroxide ion from the intermediate upon ring closure to give back the arene oxide (k_{-1}), followed by hydroxide ion attack on the oxide (k_2) to give the trans dihydro diol. The first-order dependence on hydroxide ion concentration observed in region E would require direct attack of hydroxide ion on the intermediate (k_3). There are, however, several pieces of evidence that argue against this mechanism. The required intermediate could not be detected spectrophotometrically and repeated attempts to isolate it were unsuccessful. From Figure 5 it is apparent that the second-order rate constants for the attack of hydrazine and me-

Scheme III



thoxyamine are independent of $[H^+]$ from pH 5–13. If an intermediate were formed, it would be the arene oxide that is attacked by amines from pH 5–7 and the intermediate at pH's greater than about 9. The data of Figure 5 would thus require that the two species be equally susceptible to nucleophilic attack by amines. When a plot is made of the log of the second-order rate constant for nucleophilic attack on phenanthrene 9,10-oxide vs. the same value for attack on ethylene oxide, a good linear correlation is obtained. When k_2 of eq 10 is employed as the second-order rate constant for hydroxide ion attack on the arene oxide, hydroxide ion gives a positive deviation of more than five log units on the phenanthrene 9,10-oxide vs. ethylene oxide plot. When, however, k_6 of Scheme II is employed, the point for hydroxide ion falls precisely on the line. Lastly, nucleophilic attack of hydroxide ion on the para dihydro diol intermediate would not be expected to result in exclusive formation of the trans dihydro diol that is observed in region E.

Because of (1) the insolubility of benzo[*a*]anthracene 5,6-oxide (X), pyrene 4,5-oxide (XI), and benzo[*a*]pyrene 4,5-oxide (XII) in water and (2) the very slow rate of reaction of these compounds in 50% (v/v) dioxane water in the neutral to basic regions of pH, a comparison of only the rates of the acid-catalyzed solvolysis of X, XI, and XII with those of other arene oxides could be made. Inspection of Table I indicates that both K-region and non-K-region oxides possess values of k_H which are within an order of magnitude of each other. On the other hand, the rate of the ring opening reaction which can readily be measured in dioxane–water for the non-K-region arene oxides, occurs much too slowly in the case of the K-region oxides to be measured in that solvent. From the relative rates of ring opening of the isomeric phenanthrene oxides in water (Table I), it can be seen that the rate of ring opening when the oxide is at the K-region occurs more than 100 times more slowly than when the oxide is at a non-K-region position.

To this point in the discussion, the K-region arene oxide (III) has been assumed to produce 9-phenanthrol via the NIH-shift pathway, followed by non-K-region arene oxides. Since this K-region arene oxide (presumably typical of all other K-region arene oxides) has demonstrated kinetic properties widely divergent from the non-K-region arene oxides previously studied, the NIH shift at the K-region has been examined. Rearrangement of [9-^{2}H]-III was studied in the acid region (pH 2 and 4) where 9-phenanthrol is the principal product. The actual deuterium content in the 9-phenanthrol produced at these pH values was 67 and 56% for substrate which was initially 86% monodeuterated. This corresponds to 81 and 72% deuterium retained after correction for exchange and the extent to which the substrate was deuterated (see Results).

Calculation of the expected extent of migration and retention for [9-^{2}H]-III requires inspection of Scheme III. Since the rate of opening of arene oxides to carbonium ions or zwitterions is independent of substitution by deuterium (this study and reference 18), k_1 must equal k_2. If the NIH shift does not occur for this substrate ($k_3 = k_4 = 0$) and if there is no isotope effect for the loss of hydrogen or deuterium ($k_5 = k_6$), then retention of deuterium by this symmetric substrate would be 50%. Even if k_6 is much greater than k_5 due to a primary isotope effect, the retention of deuterium still could not exceed 50% since k_{-1} and k_{-2} are small compared with k_5 and k_6. Alternatively, if complete migration occurs (k_3 and $k_4 \gg k_5$ and k_6), the extent of deuterium retained will depend only on the isotope effect for the enolization of the keto tautomer of the phenol. Assuming a reasonable value of 4 as the isotope effect,[27] the calculated deuterium retention for [9-^{2}H]-III is 80%, which corresponds well with the experimental results. Thus, as was the case for deuterated toluene[28] and naphthalene[27] oxides, [9-^{2}H]phenanthrene 9,10-oxide also displays the NIH shift.

In conclusion it can be stated that the difference in the chemistry of non-K-region and K-region phenanthrene oxides is that under acidic conditions the non-K-region oxides produce only phenolic products while the K-region oxide gives diols in addition to the phenolic products since trapping of the initially formed carbonium ion by solvent water can compete with the NIH shift. Both K-region and non-K-region arene oxides display the NIH shift on isomerization to phenols. In neutral and basic solutions, the K-region oxide does not exhibit typical arene oxide behavior but behaves as an ordinary epoxide. This finding led to the investigation of the susceptibility of phenanthrene 9,10-oxide to attack by nucleophiles. The results of this study are presented in the following paper.

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Nucleophilic Displacement on the Arene Oxides of Phenanthrene

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Abstract: Phenanthrene 9,10-oxide, a K-region arene oxide, undergoes nucleophilic attack by oxygen bases and a wide variety of amines as a result of its relatively slow rate of ring opening to carbonium ion and the decreased rate of rearrangement of the carbonium ion to phenol. The rate of reaction of this oxide with nucleophiles is comparable with that of ethylene oxide. The second-order rate constants for attack by primary and secondary amines give a β_{nuc} value of 0.4. Certain tertiary amines (trimethylamine and quinuclidine amines) exhibit enhanced nucleophilic reactivity. This is suggested to be due to preequilibrium complex formation prior to nucleophilic attack. The quinuclidine amines give a β_{nuc} value of 0.1. Oxygen bases are less reactive nucleophiles and give a β_{nuc} value of 0.2. In the case of non-K-region arene oxides (phenanthrene 1,2-oxide, phenanthrene 3,4-oxide, benzene oxide, and naphthalene oxide), nucleophilic attack by amines and oxygen bases is not sufficiently rapid to compete with the spontaneous aromatization reaction. Thiolate anions exhibit considerably greater nucleophilic reactivity than do amines and, consequently, react with both the K-region and non-K-region arene oxides. The second-order rate constants for attack by thiolate anions result in a β_{nuc} value of 0.2 for each of the arene oxides investigated. Glutathione is no more reactive a thiol than would be predicted from its pK_a. NMR studies of the nucleophilic adducts show that nucleophilic attack is stereospecific and results in trans adducts. Thus either direct SN2 attack or nucleophilic trapping of tight ion pairs is occurring. An index of nucleophilic susceptibility is defined for epoxides and arene oxides: ethylene oxide = 1, phenanthrene 9,10-oxide = 0.3, and the non-K-region arene oxides are all <0.01.

Introduction

During the normal course of metabolism of aromatic compounds, arene oxides occur as intermediates.[2] For quite some time certain arene oxides generated from xenobiotic hydrocarbons have been considered to be carcinogenic.[3] It is currently thought that the carcinogenic behavior may be the result of covalent binding of the arene oxide to proteins and nucleic acids.[4] Consequently, studies of the reactivity of arene oxides toward nucleophilic attack[5a] have been carried out to determine the feasibility of this hypothesis.[5a,b] The results of these studies have shown that while polarizable nucleophiles such as thiols and azide readily attack arene oxides, nonpolarizable nucleophiles such as amines and hydroxide ion show no reactivity. In the previous paper[6] we have shown, in a study of the comparative mechanisms of solvolysis of the K-region and non-K-region arene oxides of phenanthrene, that the major product of solvolysis of the K-region arene oxide in neutral and basic solution is the trans diol while under the same conditions the non-K-region arene oxides aromatize exclusively to phenols. The K-region arene oxide readily undergoes nucleophilic attack by hydroxide ion and water and thus appears to be more epoxide-like in its reactivity than the non-K-region oxides. Since it is the K-region arene oxides that show carcinogenic activity[7] and bind covalently to cellular constituents,[8] and since previous studies of nucleophilic reactivity have been carried out only on benzene oxide and other simple non-K-region arene oxides, it is apparent that an investigation of the susceptibility of a K-region oxide to nucleophilic attack is necessary. In the present study, we have undertaken an investigation of the reactivity of nitrogen, oxygen, and sulfur nucleophiles on phenanthrene 9,10-oxide, the K-region arene oxide of phenanthrene, and for comparative purposes on phenanthrene 1,2-oxide and phenanthrene 3,4-oxide, the isomeric non-K-region arene oxides. The kinetics of the reaction have been studied and the stereochemistry of the products established.

Experimental Section

Materials. The preparations of the arene oxides used in the present study have been described previously.[6] The hydrochlorides of me-