Acid-Catalyzed Rearrangement of K-Region Arene Oxides: Observation of Ketone Intermediates and a Sterically Induced Change in Rate-Determining Step

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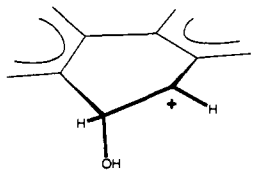
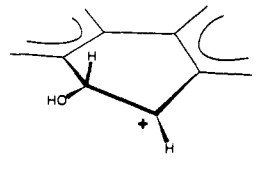
Abstract: K-region arene oxides rearrange to phenols in acetonitrile in two acid-catalyzed steps: rapid rearrangement of the arene oxide to positionally isomeric keto tautomers of K-region phenols, followed by slow enolization. Accumulation of the ketones, proposed intermediates in the acid-catalyzed solvolyses of arene oxides in aqueous solution, allowed their direct spectroscopic observation and characterization for the first time under solvolytic conditions. Rate constants and products are reported for the K-region arene oxides of benz[*a*]anthracene, its 1-, 4-, 7-, 11-, 12-methyl, and 7,12-dimethyl substituted derivatives, benzo[*a*]pyrene, benzo[*c*]phenanthrene, 3-bromophenanthrene, chrysene, dibenz[*a,h*]anthracene, phenanthrene, and pyrene. No primary kinetic isotope effect is observed *for ketone formation* from phenanthrene 9,10-oxide. A linear correlation with a slope of 1.07 is observed between the logarithm of the second-order rate constants for acid-catalyzed reaction of the arene oxide at each K-region position in acetonitrile (first step) and in methanol (where ketone does not accumulate). Negative deviations from this correlation are observed for the formation of ketones in which the carbonyl oxygen is peri to a methyl substituent. These results are discussed in terms of a mechanism in which pseudoaxial opening of the epoxide gives an initial carbocation that must undergo conformational isomerization in order to produce phenolic products by migration of a pseudoaxial hydrogen. For compounds that follow the correlation, the rate-determining step in both methanol and acetonitrile is formation of the carbocation. For those compounds that deviate from the correlation and whose carbocations have their hydroxyl group in a peri position to a methyl ring substituent, the rate-determining step changes from formation of the carbocation (methanol) to its conformational inversion (acetonitrile). With few exceptions, NMR and kinetic evidence show that the regioisomeric K-region keto tautomers from a given arene oxide enolize with very similar rates (k_{slow}). Rates of enolization are decreased by electron withdrawing groups and by steric factors that favor nonplanarity of the ring system. A large primary kinetic isotope effect ($k_H/k_D = 4.4$) is observed for the *acid-catalyzed enolization* of the K-region ketone derived from phenanthrene. Slow abstraction of a proton by the solvent acetonitrile from the α-methylene group of the O-protonated ketone is proposed to account for these results and for the fact that ketone does not accumulate in more basic solvents. The major driving force for enolization (k_{slow}) is development of aromaticity in the phenol. For unsubstituted keto tautomers, a linear relationship, $\log k_{slow} = 31.8-39.2$ (X), is observed, where X is the Hückel π-bond character for the K-region bond of the parent hydrocarbon.

Introduction

In Scheme II of the preceding paper,[1] we proposed a mechanism for the acid-catalyzed reaction of K-region arene oxides in aqueous solvents and methanol.[1,2] According to this mechanism, initial protonation of the K-region arene oxide followed by pseudodiaxial ring opening of the epoxide leads to carbocation conformation I. Carbocation conformation I, which has the hydroxyl group in the pseudoaxial orientation, may react with a nucleophilic solvent (k_4[Nu]), to yield cis and trans addition products, or undergo conformational isomerization (k_3) to conformer II. Carbocation conformer II, once formed, is committed to undergo the hydride



Conformation I



Conformation II

shift ($k_5 \gg k_{-3}$) that leads to the K-region ketone, so that the product distribution is determined by the relative values of k_3 and k_4[Nu]. The conformational isomerization step (k_3) is sensitive to various steric effects. For example, k_3 is substantially retarded by steric effects of substituents peri to the K-region hydroxyl group of the carbocation because of the requirement that this hydroxyl group must become pseudoequatorial. Carbocations bearing such peri substituents yield exclusively the corresponding solvent addition products.[2] For *unsubstituted* arene oxides in water and in methanol, k_3 and k_4[Nu], where Nu represents a solvent molecule, are of comparable magnitude, as demonstrated by the observation that cis and trans addition products as well as phenols are formed.

The present study was undertaken to investigate the mechanism of the acid-catalyzed reaction of K-region arene oxides in a *nonnucleophilic* solvent, where k_4[Nu] = 0. Under these conditions, sensitivity of the rate to factors that are known to affect preferentially the k_3 process (as opposed to epoxide ring opening) can be used as a diagnostic criterion for rate-determining conformational inversion. Acetonitrile was the solvent of choice, since its dipole moment and dielectric constant are similar to those for methanol,[3] the solvent employed in previous solvolytic studies.[1,2] Thus, solvent nucleophilicity should be the predominant determining factor in any mechanistic differences between the acid-catalyzed reactions of K-region arene oxides in the two solvents. In this report, kinetics and products of the acid-catalyzed rearrangement of the K-region arene oxides of benz[*a*]anthracene (BA-O), its 1- (1-MBA-O), 4- (4-MBA-O), 7- (7-MBA-O), 11- (11-MBA-O), 12-methyl (12-MBA-O), and 7,12-dimethyl (DMBA-O) substituted derivatives, benzo[*a*]pyrene (BaP-O), benzo[*c*]phenanthrene (BcP-O), 3-bromophenanthrene (3-BrPhe-O), chrysene (Chr-O), dibenz[*a,h*]anthracene (DBA-O), phenanthrene (Phe-O), and pyrene (Pyr-O) in acetonitrile (cf. Figure 1 of the preceding paper)[1] are reported.

Results and Discussion

Characterization of the Ketone Intermediate. K-region arene oxides undergo rearrangements catalyzed by ethanesulfonic acid

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(1) Nashed, N. T.; Bax, A.; Loncharich, R. J.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Nashed, N. T.; Balani, S. K.; Loncharich, R. J.; Sayer, J. M.; Shipley, D. Y.; Mohan, R. S.; Whalen, D. L.; Jerina, D. M. *J. Am. Chem. Soc.* **1991**, *113*, 3910.

(3) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1976; pp 86-87.

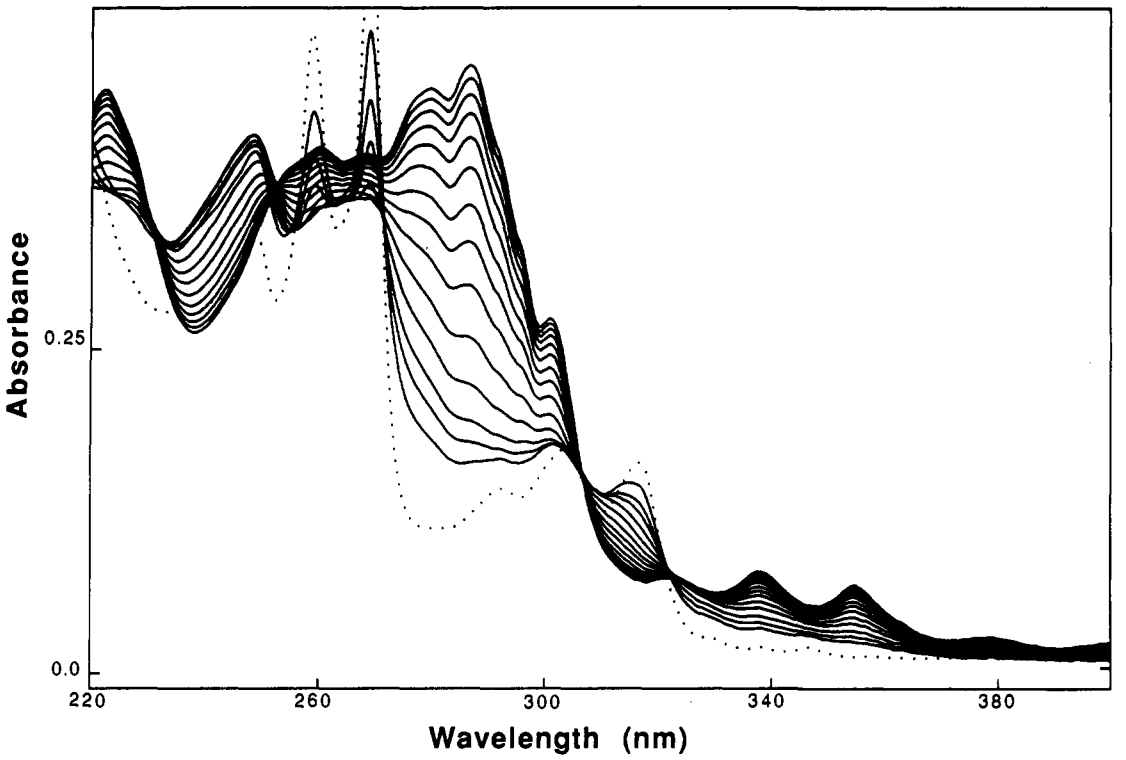
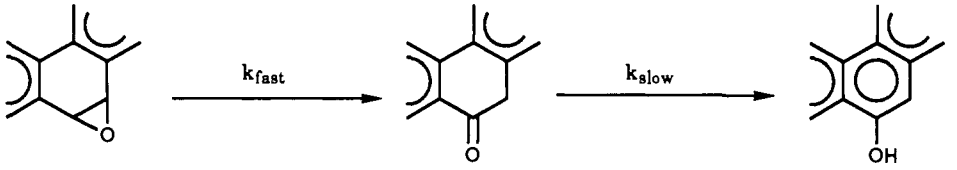


Figure 1. UV spectra measured as a function of time for the acid-catalyzed reaction of BA-O in acetonitrile (2.9×10^{-4} M ethanesulfonic acid, at 25 °C). The time interval is 10 s between the first five spectra and 60 s thereafter. The dotted line is the spectrum of the starting oxide.

Scheme I



in acetonitrile to give K-region phenols. The reaction proceeds in two steps (Scheme I). The initial fast step corresponds to the rearrangement of the arene oxide to a mixture of regioisomeric K-region ketones, whereas the second, slow step corresponds to tautomerization of these ketones to phenolic products. Accumulation of the intermediate ketones was demonstrated by UV, IR, and NMR spectroscopy.

Measurement of the UV spectra of reaction mixtures as a function of time (cf. Figure 1) indicated a lack of isosbestic points in the region of the spectrum where a rapid initial change, corresponding to disappearance of the arene oxide, takes place. For example, in the reaction of BA-O, there is a rapid decrease in absorbance at 259 and 269 nm that is complete in less than 1 min, followed by a slow increase over a period of 1–2 h. In contrast, clean isosbestic points are exhibited over the entire spectral range for the acid-catalyzed reactions of all the K-region arene oxides in methanol[1,2] and of DBA-O in both dimethylformamide and tetrahydrofuran at 25 °C.

The reaction intermediate was identified as the K-region ketone by IR and NMR spectroscopy. FTIR spectra for the acid-catalyzed reaction of BA-O in acetonitrile measured as a function of time demonstrated the appearance and disappearance of an absorption centered around 1689 cm^{-1} and the subsequent appearance of an absorption at 1636 cm^{-1} at the expense of this absorption. The position of the band at 1689 cm^{-1} is in close agreement with that at 1695 cm^{-1} observed for the keto tautomer of 9-phenanthrol obtained by photolysis of Phe-O in Nujol at 77 K.[4] NMR spectra of reaction mixtures in acidic acetonitrile-d_3 show the time dependent appearance and disappearance of singlets corresponding to the methylene protons of the ketones at $\delta \sim 4$ ppm, and the appearance of characteristic K-region phenol signals downfield (typically at 7–7.4 ppm), at the expense of the signal(s) at ~4 ppm (for example see Figure 2). For unsymmetrical K-region arene oxides, with the exception of Chr-O and 4-MBA-O, the ratios of the two regioisomeric K-region ketones and the corresponding ratios of the regioisomeric phenols remain constant throughout the reaction. This observation is indicative of identical

Table I. Chemical Shifts of the K-Region Protons of the K-Region Ketones and Phenols

	chemical shifts,[a] ppm			
	ketone[b] methylene protons		phenol[c] ortho proton	
compd	major	minor	major	minor
BA-O	4.13	4.01	7.14	7.00
BaP-O	4.41	4.37	7.36	7.31
BcP-O	4.01	3.99	7.23	7.29
3-BrPhe-O	3.89	3.94	7.08	7.11
Chr-O	4.35	4.19	8.09	7.41
DBA-O	4.27	4.08	7.36	7.13
DMBA-O	3.93		7.32	
1-MBA-O	4.03	3.94	7.12	6.97
4-MBA-O	3.88	4.07	7.21	7.08
7-MBA-O	4.05		7.44	
11-MBA-O	4.13	4.02	7.13	7.01
12-MBA-O	4.00	3.91	7.01	6.93
Phe-O	3.97		7.10	
Pyr-O	4.31		7.44	

[a] In CD_3CN. [b] Singlet for 2 H. [c] Ortho to the phenol hydroxyl group.

(4) Jerina, D. M.; Witkop, B.; McIntosh, C. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1974**, *96*, 5578.

Table II. Products of the Acid-Catalyzed Reactions of K-Region Arene Oxides in Acetonitrile and Methanol

	major carbocation			
	in acetonitrile-d_3		in methanol[c]	
compd	K-region position	%[a,b] product	K-region position	% products
BA-O	C_6	77	C_6	63
BaP-O	C_5	59	C_5	55
BcP-O	C_6	93	C_6	87
3-BrPhe-O	C_{10}	57	C_9	53
Chr-O	C_5	97	C_5	93
DBA-O	C_6	91	C_6	76
DMBA-O	C_6	100	C_6	88
1-MBA-O	C_6	65	C_5	50
4-MBA-O	C_5	90	C_5	54
7-MBA-O	C_6	100	C_6	70
11-MBA-O	C_6	78	C_6	60
12-MBA-O	C_6	88	C_6	90
Phe-O	C_9	100	C_9	100
Pyr-O	C_4	100	C_4	100

[a] Determined by NMR integration. [b] The K-region arene oxides were converted to the K-region phenols in quantitative yield. The minor K-region phenol accounts for the balance of material. [c] Results from refs 1 and 2.

or very similar rates of enolization of the regioisomeric ketones. In the case of both Chr-O and 4-MBA-O, the major (C_6) ketone is almost all converted to phenol before any significant amount of the minor (C_5) ketone is converted to phenol. Table I summarizes the chemical shifts of the K-region methylene protons of the intermediate ketones and of the K-region aromatic protons ortho to the phenolic hydroxyl groups. Product distributions from the acid-catalyzed reaction of the K-region arene oxides in acetonitrile-d_3 are listed in Table II.

Although the keto tautomers have been postulated to be intermediates in the isomerization of arene oxides to phenols[5] (NIH shift) under solvolytic conditions, the direct observation of such intermediates has not previously been reported, as a result of the rapid enolization of the ketone in aqueous and methanolic solutions. Newman and co-workers[6] have observed that the K-region ketones derived from benz[*a*]anthracenes that have a methyl substituent in the bay region are unusually stable and exist in equilibrium with the corresponding phenols in solution. They attributed this unusual stability of the keto tautomer to the steric strain introduced by the methyl substituent in the bay region and suggested qualitatively that the relief of strain on going from the phenol to the nonplanar ketone structure offset the concomitant loss in resonance energy. With the exception of these K-region ketones derived from strained aromatic systems,[6,7] the keto tautomers of polycyclic phenols have been observed only under special conditions. The keto tautomers of 1-naphthol and 9-phenanthrol were observed as reaction intermediates at 77 K in Nujol during the photochemical rearrangements of naphthalene 1,2-oxide and Phe-O, respectively.[4] Several phenols derived from polycyclic aromatic hydrocarbons undergo ketone-like addition–elimination reactions even though no carbonyl IR bands are observed in their spectra.[6] For example, K-region phenols derived from phenanthrene and from methyl substituted and unsubstituted benz[*a*]anthracenes react with 2,4-dinitrophenylhydrazine to produce the corresponding 2,4-dinitrophenylhydrazone derivatives.[6] These phenols and others react in acidic methanol to produce methyl ethers, presumably through the keto tautomer. In the present study, accumulation of the ketone intermediate is a kinetic effect which we ascribe to the very low basicity of the acetonitrile solvent and the resultant slow rate of the C–H proton abstraction required for enolization (vide infra).

Kinetics of Ketone Formation. Good first-order kinetics were obtained for the first step of the reaction when it was followed spectrophotometrically at an isosbestic point for the subsequent slow step. In all cases, plots of the observed first-order rate constant for ketone formation vs the concentration of ethanesulfonic acid were linear. Second-order rate constants, calculated from the slopes of these lines, are listed in Table III, along with the corresponding rate constants in acidic methanol[1,2] for comparison.

Table III. Rate Constants for the Acid-Catalyzed Reaction of K-Region Arene Oxides in Acetonitrile and Methanol[a,b]

	in acetonitrile		in methanol[c]
compd	k_{fast}, M^{-1} s^{-1}	k_{slow}, M^{-1} s^{-1}	k_H, M^{-1} s^{-1}
BA-O	151	10.7	476
BaP-O	244	12.5	431
BcP-O	901	29.3	823
3-BrPhe-O	34.7	18.5	40.8
Chr-O	1910	135.0	1370
DBA-O	361	20.3	424
DMBA-O	17400	2.79	15700
1-MBA-O	638	2.56	1690
4-MBA-O	710	15.9 (major) 2.3 (minor)	1900
7-MBA-O	2920	14.1	2770
11-MBA-O	224	11.2	630
12-MBA-O	913	1.81	2230
Phe-O	96	43.0	196
Phe-O-9,10-d_2	93	9.8	
Pyr-O	106	34.0	171

[a] 25 °C. [b] Standard deviation between 2 and 6% of the reported value. [c] Results from refs 1 and 2.

As shown by the results in Table II, in the absence of peri methyl substitution, the relative reactivities of the two epoxide centers of a given K-region oxide in acetonitrile are similar to those observed in methanol. In contrast, the solvent exerts a profound influence on the relative reactivities of the two epoxide centers of K-region arene oxides that have a methyl substituent in a peri position. The acid-catalyzed reactions of 7-MBA-O and DMBA-O in acetonitrile produce only 5-hydroxy-7-MBA and 5-hydroxy-DMBA, respectively, whereas in methanol these two oxides yield products from reaction at both the K-region positions. Similarly, 4-MBA-O undergoes acid-catalyzed reaction in acetonitrile to produce a major product, 6-hydroxy-4-MBA (90%), and a minor product, 5-hydroxy-4-MBA (10%), whereas in methanol equal amounts of the products from reaction at each position are obtained.

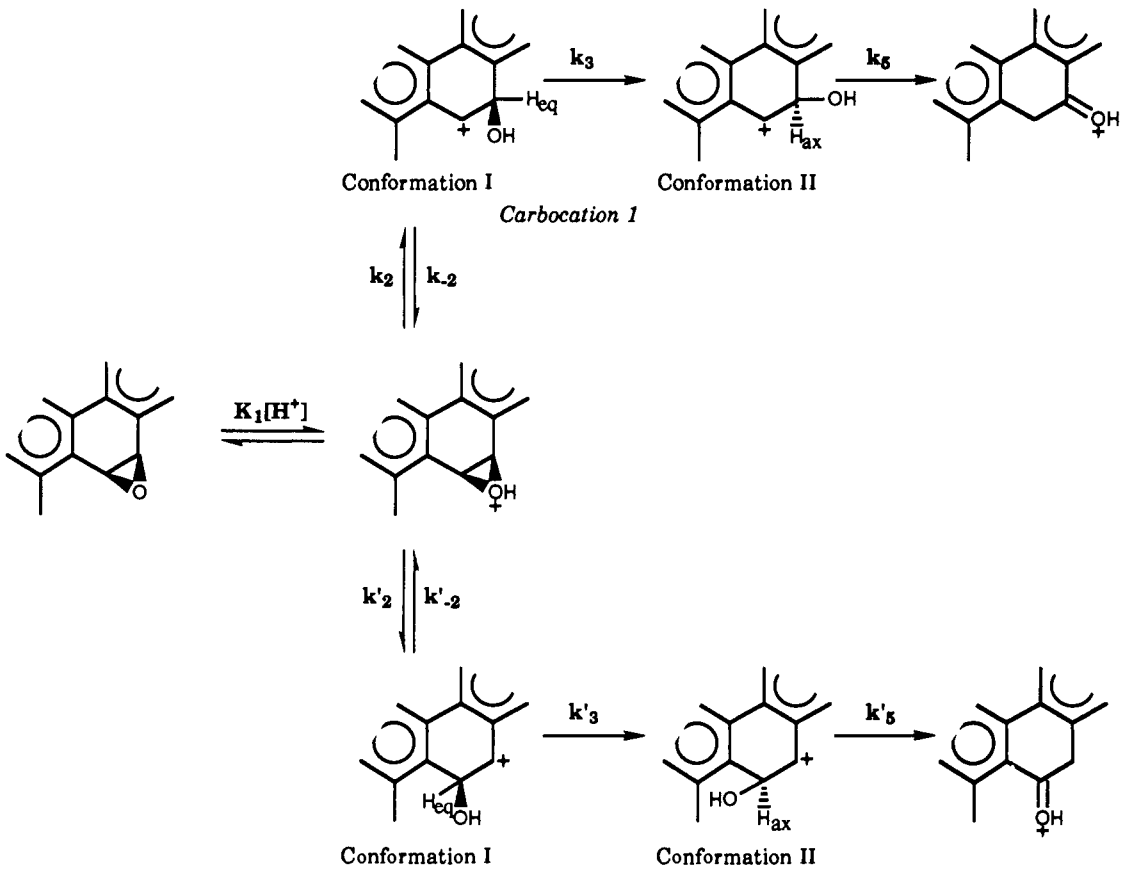
The rate constants in Table III for ketone formation show that the reactivities of the K-region arene oxides in acidic acetonitrile are similar (within a factor of 2–3) to those observed for the same arene oxides in acidic methanol. In both methanol and acetonitrile bromine substitution decreases and methyl substitution increases the reactivity relative to unsubstituted K-region arene oxides. A plot of log k_{MeCN} for the fast step vs log k_{MeOH} at the same site is shown in Figure 3; k_{MeCN} and k_{MeOH} are the fractional rate constants for reaction at a given position of the arene oxide and are equal to $k_{obsd}f_{prod}$, where f_{prod} is the mole fraction of product derived from the hypothetical cation at the specified position. The data fit a straight line with a slope of 1.07 ± 0.09, an intercept of –0.4 ± 0.2 and a correlation coefficient of 0.88. Three clearly deviant points (open circles), which represent reactions that yield K-region phenols in which the hydroxyl group occupies a peri position relative to a methyl substituent, were excluded in calculating the slope and intercept of the line.

Mechanism and Rate-Determining Step. In conjunction with the previously proposed mechanism for acid-catalyzed solvolysis of K-region arene oxides in methanol,[1] comparison of the rates and product distributions for these arene oxides in methanol and acetonitrile permits the assignment of rate-determining steps, based on the following considerations.

(1) For reactions that proceed via a hydroxy carbocation in which the hydroxyl group is not peri to a methyl substituent, there is a satisfactory linear correlation (Figure 3) with a slope close to 1.0 between log k_{MeCN} and log k_{MeOH}. From this linear correlation, we conclude that the rate-determining step for these arene

(5) Bruice, T. C.; Bruice, P. Y. *Acc. Chem. Res.* **1976**, *9*, 378.
(6) Newman, M. S.; Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237.
(7) Newman, M. S.; Olson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 6207.

Scheme II



oxides is the same *in both solvents*.

(2) Several of the arene oxides, namely 1-MBA-O and 12-MBA-O, produce exclusively addition products in methanol[2] (k_4[Nu] $\gg k_3$) and exclusively rearrangement products in acetonitrile where k_4[Nu] = 0. However, their rate constants fit the linear correlation described above, and hence their mechanism and rate-determining step must be the same in both solvents. Thus, we conclude that the rate-determining step cannot be one which commits the arene oxide to a specific product or set of products, and hence the most reasonable assignment of rate-determining step for reactions which follow the linear correlation of Figure 3 is acid-catalyzed ring opening (k_2). This result is in agreement with previous observations with other benzylic epoxides.[8]

(3) For reactions of arene oxides via cations bearing a methyl substituent peri to the hydroxyl group, substantial negative deviations of k_{MeCN} from the linear correlation are observed. This observation is most reasonably explained by a change in rate-determining step, such that for these cations in acetonitrile (but not in methanol), the rate-determining step is either the conformational isomerization (k_3) of the initially formed conformer I to conformer II which can rearrange to ketone, the hydride transfer (k_5), or some combination of these two processes. Different rate-determining steps in methanol and in acetonitrile are observed for these arene oxides because the solvent trapping pathway (k_4) is not available in acetonitrile. Thus, the only available reaction pathways for the initially formed carbocation conformer I are conformational inversion (k_3) or return to the protonated epoxide (k_{-2}), and a change of rate-determining step will occur if k_3 or k_3k_5/k_{-3} becomes smaller than k_{-2}. For the arene oxides with a peri methyl substituent, the conversion of conformer I to II is expected to be both thermodynamically unfavorable (k_3k_5/k_{-3} small) and slow (k_3 small), as a result of steric interactions between the hydroxyl and methyl groups. Such conformational restrictions imposed by peri methyl substitution are well documented.[1,2]

Scheme II shows a mechanism for acid-catalyzed conversion of a K-region arene oxide with a peri methyl substituent to ketone products, the observed reaction pathway in a nonnucleophilic solvent. This mechanism accounts for the observed increase in the regioselectivities for the acid-catalyzed reactions of K-region arene oxides with a peri methyl substituent in acetonitrile as compared with methanol. According to this mechanism, ring opening (k_2) and the conformational change (k'_3) are the rate-determining steps for carbocations 1 and 2, respectively. Initially, the protonated K-region arene oxide would open to carbocations 1 and 2 in a ratio reflecting the true relative chemical reactivities of the two epoxide centers (k_2:k'_2). Carbocation 1 has the hydroxyl group away from the methyl substituent, and thus the initially formed conformer I (hydroxyl group pseudoaxial) can rapidly undergo the conformational change (k_3) that leads to product. For such carbocations, k_2 is rate-determining, and their observed rate constants fit the correlation (Figure 3) for rate-determining ring opening of other K-region arene oxides. In contrast, carbocation 2 conformer I has the hydroxyl group peri to the methyl group. The energy barrier for recyclization to the oxide (k'_{-2}) is assumed to be relatively insensitive to the methyl substituent, whereas both k'_3 and the equilibrium constant (k'_3/k'_{-3}) for conformational isomerization of I to II will be decreased by peri methyl substitution, since in this conformer the hydroxyl group and the peri methyl group are in the same plane. Thus, either k'_3 or k'_5 (hydride migration involving an energetically unfavorable intermediate, conformer II) are likely candidates for the rate-determining step for this class of carbocations in acetonitrile. When a peri substituent is present, carbocation 2, although formed, does not necessarily give rise to any net reaction since it can return to starting material more rapidly than it goes forward to product. Thus, unlike the product distribution in methanol where ring opening is rate-determining for the reactions at both arene oxide centers, the product distribution in acetonitrile does not reflect the true relative chemical reactivities of the K-region oxide centers

(8) Sayer, J. M.; Grossman, S. J.; Adusei-Poku, K. S.; Jerina, D. M. *J. Am. Chem. Soc.* **1988**, *110*, 5068.

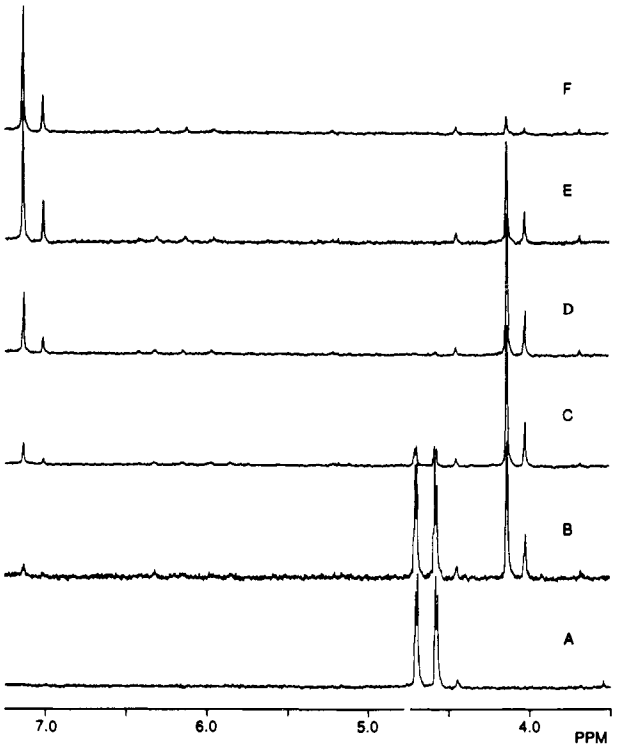


Figure 2. Partial NMR spectra measured as a function of time for the acid-catalyzed reaction of 11-MBA-O in acetonitrile-d_3: (A) no acid added, (B) after addition of ethanesulfonic acid at a final concentration of 100 μM, (C) after increasing the acid concentration to 600 μM, (D) after 10 min in the presence of 600 μM acid, (E) after 20 min, and (F) after 35 min.

when the rate-determining step is different for the two regioisomeric cations.

The following line of reasoning may be used to estimate the ratio, k'_{-2}/k'_3, for partitioning of carbocation 2 between return to protonated arene oxide and conformational isomerization (Scheme II). The ratio of products is determined by the ratio of the rate constants leading to their formation. The rate constant for formation of products from carbocation 1 is k_2, since its formation is rate determining. The overall rate constant for formation of products from carbocation 2 is

$$k'_2k'_3/(k'_{-2} + k'_3)$$

with no assumption made concerning the rate-determining step for this process. Thus, the product ratio in acetonitrile, P_1/P_2 is given by eq 1, where P_1 and P_2 represent products derived from

$$P_1/P_2 = k_2(k'_{-2} + k'_3)/k'_2k'_3 \quad (1)$$

the reaction in acetonitrile of carbocations 1 and 2, respectively. The analogous product ratio in methanol where the rate-determining step for both cation is their formation is k_2/k'_2. As an example, the ratio of the products from the C_6 carbocation (carbocation 1) formed from 7-MBA-O to those from the C_5 carbocation (carbocation 2) is 2.39. The analogous values of k_2/k'_2 for 4-MBA-O and DMBA-O are 1.15 and 7.26, respectively.[2] Rearrangement of eq 1 gives eq 2. If we assume that k_2/k'_2 is

$$P_1k'_2/P_2k_2 = (k'_{-2}/k'_3) + 1 \quad (2)$$

insensitive to solvent, substitution of k_2/k'_2 from the product ratio in methanol enables the estimation of k'_{-2}/k'_3, the partitioning ratio of carbocation 2 between ring reclosure and rearrangement in acetonitrile. In acetonitrile, 7-MBA-O and DMBA-O produced no detectable products corresponding to the C_5 cation, carbocation 2. If an upper limit of 1% is placed on the amount of product formed from this cation, k'_3 must be at least 41 and 13 times slower than k'_{-2}, for 7-MBA-O and DMBA-O, respectively. In the case of 4-MBA-O, carbocation 2 corresponds to the C_6 cation, which gives a measurable amount (10%) of minor product in acetonitrile. From this result, k'_3 is estimated to be 6.8 times slower than k'_{-2}. Thus, for carbocation 2 in which oxygen is peri to a methyl group, k'_3 is at least 7–41 times smaller than k'_{-2}.

Given the partitioning ratio, we may then estimate the effect of a peri methyl group (relative to no substituent) on the magnitude of k'_3 provided we assume that k_{-2} (or k'_{-2}) is relatively insensitive to methyl substitution, i.e., $k_{-2} \sim k'_{-2}$. In the absence of peri methyl substitution (carbocation 1 or carbocations derived from unsubstituted K-region arene oxide), epoxide ring opening is the rate-determining step, i.e., $k_3 > k_{-2}$. Thus, k_3 for a BA-O lacking

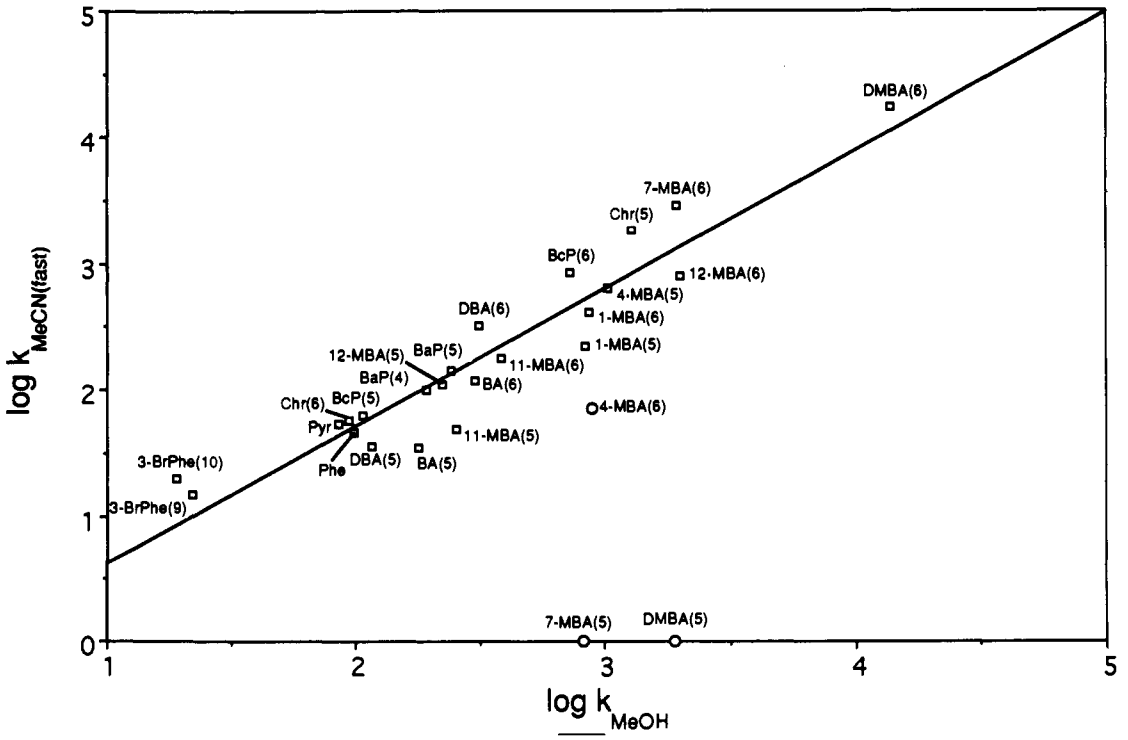
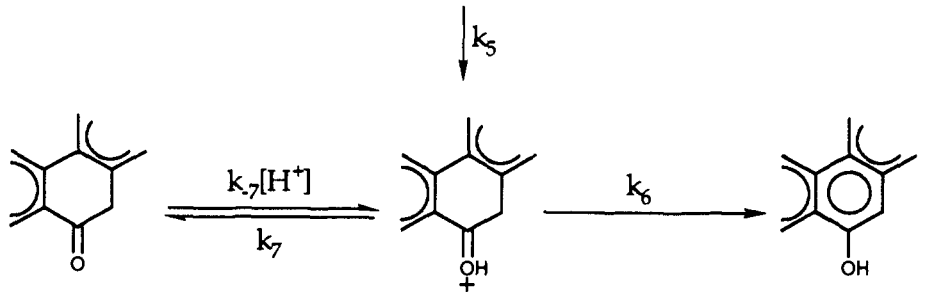


Figure 3. Plot of log $k_{MeCN(fast)}$ vs log k_{MeOH}. Abbreviations used in the figure are shown in Figure 1 of the preceding paper.[1] The number following each abbreviation shows the site of reaction.

Scheme III



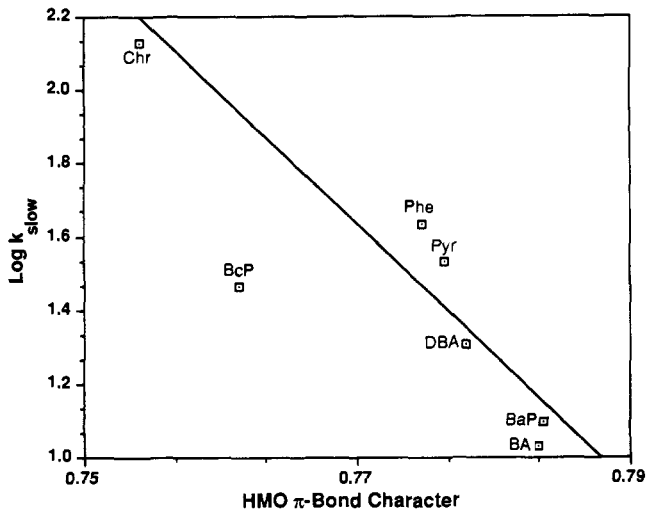


Figure 4. Plot of log k_{slow} vs Hückel molecular orbital π-bond character calculated for the K-region bond of the parent hydrocarbon.

peri methyl substitution must also be greater than k'_{-2}, if $k'_{-2} \sim k_{-2}$. In the presence of a peri methyl group, the fact that k'_3 is rate-determining in acetonitrile requires that $k'_{-2} > k'_3$ (see preceding paragraph), and thus $k_3 > k_{-2} \sim k'_{-2} > k'_3$. Hence, we conclude that k_3 must be *more than* 7–41 times faster than k'_3. Therefore, methyl substitution in a peri position to the carbocation hydroxyl group increases the energy barrier for k'_3 by more than 1.2–2.2 kcal/mol.

This is in contrast to the steric effects arising from a methyl substituent in the bay region. For such bay-region-substituted compounds the transition states for both cyclization (k_{-2}) and conformational isomerization (k_3) are more strained than the carbocation because of steric contact between the methyl substituent at C_1 or C_{12} and H_{12} or H_1, respectively. Thus, methyl substitution in the bay region is expected to raise the energy barrier to both the conformational isomerization step (k_3) and the cyclization step (k_{-2}) by approximately equal amounts, so that the *relative heights* of the energy barriers remain unchanged, and no change in rate-determining step is observed for 1-MBA-O or 12-MBA-O.

Chr-O, in which the K-region is a part of a bay region, undergoes acid-catalyzed reaction in methanol and acetonitrile to produce 7% and 3%, respectively, of products arising from the carbocation at C_6 with the hydroxyl group in a bay-region position. A hydroxyl group in a bay-region position has steric requirements that are similar to those of a hydroxyl group peri to a methyl substituent and is thus forced into the pseudoaxial orientation.[1] In methanol, this carbocation produced mostly addition products and a trace amount of phenol, whereas its C_5 regioisomer produced mostly phenol.[1] Somewhat surprisingly, the rate for ketone formation via the C_6 carbocation correlated well with those for the other carbocations in the linear relationship shown in Figure 3 indicating that k_2 is the rate-determining step in acetonitrile ($k_3 \gg k_{-2}$). Thus, in spite of its steric similarity with the carbocations in which a hydroxyl group is peri to a methyl substituent, the C_6 carbocation of chrysene exhibits the same rate-determining step as the carbocations from "unhindered" arene oxides, and the relative heights of the energy barriers for the conformational change (k_3) and cyclization to the protonated epoxide (k_{-2}) are unchanged by the steric effects of a bay region.

Enolization. In acetonitrile, accumulation of ketone intermediate(s) from all 14 K-region arene oxides studied allowed the determination of the rates of conversion of these ketones to the corresponding phenol(s). In most cases, this process exhibited good pseudo-first-order kinetics, even when both isomers of the ketone were initially formed. Thus, the rates of enolization of both regioisomeric ketones from a given arene oxide must be similar. This conclusion was borne out by the NMR spectral observation that the ratio of the two isomeric ketone intermediates (or of the two phenol products) remained constant throughout the course of reaction. The isomeric K-region ketones of 4-MBA were exceptional, in that the kinetics of their enolization were clearly biphasic and showed a good fit to two concurrent first-order reactions. In all cases, plots of the observed first-order rate constants for enolization vs the acid concentration were linear, and the second-order rate constants (Table III) were calculated from the slopes of the lines. The minor 5-ketone from Chr-O was produced in such a small amount (3%) that its rate of enolization could not be determined.

Mechanism of Enolization. The mechanism in Scheme III is proposed for the acid-catalyzed enolization. In this mechanism, the protonated keto tautomer is formed from carbocation conformer II by a hydride shift (k_5, cf. Scheme II in the preceding paper[1]). Although this protonated ketone may equilibrate with the unprotonated form (k_7/k_{-7}), the observation of acid catalysis indicates that the reactive species is protonated. The large primary kinetic isotope effect ($k_H/k_D = 4.4$) observed for enolization of the keto tautomer of 9-phenanthrol is indicative of rate-determining C–H bond breaking (k_6). The involvement of the solvent as a proton acceptor is apparent from the observation that no keto tautomers accumulate during the acid-catalyzed reaction of the K-region arene oxides in methanol[1,2] or in water.[2,5] Also, the observation of isosbestic points in the time-dependent UV spectra of the acid-catalyzed reaction of DBA-O in dimethylformamide and tetrahydrofuran indicated that no keto tautomer accumulated in these solvents. The pK_a values of protonated acetonitrile, dimethylformamide, methanol, tetrahydrofuran, and water are −10, −0.01, −2.2, −2.08, and −1.8, respectively.[9] Thus, acetonitrile is almost 8 orders of magnitude less basic than methanol. In acetonitrile, the rate of proton abstraction from the α-methylene group becomes smaller than the overall rate of formation of the ketones, and the keto tautomer accumulates.

The mechanism shown in Scheme III is essentially identical to that proposed for the acid-catalyzed enolization of aliphatic and benzylic ketones in aqueous solution.[10–12] However, the detailed timing of the proton-transfer process involving the carbonyl oxygen is probably different in the present case and in the

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acid-catalyzed enolization of 4-bromo-2,5-cyclohexadienone and its derivatives.[13-15] The enolization of 4-bromo-2,5-cyclohexadienone to *p*-bromophenol in aqueous solution shows both general-acid catalysis with Brønsted $\alpha = 0$ and general-base catalysis with Brønsted $\beta = 0.54$ in aqueous solution.[14,15] These results led Tee and co-workers to propose a concerted acid/base-catalyzed mechanism in which a molecule of acid donates a proton to the carbonyl oxygen, while a water molecule acts as a general base by abstracting a proton from C_4. In the case of the K-region ketones, proton transfer to the carbonyl oxygen is presumably complete since the fully protonated ketone is an obligatory intermediate in the rearrangement of the epoxide. Thus, the transition state for enolization corresponds to specific acid catalysis ($\alpha = 1.0$). In addition to the obvious structural differences between the ketones involved, the difference in the basicity of water and acetonitrile may account for the observed differences in transition-state structure. The much stronger general base water should be able to abstract a proton from the α-carbon of a ketone that is partially protonated (or unprotonated) at oxygen ($\alpha = 0$), whereas a much weaker base could only abstract a proton from the fully protonated ketone ($\alpha = 1$).

Steric Effects on Enolization. Hückel molecular orbital (HMO) calculations suggest that a major driving force for the acid-catalyzed enolization reaction is the development of aromaticity of the product phenols as measured by the calculated π-bond character of the K-region bond.[16] Large values for the HMO π-bond character of the K-region bond in the hydrocarbon (a measure of its resemblance to an isolated double bond, as opposed to an aromatic bond) correspond to slower rates of acid-catalyzed enolization. A good linear relation according to eq 3, with a correlation coefficient of 0.91, is observed for the unsubstituted

$$\log k_{slow} = (31.8 \pm 0.2) - (39.2 \pm 6.2)X \qquad (3)$$

K-region ketones where k_{slow} is the second-order rate constant for acid-catalyzed enolization in acetonitrile and X is the calculated π-bond character for the K-region bond of the parent hydrocarbon. The only unsubstituted K-region ketones to deviate from the linear correlation are those of BcP which fall below the line by a factor of ~3.3. BcP is known from X-ray crystallography to be nonplanar due to the steric interaction between H_1 and H_{12} in the fjord region.[1,17] Since the fully aromatic phenol should prefer a more planar structure than the ketone, strain will arise in the transition states for enolizations of these ketones because of the steric interactions between H_1 and H_{12}, with resultant rate retardation.[18]

Retardation of the rate of acid-catalyzed enolization by a remote steric interaction is also observed with K-region ketones derived from BA-O which have a methyl substituent in the bay region. The rates of the acid-catalyzed enolization of the K-region ketones of 1-MBA and 12-MBA are 4.2 and 5.9 times slower than those of the K-region ketones of BA, and the rate for the keto tautomer of 5-hydroxy-DMBA is 5.1 times slower than that for the corresponding tautomer of 5-hydroxy-7-MBA. A methyl substituent in the bay region of BA is expected to exert a modest electronic rate enhancement on acid-catalyzed enolization (see below) and to have little or no effect on the π-bond character of the K-region bond. On the other hand, the steric effect introduced by a methyl substituent in the bay region of BA is well documented[1,2] and should lead to a retardation of the enolization reaction as described above for BcP. The destabilizing effect of a remote bay-region methyl substituent on the transition state of the enolization reaction can be estimated by comparison of the rate constant for enolization of unsubstituted and bay-region methyl substituted ketones derived from BA, and the estimate is approximately 1 kcal/mol. These results are in agreement with the qualitative explanation proposed by Newman and co-workers[6] for the unusual stability of the K-region ketones derived from BA bearing a bay-region methyl substituent.

Steric effects are not the only reason for this unusual stability of these ketones. Among all the hydrocarbons studied, the K-region bond of BA has the highest double bond character or the least to gain from the delocalization of the K-region electrons. The steric effect of the crowded fjord region in BcP is comparable to that induced by methyl substitution in the bay region of BA, but the K-region ketones of BcP are not as stable as those of bay-region methyl substituted BA.[6] Therefore, the unusual stability of the latter K-region ketones is due to a combination of the steric effects induced by the methyl substitution in the bay region and the high double bond character of the K-region bond of BA.

Electronic Effects on Enolization. The rate constants (k_{slow}) in Table III for acid-catalyzed enolization are consistent with small electronic substituent effects on this reaction. An electron withdrawing substituent (Br) decreases the rate of tautomerization of 3-bromo-9-keto-9,10-dihydrophenanthrene relative to its unsubstituted analog by a factor of ~2. Electron donating methyl substituents slightly increase the rate. The keto tautomers of 6-hydroxy-4-MBA and 5-hydroxy-7-MBA enolize 49% and 32%, respectively, faster than the corresponding unsubstituted derivatives of BA. Also, the keto tautomer of 5-hydroxy-DMBA enolizes at twice the rate of the corresponding ketone from 12-MBA that lacks a 7-methyl substituent. The magnitude of the rate enhancement by methyl substituents seems to depend on the proximity of the methyl group to the K-region. For example, the rate of enolization of the K-region ketones of 11-MBA is essentially the same as that of the BA derivatives. These small substituent effects on the acid-catalyzed enolization reaction may be due to effects on the pK_a of the carbonyl oxygen, which would affect the equilibrium concentration of the protonated keto tautomers: electron withdrawing substituents decrease and electron donating substituents increase the pK_a of O-protonated substituted acetophenones.[19]

Unlike the keto tautomers of 6-hydroxy-4-MBA and 5-hydroxy-7-MBA, whose methyl substituent is not in a peri position relative to the incipient hydroxyl group, and which exhibit a small rate acceleration due to the electronic effect of the methyl group, the keto tautomer of 5-hydroxy-4-MBA undergoes acid-catalyzed enolization 4.8 times slower than the corresponding ketone from BA. This rate retardation is ascribed to steric interaction in the transition state between the oxygen atom and the peri methyl group. Enolization of the nonplanar ketone brings the oxygen atom into the plane of the aromatic system, such that unfavorable interactions with the peri methyl group (as previously discussed)[1,2] are enhanced. The strain energy caused by the peri methyl substituent is estimated to be 1.17 kcal/mol, from the 7.1-fold difference in rate constants for enolization of the two isomeric K-region ketones of 4-MBA. The acid-catalyzed enolization of the 5-ketone derived from Chr, where the keto group occupies a bay-region position, exhibited qualitatively similar rate retardation due to the steric interaction between the incipient hydroxyl group and H_4.

Summary and Conclusions

K-region arene oxides rearrange in acetonitrile to the isomeric K-region phenols in two acid-catalyzed steps: formation of K-region ketones and their subsequent enolization to phenols. The accumulation of ketone intermediates due to the weak basicity of acetonitrile allowed their observation and characterization for the first time by spectroscopic methods under conditions comparable to those used in solvolysis studies.

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The first "step", *ketone formation*, is itself composed of three kinetically distinct elementary steps: (i) C–O bond cleavage to form the hydroxy carbocation, (ii) conformational isomerization of this initially formed cation, and (iii) hydride migration. For sterically unhindered hydroxy carbocations, the rate-determining step is their rate of formation from the arene oxide, whereas for hydroxy carbocations with a methyl group peri to the hydroxyl group, the rate-determining step in acetonitrile is their conformational isomerization. Steric hindrance in a bay region remote from the reacting epoxide group, which should also retard conformational isomerization of the hydroxy carbocation, does not result in this step becoming rate-determining, because such steric hinderance also retards the recyclization of the hydroxy carbocation to arene oxide. Thus, it does not alter the *relative heights* of the energy barriers for these two steps.

Subsequent to its formation the ketone undergoes acid-catalyzed *enolization*, via a mechanism similar to that proposed for enolization of a aliphatic ketones in aqueous solution.[10-12] The energy of aromatization is the major driving force for the enolization reaction. In addition, the rate is affected by steric factors such that nonplanarity of the aromatic system or steric interference between the phenolic hydroxyl group and a peri substituent retard this reaction.

Experimental Section[20]

Product Analyses. To 0.5 mL of a solution of 1–5 mg of K-region arene oxide in acetonitrile-d_3 in an NMR tube was added 5–100 μL of 12.3 mM ethanesulfonic acid in acetonitrile-d_3. NMR spectra were obtained as a function of time. The ratios of the isomeric K-region ketones and phenols were determined by integration of the NMR signals (cf. Table I) at various time intervals. The reaction of DMBA-O produces only 5-hydroxy-DMBA, which is identical to the major product obtained from the dehydration of the K-region *cis*-dihydrodiol of DMBA.[7] This product was converted to the well characterized 5-methoxy-DMBA[7,21] on treatment with diazomethane in ether. The phenolic products of the acid-catalyzed reactions of BcP-O,[1] Chr-O,[1] 4-MBA-O,[2] and 12-MBA-O[2] were converted to their methyl ethers by treatment with diazomethane in ether, and the methyl ethers were compared to authentic samples. Other K-region phenolic products were compared to authentic samples of K-region phenols or to mixtures of the K-region phenols with known composition.[1,2]

Kinetics. In a typical measurement, a 1-mL solution of the K-region arene oxide in acetonitrile (HPLC grade acetonitrile used without further purification) was incubated at 25 °C for 10 min. Reaction was initiated by the addition of a solution of ethanesulfonic acid in acetonitrile, and the reaction was followed for 8–10 half-lives. The initial fast phase of reaction was monitored at a wavelength that corresponded to an isosbestic point for the subsequent slow reaction. The fast reactions were followed by monitoring the increase in absorption at 253.5 nm for BA-O, 277 nm for Chr-O, 284 nm for 4-MBA-O, and 255 nm for 11-MBA-O and 12-MBA-O and the decrease in absorption at 262 nm for BaP-O, 325 nm for BcP-O, 288 nm for 3-BrPhe-O, 284 nm for DBA-O, 272 nm for 7-MBA-O and DMBA-O, 307 nm for 1-MBA-O, 277 nm for Phe-O, and 247 nm for Pyr-O. These wavelengths are rounded to the nearest whole number. In a trial kinetic run, the fast reaction was allowed to proceed to completion, and the wavelength was adjusted manually in increments of 0.1 nm until no further change in absorption could be observed. The slow reactions were followed by monitoring the increase in absorption at the following wavelengths: 286 nm for BA-O, 375 nm for BaP-O, 288 nm for BcP-O, 249 nm for 3-BrPhe-O and Phe-O, 270 nm for Chr-O, 292 nm for DBA-O, 298 nm for DMBA-O, 280 nm for 1-MBA-O, 291 nm for 4-MBA-O, 293 nm for 7-MBA-O, 289 nm for 11-MBA-O, 291 nm for 12-MBA-O, and 345 nm for Pyr-O.

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(20) NMR spectra were measured at 300 MHz. Chemical shift data are reported in parts per million (δ) downfield from tetramethylsilane using the solvent peak as reference and coupling constants (J) are reported in hertz. IR spectra were obtained with a Bomem Michelson-100 FT-IR spectrometer. K-region arene oxides and phenols were obtained as described in refs 1 and 2.

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