Solvolysis of K-Region Arene Oxides: Substituent Effects on Reactions of Benz[a]anthracene 5,6-Oxide[1]

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Abstract: The solvolytic reactivity and products formed from benz[a]anthracene 5,6-oxide (BA-O) on substitution of a methyl group at positions 1 (1-MBA-O), 4 (4-MBA-O), 7 (7-MBA-O), 11 (11-MBA-O), and 12 (12-MBA-O), on 7,12-dimethyl substitution (7,12-DMBA-O), and on 7-bromo substitution in 1:9 dioxane–water and in methanol at 25 °C are reported. These substitutions result in >150-fold differences in their rates of acid-catalyzed solvolysis and cause marked changes in the distribution of solvent adducts and phenols resulting from isomerization. Optically pure BA-O, 7-MBA-O, 12-MBA-O, and 7,12-DMBA-O as well as their optically pure trans dihydrodiols were utilized to determine the point of attack by water in the hydrolysis reactions. In general, the reactions in aqueous dioxane (0.1 M $NaClO_4$) obeyed the rate equation $k_{obsd} = k_H[H^+] + k_0$, where k_H is the second-order rate constant for acid-catalyzed reaction and k_0 is the first-order rate constant for spontaneous reaction, to provide biphasic pH–rate profiles. When ionic strength was maintained with 0.5 M KCl, however, more complex pH–rate profiles were observed for some of the arene oxides due to attack of chloride on the neutral epoxide to produce steady-state concentrations of chlorohydrins. Rate enhancement on methyl substitution is largest (k_H, ca. 5-fold) when the methyl group is present in the hindered bay region (C_1 or C_{12}) or adjacent to the epoxide at C_7. The combined effect of two methyl groups (7,12-DMBA-O) is additive (ca. 25-fold). Theoretical calculations (molecular mechanics by PCMODEL-PI and ab initio by GAUSSIAN 86 and 88 programs) of carbocation stability indicate the importance of steric factors in determining relative reactivity and types of products formed from substituted benz[a]anthracene 5,6-oxides.

Introduction

K-Region arene oxides are potent mutagenic metabolites of several polycyclic aromatic hydrocarbons.[2,3] Detoxification of these metabolites involves enzymatic hydrolysis catalyzed by epoxide hydrolase as well as conjugation with glutathione catalyzed by glutathione *S*-transferases.[2] Since an understanding of these reactions depends on knowledge of the solution chemistry of the arene oxides, their hydrolysis reactions have been studied extensively in aqueous solutions.[2a,4-10] The hydrolysis reactions of K-region arene oxides derived from benzo[a]pyrene,[5,6] phenanthrene (Phe)[6,7] and several of its derivatives,[8] benz[a]anthracene (BA),[6,9] 7,12-dimethylbenz[a]anthracene (7,12-DMBA),[10] dibenz[a,h]anthracene,[9] and 3-methylcholanthrene[9] have been reported in water and mixed aqueous solvents. Phenanthrene 9,10-oxide (Phe-O), for example, undergoes hydronium ion catalyzed hydrolysis at low pH, spontaneous hydrolysis at intermediate pH values (ca. 7–12), and hydroxide ion catalyzed hydrolysis at pH > ca. 12.[6] The acid-catalyzed hydrolysis of Phe-O in water yields mostly 9-phenanthrol (75–80%), in addition to cis and trans dihydrodiols (20–25%, 1:2 ratio, respectively). The spontaneous reaction, however, produces mostly trans dihydrodiol (ca. 66%) and a reduced but still significant yield of phenol (ca. 33%).[7] Less than 1% of the cis dihydrodiol is formed from this reaction. In 1:1 dioxane–water, the major products (ca. 75%) from the acid-catalyzed hydrolysis of 7,12-DMBA-O are the cis and trans dihydrodiols in a 1:7 ratio.[10] Smaller amounts (ca. 25%) of the C_5 and C_6 ketones, precursors to the corresponding phenols, constitute the balance of the products. The reduced yields of ketones from 7,12-DMBA-O were attributed to a retarding of the NIH shift pathway, relative to trapping of the carbocations by water, because of the dihedral twist in the ions formed from acid-catalyzed opening of the epoxide. It was postulated[10] that the effect of this twist may "inhibit full cyclic conjugation in the NIH shift transition state, or cause the reacting C-H bond to overlap less with the adjacent empty p orbital".

In order to understand more fully the effects of substituents on the acid-catalyzed hydrolysis reactions of K-region arene oxides of BA, we have carried out kinetic and product studies of the hydrolysis and methanolysis reactions of 1-methyl, 4-methyl, 7-methyl, 11-methyl, 12-methyl, and 7,12-dimethyl derivatives of BA 5,6-oxide as well as methanolysis of its 7-bromo derivative (Scheme I). Product studies of optically active arene oxides in aqueous media and racemic arene oxides in acidic methanol allow determination of the regiospecificities for these reactions. The results of molecular mechanics calculations are used to gain insights into the effects of specific methyl substitutions on the geometries and relative energies of the arene oxides and carbocations formed from their acid-catalyzed opening.

Results

Kinetics. General Results. The observed pseudo-first-order rate constants for the reactions of 4-MBA-O, 7-MBA-O, 12-MBA-O, and 7,12-DMBA-O in 1:9 dioxane–water (v/v) solutions at 25 °C containing 0.1 M $NaClO_4$ accurately fit eq 1, where k_H is the second-order rate constant for the hydronium ion catalyzed re-

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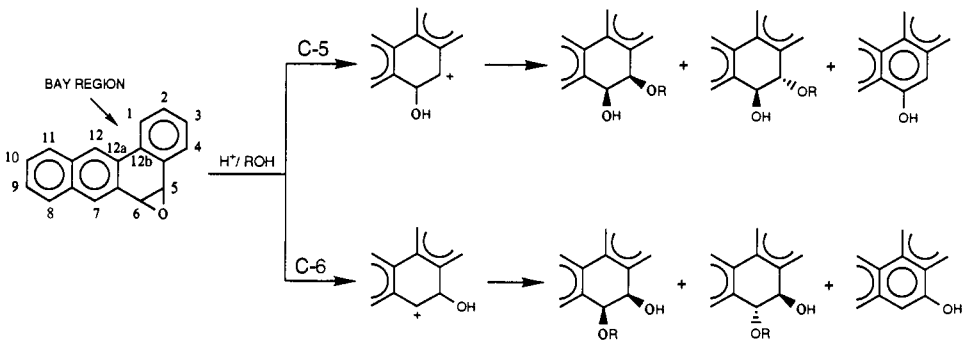
Scheme I[a,b]



[a] ROH = methanol or water. [b] Key: BA 5,6-oxide (BA-O), 1-methyl (1-MBA-O), 4-methyl (4-MBA-O), 7-methyl (7-MBA-O), 11-methyl (11-MBA-O), 12-methyl (12-MBA-O), 7,12-dimethyl (7,12-DMBA-O), 7-bromo (7-BrBA-O).

Table I. Rate Constants for the Hydrolysis Reactions of BA-O and its Methyl-Substituted Derivatives in 1:9 Dioxane–Water (25 °C)

Solutions Containing 0.1 M $NaClO_4$

compd	$10^{-2}k_H$, M^{-1} s^{-1}	10^5k_0, s^{-1}	k_H (rel)
BA-O	0.89 ± 0.06		1.0
1-MBA-O	5.0 ± 1.0		5.6
4-MBA-O	2.3 ± 0.2	4.4 ± 0.5	2.6
7-MBA-O	4.7 ± 0.2	3.3 ± 0.2	5.3
11-MBA-O	1.1 ± 0.2		1.2
12-MBA-O	4.2 ± 0.2	7.0 ± 0.3	4.7
7,12-DMBA-O	23 ± 3.0	35 ± 4.0	25.8
Phe-O	0.39 ± 3[a]		

Solutions Containing 0.5 M KCl

compd	$10^{-2}k_H$, M^{-1} s^{-1}	10^5k_0, s^{-1}	10^3k_2, M^{-1} s^{-1}	$k_{-2}K_a/k_3$, M
7-MBA-O	4.6 ± 0.2	0.34 ± 0.02	0.48 ± 0.05	$(2.9 \pm 0.7) \times 10^{-8}$
12-MBA-O	4.3 ± 0.4	5.7 ± 0.6		
7,12-DMBA-O	24 ± 2.0	34 ± 3.0	1.5 ± 0.2	$(1.4 \pm 0.8) \times 10^{-9}$

[a] For comparison, values of k_H for Phe-O in water at 30 °C were 100 M^{-1} s^{-1} in the presence of 1.0 M KCl (ref 6) and 115 M^{-1} s^{-1} in the presence of 0.1 M $NaClO_4$ (ref 7).

Table II. Listing of the Partial Rate Constants k_5 and k_6,[a] Along with Relative Values Compared to those of BA-O,[b] for Acid-Catalyzed Methanolysis of Arene Oxides (25 °C)

compd	$10^{-2}k_H$, M^{-1} s^{-1}	k_H (rel)	$10^{-2}k_5$, M^{-1} s^{-1}	$10^{-2}k_6$, M^{-1} s^{-1}	k_5 (rel)	k_6 (rel)
BA-O	4.76	1.0	1.76	3.00	1.0	1.0
1-MBA-O	16.9	3.6	8.45	8.45	4.8	2.8
4-MBA-O	19.0	4.0	10.3	8.7	5.9	2.9
7-MBA-O	27.7	5.8	8.3	19.4	4.7	6.5
11-MBA-O	6.3	1.3	2.5	3.8	1.4	1.3
12-MBA-O	22.3	4.7	2.2	20.1	1.2	6.7
7,12-DMBA-O	157.0	33.0	19.0	138.0	10.8	46.0
7-BrBA-O	1.1	0.23	1.05	0.05	0.6	0.017

[a] Values of k_5 and k_6 were calculated by multiplying k_H (standard deviation 2–6% of reported values) times the fraction of product arising from the C_5 and C_6 carbocations, respectively. [b] Values of k_5 (rel) and k_6 (rel) for each compound are relative to those for BA-O. Thus, comparisons *between* columns for k_5 (rel) and k_6 (rel) cannot be made.

action and k_0 is the first-order rate constant for the spontaneous reaction. This rate law corresponds to a biphasic pH–rate profile

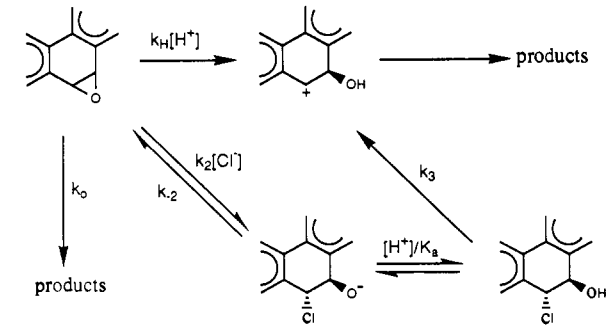
$$k_{obsd} = k_H[H^+] + k_0 \quad (1)$$

in which k_{obsd} is dependent on the hydronium ion concentration at low pH but becomes pH-independent near or above neutrality. Rate constants k_H and k_0 for those arene oxides studied are given in Table I. Rate data for the hydrolysis of BA-O, 1-MBA-O, and 11-MBA-O did not follow good pseudo-first-order kinetics at pH > ca. 5, possibly due to instability of the phenolic products, and therefore complete pH–rate profiles for these compounds were not determined.

Second-order rate constants for the acid-catalyzed reactions of the K-region arene oxides in methanol (Scheme I) were obtained as described in the Experimental Section. These rate constants, the partial rate constants for reaction at C_5 and C_6, and their relative values compared to those for BA-O are listed in Table II.

Specific Chloride Ion Effects. The pH–rate profile for the hydrolysis of 12-MBA-O in 0.5 M KCl is indistinguishable from

Scheme II



that in 0.1 M $NaClO_4$ solutions (Figure S-1, supplementary material). In contrast, the pH–rate profiles for the reaction of 7-MBA-O and 7,12-DMBA-O are more complicated in 0.5 M KCl than in 0.1 M $NaClO_4$ such that a plateau region is observed at pH ca. 6–10 in which k_{obsd} is significantly larger than expected

Table III. Distribution of Products between Phenols and Dihydrodiols on Acid-Catalyzed Hydrolysis of Benz[a]anthracene 5,6-Oxides in 1:9 Dioxane–Water at 25 °C Containing 0.1 M NaClO[a]

	phenols		diols		ratio C_6:C_5 for trans diols	
compd	% 5-OH	% 6-OH	% cis	% trans	k_H	k_0
BA-O	42	21	18	19	62:38	51:49
1-MBA-O	18	17	37	28		
4-MBA-O	ND	35	22	43		
7-MBA-O	27	ND	33	40	37:63	73:27
11-MBA	38	20	21	21		
12-MBA-O	11	3	15	71	90:10	72:28
7,12-DMBA-O	ND	ND	12	88	88:12	85:15

[a] Ratios of hydrolysis at C_5 versus C_6 for the trans dihydrodiols were determined with chiral substrates. Percentages of phenols and dihydrodiols from each arene oxide were determined from NMR spectra of the total reaction products by integration of selected peak areas. Ratios of cis to trans dihydrodiols were confirmed by HPLC. ND indicates the compound was not detected in the NMR spectrum of the product mixture. See Experimental Section for carbocation origin of trans dihydrodiols.

on the basis of k_H and k_0 values measured at lower and higher pH values, respectively (Figure S-2, supplementary material). Similar specific chloride ion effects have been observed in the reaction of indene 1,2-oxide,[11] 1,3-cyclohexadiene 1,2-oxide,[12] and Phe-O[7] in KCl solutions. The mechanism shown in Scheme II has been proposed to account for this effect, which is observable only when $k_2[Cl^-] \geq k_0$. We attribute the kinetic behavior of 7-MBA-O and 7,12-DMBA-O in KCl solutions ($k_2[Cl^-]$:k_0 ratios are 7.3 and 2.1, respectively) to this same specific effect of chloride ion. The rate expression for a reaction that proceeds by the mechanism outlined in Scheme II is given by eq 2. Summaries

$$k_{obsd} = k_H[H^+] + \frac{k_2[Cl^-]}{1 + (k_{-2}K_a/k_3[H^+])} + k_0 \qquad (2)$$

of rate constants k_H, k_2, $k_{-2}K_a/k_3$, and k_0 for reactions of 7-MBA-O and 7,12-DMBA-O, as well as k_H and k_0 for 12-MBA-O, in 0.5 M KCl solutions are provided in Table I. A basis for predicting which arene oxides will show a chloride effect is presently unavailable.

Product Studies. Hydrolysis. Yields and ratios of trans and cis dihydrodiols and isomeric K-region phenols from the acid-catalyzed hydrolysis of BA-O and its methyl-substituted derivatives in 1:9 dioxane–water are provided in Table III. These products are readily rationalized by the mechanism outlined in Scheme I where protonated epoxide undergoes rate-determining C–O bond cleavage to yield C_5 and C_6 carbocation intermediates. These cations either react with water to yield cis and trans dihydrodiols (methyl ethers in methanol) or rearrange to phenols.

To determine the regioselectivity of the trans hydration reaction, acid-catalyzed hydrolyses of chiral BA-O, 7-MBA-O, 12-MBA-O, and 7,12-DMBA-O were carried out and the enantiomeric compositions of the trans dihydrodiol products were determined. For example, acid-catalyzed hydrolysis of (+)-(5*S*,6*R*)-BA-O yielded 38% of the 5*R*,6*R* and 62% of the 5*S*,6*S* enantiomer. Thus, 62% of the trans dihydrodiol is formed from the C_6 carbocation and the remaining 38% from the C_5 carbocation. Table III summarizes the amounts of trans dihydrodiol formed from the C_5 and C_6 carbocations of each of the optically active arene oxides studied.

Spontaneous reaction (pH > ca. 7.5, 0.1 M $NaClO_4$) of BA-O, 7-MBA-O, 12-MBA-O, and 7,12-DMBA-O gave mainly or entirely dihydrodiols in which the trans to cis ratio was >98:2. In contrast to the results in $NaClO_4$ solutions, a significant amount (12–14%) of cis dihydrodiol is formed in addition to the trans dihydrodiol from the hydrolysis of 7,12-DMBA-O at pH 8 in the presence of chloride ion. Under these conditions, reaction occurs in part via an intermediate chlorohydrin (Scheme II), whereas in 0.1 M $NaClO_4$ at the same pH the k_0 reaction predominates. As in the case of Phe-O, the cis diol presumably arises from the chlorohydrin via a hydroxy carbocation intermediate identical with that formed in the k_H reaction, whereas the k_0 reaction gives exclusively trans dihydrodiol in the absence of chloride ion.[7] The pronounced chloride ion effect on the pH–rate profile and products of hydrolysis of some arene oxides but not others (e.g., 12-MBA-O) points out the necessity for caution in studying these reactions in solutions containing chloride or other nucleophilic ions.

Table IV. Effects of Substitution on Product Distribution for the Acid-Catalyzed Methanolysis of Benz[a]anthracene 5,6-Oxides[a]

compd	% product from each carbocation	% trans addition	% cis addition	% phenol
BA-O	C_5 37	23	6	8
	C_6 63	38	9	16
1-MBA-O	C_5 50	44	6	ND
	C_6 50	40	10	ND
4-MBA-O	C_5 54	24	15	15
	C_6 46	44	2	ND
7-MBA-O	C_5 30	28	2	ND
	C_6 70	36	22	12
11-MBA-O	C_5 40	19	6	15
	C_6 60	30	11	19
12-MBA-O	C_5 10	10	trace	ND
	C_6 90	85	5	ND
7,12-DMBA-O	C_5 12	11	1	ND
	C_6 88	81	7	ND
7-BrBA-O	C_5 95	94	1	ND
	C_6 5	4	1	ND

[a] Distribution of products is based on integration of NMR spectra. The ratio of cis to trans methanol adducts obtained by integration of peak areas on HPLC matched that from integration of NMR peak areas. Note that a phenolic 6-hydroxyl group derives from a C_5 carbocation. ND indicates that the product was not detected by either analytical method.

Methanolysis. Solvolysis in methanol has the advantage that the cis and trans methanolysis reactions each yield two positionally distinct monomethyl ether adducts (Scheme I), one derived from the C_5 carbocation and the second from the C_6 carbocation. As expected, the acid-catalyzed methanolysis produced cis and trans adducts from both K-region carbocations. When the monomethyl ethers and phenols are characterized, the total amount of product derived from the C_5 versus the C_6 carbocations can be determined. Table IV summarizes the amounts of cis and trans dihydrodiol methyl ethers and phenols formed from the C_5 and C_6 carbocations from the studied arene oxides.

Discussion

Solvent Effects. Comparison of acid-catalyzed reaction rates (k_H) in 1:9 dioxane–water (Table I) versus methanol (Table II) indicates that relative reactivity for several arene oxides is similar in both solvents. Absolute reaction rates in methanol are 3-fold (1-MBA-O) to 8-fold (4-MBA-O) higher than in 1:9 dioxane–water, perhaps due to the stronger acidity of $CH_3OH_2^+$ compared to H_3O^+.[13] The other apparent difference between the reactions in methanol and in 1:9 dioxane–water is the change in gross distribution of products between total phenols and total solvent adducts (cf. Tables III and IV). Significantly more trans methanol adducts are formed compared to trans dihydrodiols. This occurs mainly at the expense of phenols since the cis methanol adducts are only slightly reduced compared to cis dihydrodiols. The more nucleophilic methanol probably intercepts the carbocation intermediate faster than water, thus competing more favorably with the hydride migration pathway to phenols.

In the cases of BA-O, 7-MBA-O, 12-MBA-O, and 7,12-DMBA-O, the regioselectivity of the trans addition of water can

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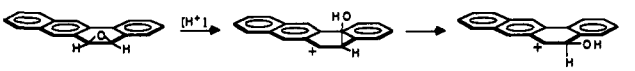
be directly compared to that of methanol since optically active arene oxides were used in the aqueous reactions. For BA-O, 12-MBA-O, and 7,12-DMBA-O, the ratio of trans adduct derived from attack at C_5 versus C_6 was unaffected by solvent (water versus methanol), and for 7-MBA-O the effect of solvent on this ratio is small. If one assumes that the carbocation origin of the cis dihydrodiols is identical with that of the cis methanol adducts, then the estimated distribution of *total products* derived from the C_5 and C_6 carbocations in water is similar to that determined in methanol, at least in the cases of BA-O, 7-MBA-O, 12-MBA-O, and 7,12-DMBA-O. Product studies of the methanolysis of the BA oxides (Table IV) provide complete regiochemistries of carbocation formation. Although there are some differences between the reactions in methanol and in 1:9 dioxane–water as described above, the order of reactivity and regioselectivities in both solvents are very similar. *Thus, the mechanisms of reaction in both solvent systems appear to be quite similar.*

Substituent Effects on the Rates and Regiochemistry of Ring Opening of BA Oxides. The reactivity of BA-O is approximately twice that of Phe-O. For the acid-catalyzed reaction of BA-O (Table I), the ratio of k_6:k_5 is 1.7:1 in methanol and is estimated to be 2.1:1 in 1:9 dioxane–water. These data are consistent with earlier results that show that the solvolytic rate constants for benzyl and 2-naphthylmethylene substrates are very similar.[14] The *total kinetic effect* of a methyl substituent at the 1-, 4-, 7-, or 12-position on k_H for hydrolysis or methanolysis is rather small (3–6-fold increase; see Tables I and II). The rate effect of a methyl group at the 11-position is even smaller (1.2). The combined rate effect of the two methyl groups of 7,12-DMBA-O (Table I) accounts for its 26-fold higher reactivity relative to that of BA-O (5.3-fold for 7-MBA-O times 4.7-fold for 12-MBA-O = 24.9-fold relative to that for BA-O). Thus, the contribution of the methyl groups to the free energy of activation is additive.

In order to assess the kinetic effects of substituents on the relative amounts of C_5–O and C_6–O bond cleavage, the acid-catalyzed methanolysis reactions of BA oxides are viewed as two parallel reactions to form the C_5 and C_6 carbocations (Scheme I). Thus, the observed rate constant k_H (Table II) is the sum of the partial rate constants ($k_5 + k_6$), and the ratio of C_5 products to C_6 products is k_5:k_6. From the observed rate constants for methanolysis of the BA oxides and the yields of C_5 and C_6 products, values of k_5 and k_6 for each arene oxide are calculated (Table II). For comparison, a methyl substituent in the meta position usually enhances the rate of solvolysis of benzyl systems by a factor of 2 or less,[15] and *p*-methylstyrene oxide is 19 times more reactive toward acid-catalyzed hydrolysis than styrene oxide.[16] These factors can be used to estimate the expected electronic effect of a methyl group on k_H in the acid-catalyzed solvolysis of the K-region arene oxides. For example, a 12-methyl group should behave like a meta substituent relative to the 6-position in a substituted BA 5,6-oxide, whereas a 7-methyl group should have a much greater rate effect (analogous to an ortho or para substituent) because of the possibility of direct resonance interaction with a developing carbocation at this center. Since, in the present compounds, methyl substituents at the 1-, 4-, 7-, or 12-position are either peri to the epoxide group or are at sterically hindered bay-region positions, the kinetic effect may result from both electronic and steric factors and thus may differ from prediction based on simple benzylic systems. Furthermore, the extended conjugation in the BA system may complicate the interpretation of electronic effects. The regiochemistry of epoxide ring opening of BA-O, like the overall rate, is relatively insensitive to the effect of methyl substituents at the 1-, 4-, 7-, and 11-positions (cf. Tables III and IV). Thus, methyl substitution at one of these positions does not selectively favor ring opening at either C–O bond. Rather, the kinetic effect must increase the rates of formation of both the C_5 and C_6 carbocations. For example, a methyl substituent at the 7-position increases the rate of epoxide ring opening at both C_6 and C_5 by approximately the same factor (ca. 5–6). The effect on C_6 is smaller than that expected for a substituent in a direct conjugation with the carbocation center, on the basis of the ca. 20-fold acceleration predicted for the electronic effect of a *para*-methyl group (see preceding discussion). A methyl substituent at the 4-position, another peri location, also increases the rate of epoxide ring opening at both the C_5 and C_6 positions. In each case, the effect of the *peri*-methyl group is to increase the rate of ring opening at the adjacent epoxide position slightly more than at the more distant epoxide center. The small magnitude of the effect of a methyl group upon reactivity at the adjacent center may be a consequence of opposing steric and electronic effects. The steric effect could rise from unfavorable interaction between the hydrogen at the carbocation center and the *peri*-methyl group. A bromine substituent in the 7-position peri to the epoxide retards opening at C_6 by a factor of ca. 62, presumably due mainly to an electronic effect, and has a relatively small effect on epoxide opening at C_5.

Scheme III



Effect of a *peri*-Methyl Group on Phenol Formation. Significant amounts of both isomeric K-region phenols are formed on the acid-catalyzed hydrolysis and methanolysis of BA-O and 11-MBA-O (Tables III and IV). The yields of phenols from both hydrolysis and methanolysis of the arene oxides with *peri*-methyl substitution (4-MBA-O and 7-MBA-O) are significantly lower. *A particularly interesting observation is that 4-MBA-O yields only C_6 phenol and 7-MBA-O yields only C_5 phenol, whereas similar amounts of C_5 and C_6 phenols are formed from both BA-O and 11-MBA-O in either solvent.* The reduced yields of phenol product from 4-MBA-O and 7-MBA-O indicate that the *peri*-methyl group in each case inhibits phenol formation at the adjacent K-region carbon center. This observation can be rationalized by the mechanism outlined in Scheme III for for the formation of the C_5 phenol from BA-O. Assuming axial opening of the C_6–O bond of protonated BA-O, the initial carbocation must have a pseudoaxial hydroxyl group. In order for the C_5 phenol to be formed, the C_5 hydrogen must migrate to C_6. It is therefore reasonable to assume that, along the reaction coordinate for phenol formation, conformational reorganization of this cation must occur to a structure in which the C_5 hydrogen is in a pseudoaxial position. Such a conformation would have the C–H bond periplanar to the empty p orbital which is favorable for hydride migration to C_6.[17] In the corresponding mechanism for the acid-catalyzed reaction of 4-MBA-O, a methyl group rather than a hydrogen is at the C_4 position. The additional steric strain caused by the peri interaction between the C_4 methyl and C_5 hydroxyl groups would make this conformational isomerization slower and/or less favorable thermodynamically than in the parent BA-O system. Such an effect would also explain the absence of the C_6 phenol among the products of the acid-catalyzed solvolysis of 7-MBA-O. Thus, these *peri*-methyl substituents retard formation of phenols at the adjacent epoxide center.

Effect of a Bay-Region Methyl Group on Phenol Yields and Regioselectivity. Substitution of a methyl group at the bay-region 12-position of BA-O increases the rate of acid-catalyzed epoxide ring opening at the 6-position by a factor of 6.7 and has little effect on the rate of ring opening at the 5-position (Table II). The rate enhancement at C_6 is larger than that expected from a purely electronic effect, since the 12-methyl is located in a meta position relative to C_6, and the electronic effect of this group on k_H should be about 2.[15] The yield of phenols (Tables III and IV) is sensitive to methyl substitution at a bay-region position (C_1 and C_{12}). Acid-catalyzed hydrolysis of 1-MBA-O, 12-MBA-O, and 7,12-DMBA-O produced 35, 14, and 0%, respectively, of phenolic

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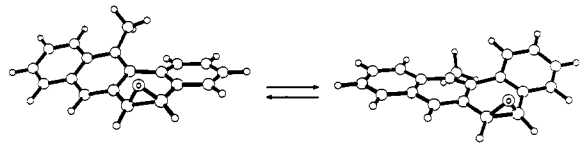
(15) Reference 14, p 41.
(16) Blumenstein, J. J.; Whalen, D. L. Unpublished results.
(17) Sayer, J. M.; Yagi, H.; Silverton, J. V.; Friedman, S. L.; Whalen, D. L.; Jerina, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 1972.

Table V. Calculated Energies for Toluene, 2-Methylnaphthalene, Benzyl Cation, and 2-Naphthylmethylene Cation and Differences in Resonance Stabilization Energies between the Cations[a]

computational level	−E, hartrees				ΔRSE,[b] kcal/mol
	$C_7H_7^+$	$C_{11}H_{10}$	C_7H_8	$C_{11}H_9^+$	
RHF/STO-3G	−265.653 99	−417.271 70	−266.475 65	−416.464 85	9.3
RHF/3-21G	−267.380 36	−420.037 26	−268.240 19	−419.189 50	7.6
RHF/6-31G*	−268.886 68	−422.392 83	−269.740 12	−421.552 11	8.0

[a] Bond lengths and angles at each level of calculation are given in the supplementary material. [b] Resonance stabilization energy for the isodesmic reaction of $C_{10}H_7CH_3 + PhCH_2^+ \rightarrow C_{10}H_7CH_2^+ + PhCH_3$.

Scheme IV



12-MBA-O-a 12-MBA-O-b

products. In contrast, ca 60% phenols were obtained from BA-O and 11-MBA-O. In methanol, BA-O and 11-MBA-O produced 24 and 35% of phenolic products, respectively, whereas no phenolic products were obtained on the solvolysis of 1-MBA-O, 12-MBA-O, and 7,12-DMBA-O.

In order to assess rigorously the potential contribution of steric factors to the rates and product distributions upon solvolysis of K-region arene oxides with methyl substitution at the bay region, theoretical calculations of the preferred conformations and energy levels of several BA oxides as well as carbocation intermediates were undertaken. Specifically, minimum energy conformations for the ground states of selected BA oxides as well as the energies of the C_5 and C_6 carbocations conformationally related to each of these ground states were calculated.

Effect of Methyl Substitution in the Bay Region on the Conformation of BA Oxides. Molecular mechanics calculations by the PCMODEL-PI program[18] indicate that 1-MBA-O and 12-MBA-O can each exist in two conformations of approximately equal energy. The two conformations of 12-MBA-O, for example, are given by structures a and b in Scheme IV. Conformation a, in which the C_{12}–C_{12a}–C_{12b}–C_1 dihedral angle is −28°, is 0.4 kcal/mol more stable than conformation b, in which this dihedral angle is 29°. Designations a and b for structures signify negative or positive values of this angle, respectively. For 1-MBA-O, the conformation with a C_{12}–C_{12a}–C_{12b}–C_1 dihedral angle of 28° is 0.3 kcal/mol more stable than a second conformation with a naphthyl–phenyl dihedral angle of −28°. The observed energy difference of 0.3 kcal/mol gives a ratio of 62:38 for the two conformations by a Boltzmann distribution calculation. Similar PCMODEL-PI calculations of 7,12-DMBA-O provide one conformation similar to conformation a, with a naphthyl–phenyl dihedral angle of −29° and a second conformation that is 1.7 kcal/mol less stable with a dihedral angle of 31°. This energy difference corresponds to a ratio of 95:5 for these conformational isomers. From X-ray structure determination, 7,12-DMBA-O has a C_{12}–C_{12a}–C_{12b}–C_1 dihedral angle of −35° in the crystalline state,[19] similar to the corresponding angle in conformation a. In contrast, the carbon framework of the parent BA-O system is calculated to be nearly planar, with the phenyl ring twisted out of the plane of the naphthyl ring by only 4°. A methyl substituent at the C_1 or C_{12} positions of the planar BA-O system has severe steric interactions with the C_{12} or C_1 hydrogen, respectively, and twisting about the naphthyl–phenyl (C_{12a}–C_{12b}) bond relieves this steric interaction. Thus, 1-MBA-O, 12-MBA-O, and 7,12-DMBA-O should each exist in two conformations with a significant barrier to interconversion, whereas BA-O most likely exists as either a single planar conformation or as two nearly planar conformations with a very small barrier for interconversion.

The products of acid-catalyzed solvolysis of 1-MBA-O, 12-MBA-O, and 7,12-DMBA-O may in principle be derived from reaction of one or both ground-state conformations. If it is assumed (vide infra) that the epoxide ring must open to a hydroxy carbocation with a pseudoaxial hydroxyl group, each conformation of the reactant epoxide corresponds to a single regiochemistry (C_5 or C_6) for C–O cleavage. Since the relative rates of competing reactions are determined only by the relative energies of their respective transition states, the observed regiochemistry of product formation will be a function of *both the equilibrium concentrations and the reactivity* of each conformation. The less stable epoxide conformation may be the more reactive, and thus the complete description of the solvolysis mechanisms of these epoxides may be rather complicated.

Calculated Energies of C_5 and C_6 Carbocations in the BA Oxide System. Ab initio calculations[20] were carried out on the C_5 and C_6 carbocations derived from BA-O, 1-MBA-O, and 12-MBA-O. As was the case for epoxide conformations (cf. Scheme IV), structure numbers for carbocation conformations, in which the dihedral angle C_{12}–C_{12a}–C_{12b}–C_1 is defined as negative or positive, are designated with an a or b, respectively. Structures were fully optimized with ab initio gradient techniques with the minimal STO-3G basis set.[21,22] Higher level ab initio calculations are prohibitively expensive due to the size of the molecular system. Three orientations of the hydroxyl hydrogen were investigated with ab initio calculations for both carbocations derived from 12-MBA-O. The calculations indicate that the conformer with the hydroxyl hydrogen anti to the carbocation center (shown later) is the lowest in energy. Rotations of the hydroxyl hydrogen over the ring and away from the ring give structures that are 1.6 and 0.7 kcal/mol, respectively, higher in energy. Therefore, all results are for the conformer with the hydroxyl hydrogen anti to the carbocation (C^+–C–O–H dihedral angle approximately 180°), unless otherwise indicated. In addition, semiempirical calculations on these carbocations were performed with Dewar's AM1 method[23] by the MOPAC 4.0 program[24] and also with the PC MODEL-PI program.[18]

For BA oxides, the C_5 carbocation has the positive center adjacent to a phenyl ring and therefore resembles a benzyl cation. The C_6 carbocation has an electron-deficient center located adjacent to a naphthyl ring and is structurally similar to the 2-naphthylmethylene cation. For comparison, ab initio calculations were also carried out with the benzyl and 2-naphthylmethylene

(18) Molecular mechanics calculations were carried out with PCMODEL-PI, a program available from Serena Software, P.O. Box 3076, Bloomington, IN 47042.

(19) Glusker, J. P.; Carrell, H. L.; Zacharias, D. E.; Harvey, R. G. *Cancer Biochem. Biophys.* **1974**, *1*, 43.

(20) Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986.

(21) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.

(22) Calculations were performed on the IBM 3090-300E vector facility with the GAUSSIAN 86 and 88 programs: (a) Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. GAUSSIAN 88; Gaussian, Inc.: Pittsburgh, PA. (b) Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Baker, J.; Fluder, E. M.; Pople, J. A. *GAUSSIAN 86*; Gaussian, Inc.: Pittsburgh PA. (c) We thank J. Douglas Ashbrook for his time and expertise for the installation of computational chemistry code running on the IBM-3090.

(23) Dewar, J. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(24) Stewart, J. J. P.; Seiler, F. J. *MOPAC*, Ver. 4.0, QCPE No. 560, Indiana University: Bloomington, IN.

Table VI. Relative Energies Calculated for the Carbocations Derived from BA-O, 1-MBA-O, and 12-MBA-O (RHF/STO-3G Bond Lengths and Angles in Supplementary Material)

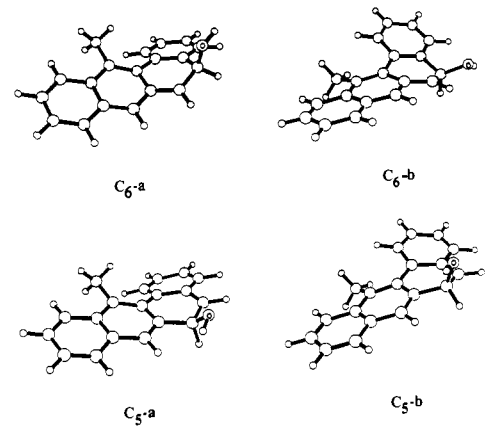
computational level	arene oxide	carbocation conformation	C_{12}–C_{12a}–C_{12b}–C_1 torsional angle	E (rel), kcal/mol
PCMODEL-PI	BA-O	C_6-a	−19	0.4
		C_6-b	21	1.5
		C_5-a	−19	1.4
		C_5-b	17	0.0
	12-MBA-O	C_6-a	−34	5.4
		C_6-b	34	6.3
		C_5-a	−35	1.2
		C_5-b	34	0.0
	1-MBA-O	C_6-a	−34	0.0
		C_6-b	35	1.0
		C_5-a	−33	6.8
		C_5-b	33	5.3
AM1	BA-O	C_6-a	−1.1	2.0
		C_6-b	6.7[a]	0.0
		C_5-a	−0.9	2.3
		C_5-b	1.7	3.0
	12-MBA-O	C_6-a	−24.2[a]	0.8
		C_6-b	27.6	0.0
		C_5-a	−23.9	1.3
		C_5-b	22.3	1.9
	1-MBA-O	C_6-a	−22.7	1.2
		C_6-b	25.0	0.0
		C_5-a	−24.3	0.2
		C_5-b	21.1	1.5
RHF/STO-3G	BA-O	C_6-a	−2.4	0.0
		C_6-b	4.7[a]	0.3
		C_5-a	−3.6	1.4
		C_5-b	2.0	1.2
	12-MBA-O	C_6-a	−29.9	0.0
		C_6-b	29.3	0.3
		C_5-a	−23.3	3.1
		C_5-b	26.0	2.5
	1-MBA-O	C_6-a	−24.7	0.0
		C_6-b	24.1	0.6
		C_5-a	−23.8	1.4
		C_5-b	24.2	1.0

[a] The C^+–C–O–H dihedral angle is not 180°.

cations (Table V). From the isodesmic reaction $C_{10}H_7CH_3 + PhCH_2^+ \rightarrow C_{10}H_7CH_2^+ + PhCH_3$, the differences in resonance stabilization energies are estimated to be 8–9 kcal/mol at several levels of theory. The calculations show a greater stabilization of the 2-naphthylmethylene cation, which would indicate a preference for the C_6 carbocation derived from BA-O, as is experimentally observed (Tables III and IV). On the basis of this rather large difference in calculated resonance energies, the rates of solvolysis of 2-naphthylmethylene substrates might be expected to be significantly greater than those of the corresponding benzyl substrates, in contrast to the actual observations.[14] The solvolysis reactions of simple benzyl and 2-naphthylmethylene substrates proceed with substantial solvent involvement, however, and therefore do not reflect this difference in resonance stabilization energy.

At the highest level of theory (Table VI, RHF/STO-3G), both the C_5 and C_6 carbocations of BA-O were calculated to exist in two conformations of very similar energies and with nearly planar geometries. The two conformations of the C_6 carbocation have the dihedral angle C_{12}–C_{12a}–C_{12b}–C_1 equal to −2.4 and 4.7°. Calculated values of this dihedral angle for the C_5 carbocations of BA-O are −3.6 and 2.0°. These four nearly planar carbocations (bond lengths, angles, and structures given in the supplementary material), unlike the exaggerated structures shown in Scheme III, have their hydroxyl groups and carbinol hydrogens oriented approximately midway between the pseudoaxial and pseudoequatorial environments. In contrast to the calculations for the BA-O cations, ab initio and semiempirical calculations provide structures of the C_5 and C_6 carbocations of 12-MBA-O in which the naphthyl and phenyl rings are twisted substantially from planarity. The C_6 carbocation of 12-MBA-O is calculated at the STO-3G level to have two energy minima, with C_{12}–C_{12a}–C_{12b}–C_1 dihedral angles of −29.9 and 29.3° (structures C_6-a and C_6-b shown in Chart I). For the isomeric C_5 carbocation, the calculated dihedral angles

Chart I. Structures of Carbocations Derived from 12-MBA-O



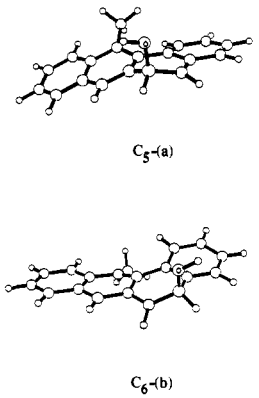
are −23.3 and 26.0° (structures C_5-a and C_5-b in Chart I). Thus, twisting about the naphthyl–phenyl bond relieves steric interactions between the C_{12} methyl group and the C_1 hydrogen. Bond lengths and angles are given in the supplementary material.

The results in Table VI show that the carbocations C_6-a and C_6-b derived from 12-MBA-O are more stable than the carbocations C_5-a and C_5-b by ~2.5 kcal/mol at the ab initio level. In the parent BA-O system, the C_6 carbocations are calculated to be ~1.4 kcal/mol more stable than the C_5 carbocations. Substitution of a methyl group at the 12-position stabilizes the C_6 carbocations relative to the C_5 carbocations and is presumably responsible for the greater yield of products derived from the C_6 carbocation from 12-MBA-O compared to that from BA-O. This conclusion is supported by the AM1 calculations but not by the lower level PCMODEL-PI calculations (Table VI). Another interesting feature of the energetic ordering of the four 12-MBA-O carbocation isomers at the STO-3G level is that the relative energy of the carbocation increases as the C_{12}–C_{12a}–C_{12b}–C_1 dihedral angle decreases.

The effects of a bay-region methyl group on rates and products from substituted BA oxides may also be rationalized by considering the interrelationships between conformers of the reactants and carbocationic intermediates. A particularly striking observation is that bay-region methyl substitution markedly retards or abolishes phenol formation from these arene oxides. A steric effect of the bay-region methyl group that increases the energy barrier for the conformational isomerization of the intermediate carbocations, relative to their capture by solvent, provides an attractive explanation for this observation.

The carbocation C_6-a derived from axial opening of 12-MBA-O conformation a (Scheme IV) is calculated at the STO-3G level to deviate significantly from planarity, with a naphthyl–phenyl dihedral angle of −29.9°. The C_5 hydrogen in this conformation is in a pseudoequatorial position and therefore is not favorably oriented for hydrogen migration to C_6. In order for the C_5 phenol to be formed, carbocation C_6-a must undergo conformational change that places the C_5 hydrogen is in a pseudoaxial position. With use of the PCMODEL-PI program, the H_5–C_5–C_6–H_6 dihedral angle is driven such that the C_5 hydrogen changes from pseudoequatorial to pseudoaxial *without* the C_{12} methyl passing by the C_1 hydrogen. The resulting structure (not shown) is calculated to be ca. 5.5 kcal/mol higher in energy than C_6-a. When the C_{12}–C_{12a}–C_{12b}–C_1 dihedral angle is driven by the PCMODEL-PI program such that the H_{12} of carbocation C_6-a of BA-O or the C_{12} methyl of carbocation C_6-a of 12-MBA-O does pass by the C_1 hydrogen, the pseudoaxial hydroxyl group becomes pseudoequatorial in both carbocations (structure analogous to C_6-b). The calculated energy barriers for the isomerizations are ca. 1 and 5.1 kcal/mol, respectively. This calculated increase of ca. 4 kcal/mol in the energy barrier for the conformational change of the carbocation due to methyl substitution in the bay region of BA is in agreement with an experimental value of 3.8 kcal/mol for the minimum difference in energy barriers for the conformational change of the K-region cis dihydrodiol dimethyl ethers

Chart II



of BA and 12-MBA ($5_{ax},6_{eq} \rightleftharpoons 5_{eq},6_{ax}$), as determined by NMR at the coalescence temperatures of the methyl ether resonances.[25] Although the energy barriers for the conformational change of the dihydrodiol dimethyl ethers are probably different from those of the corresponding carbocations, the effect of a remote substituent at the bay region should be about the same. In both the dimethyl ether and carbocation C_6-a of 12-MBA-O, a planar transition-state structure is required that places the C_{12} methyl and H_1 in close proximity. Therefore, the energy barrier for conversion of C_6-a to C_6-b, in which the C_5 hydrogen is in a pseudoaxial position favorable for migration to C_6, is so high that the reaction of the carbocation C_6-a with solvent is faster than its conformational isomerization to a species that can lead to phenol. A similar large energy barrier for conformational isomerization of C_5-b, the carbocation derived from axial opening of 12-MBA-O conformation b, to C_5-a should inhibit formation of the C_6 phenol from this intermediate.

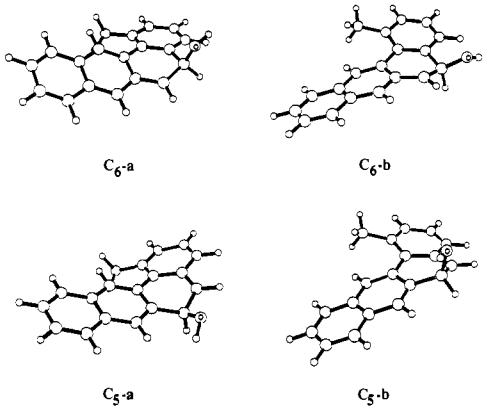
In addition to the axial openings of 12-MBA-O to C_6-a and C_5-b, carbocations C_5-(a) and C_6-(b) (Chart II) could form (from 12-MBA-O conformations a and b, respectively, in Scheme IV) without the naphthyl–phenyl dihedral angle undergoing a change in sign. PCMODEL-PI calculations show that both the C_6-a and C_5-b carbocations are energy minima in which the hydroxyl group is pseudoaxial. In contrast, both the C_5-(a) and C_6-(b) carbocations are high energy structures that minimize to structures in which the newly formed hydroxyl groups are pseudoequatorial and their geminal hydrogens are pseudoaxial. In essence, their formation would constitute equatorial openings of 12-MBA-O. If the acid-catalyzed solvolysis of 12-MBA-O occurred to any significant extent via these carbocations, significant yields of C_5 and C_6 phenols should be expected because the hydrogen α to the carbocation center is favorably oriented for migration in each case. The lack of detectable amounts of phenols from the methanolysis of 12-MBA-O, therefore, suggests that epoxide ring openings via C_5-(a) and C_6-(b) are not important reaction pathways for this arene oxide and that axial epoxide ring openings are energetically preferred in this system.

On axial opening of 12-MBA-O conformation a to produce C_6-a and conformation b to produce C_5-b, the PCMODEL-PI-calculated naphthyl–phenyl torsional angles change from −28 to −34° and from 29 to 34°, respectively. Therefore, the steric interactions between the C_{12} methyl and the C_1 hydrogen are similar or perhaps lessened slightly on ring opening. A concerted process involving ring opening and conformational inversion that occurs more or less simultaneously to give, for example, C_6-b from 12-MBA-O conformation a, would be subject to the same steric constraints as the stepwise mechanism described and thus also appears improbable.

Mechanisms similar to that described for 12-MBA-O can be invoked to account for the substituent effects and lack of phenolic products in the acid-catalyzed hydrolysis and methanolysis of 1-MBA-O and 7,12-DMBA-O. For example, axial opening of the conformational isomers of 1-MBA-O (structures not shown) is expected to give the 1-MBA-O carbocations C_5-b and C_6-a, which cannot readily isomerize to conformations C_5-a and C_6-b, respectively, the carbocations required for hydrogen migration and phenol formation. Bond lengths and angles for the four 1-MBA-O carbocations shown in Chart III are given in the supplementary material.

(25) Nashed, N. T.; Bax, A.; Loncharich, R. J.; Jerina, D. M. Manuscript in preparation.

Chart III. Structures of Carbocations Derived from 1-MBA-O



Summary and Conclusions

Results of the present study indicate that hydronium ion catalyzed solvolysis reactions of methyl-substituted, K-region BA oxides in aqueous solution and in methanol are mechanistically analogous, in that both rates and product distributions show similar trends. Use of methanol as a solvent makes possible complete elucidation of the regiochemistry of epoxide ring opening. Our most significant new conclusion is that the effect on product distribution of methyl substitution in the bay region or at a position peri to the epoxide group cannot be explained solely on the basis of electronic effects upon the intermediate carbocations and must involve significant steric effects. In particular, we propose that the initially formed carbocation, in which the hydroxyl group is in a pseudoaxial conformation, must undergo conformational isomerization to a carbocation with a pseudoequatorial hydroxyl group and a pseudoaxial hydrogen to yield phenol. A methyl substituent in the bay region (positions 1 and 12 of BA) or a position peri to the carbocation hydroxyl group increases the energy barrier for the conformational isomerization step relative to reaction with solvent, with the result that addition products predominate from those cations. A methyl substituent in a position peri to the hydroxyl group of the carbocation causes unfavorable steric interaction in the conformation of the carbocation in which the hydroxyl group is pseudoequatorial as well as in the transition state for the conformational inversion process that leads to this intermediate. Although the two conformational isomers of the carbocations with methyl substituents at the bay region are of comparable energy, conformational isomerization of either the C_5 or C_6 cation requires that a bay-region hydrogen and the methyl group pass by each other, thereby generating a highly unfavorable steric interaction in the transition state for this step.

Experimental Section

Materials and Methods. NMR spectra were determined in $CDCl_3$ at 300 MHz unless otherwise indicated. Racemic and optically active K-region arene oxides, cis dihydrodiols, and trans dihydrodiols of BA[26] and DMBA[27,28] were prepared as described, as was *cis*-5,6-dihydroxy-5,6-dihydro-7-bromobenz[*a*]anthracene.[29] Syntheses of 7-MBA and 12-MBA staring from 2-carboxybenzaldehyde (Aldrich Chemical Co.)

(26) Armstrong, R. N.; Kedzierski, B.; Levin, W.; Jerina, D. M. *J. Biol. Chem.* **1981**, *256*, 4726.
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(28) Balani, S. K.; Yeh, H. J. C.; Ryan, D. E.; Thomas, P. E.; Levin, W.; Jerina, D. M. *Biochem. Biophys. Res. Commun.* **1985**, *130*, 610.
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or 2-carboxyacetophenone[30] (generously provided by Professor M. S. Newman), respectively, and naphthalene were as described.[30-32] Optically active dihydrodiols were obtained by chromatographic separation of their diesters with (−)-(menthyloxy)acetic acid ((−)-MOA), (−)-*O*-methylmandelic acid,[33] or (−)-α-methoxy(trifluoromethyl)phenylacetic acid ((−)-MTPA) prepared as described[27] unless otherwise indicated. Free dihydrodiols were liberated by hydrolysis with NaOH in aqueous methanol–THF.[27] All chiral HPLC was done on an (*R*)-(dinitrobenzoyl)phenylglycine column (0.46 × 25 cm, Type 1-A, ionic from Regis Chemical Co.).

Kinetics. All kinetics were measured spectrophotometrically at 25 ± 0.2 °C. Dioxane was distilled from sodium and stored frozen. Solutions of 1:9 dioxane–water (v/v) containing either 0.1 M $NaClO_4$ or 0.5 M KCl were adjusted to the requisite pH with acid or 1–2 mM buffer. Buffers used were acetic acid, 3-(*N*-morpholino)-2-hydroxypropanesulfonic acid, *N*-(2-hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid), 2-(*N*-cyclohexylamino)ethanesulfonic acid, 2-(*N*-morpholino)ethanesulfonic acid, or 3-(cyclohexylamino)-1-propanesulfonic acid. Reaction was initiated by the addition of substrate in dioxane (5–15 μL, ca. 1 mg/mL) to 2.0 mL of reaction medium. Change in absorption was monitored at 271 nm for BA-O, 270 nm for 1-MBA-O, 271.5 nm for 4-MBA-O, 274 nm for 7-MBA-O, 273.5 nm for 11-MBA-O, 272.5 nm for 12-MBA-O, and 276 nm for 7,12-DMBA-O. Methanol was freshly distilled from benzoic acid before use to remove any basic contaminants. The acid-catalyzed methanolysis of arene oxides were monitored by following the decrease in absorption at 269 nm for BA-O and 1-MBA-O, 270 nm for 4-MBA-O, 271 nm for 12-MBA-O, 272 nm for 11-MBA-O, 273 nm for 7-MBA-O and 7-BrBA-O, and 275 nm for 7,12-DMBA-O. Reaction was initiated by the addition of substrate in acetonitrile (20 μL) to 1 mL of methanol containing 0.010–1.20 mM ethanesulfonic acid and monitored for 8–10 half-lives. In all cases, plots of the pseudo-first-order rate constants (10 or more determinations) versus acid concentrations were linear. Second-order rate constants were determined from the slopes of the least-squares lines obtained from plots of k_{obsd} vs acid concentrations.

Polycyclic Aromatic Hydrocarbons. 1-, 4-, and 11-MBA[34,35] were prepared from 3,4-dihydrobenz[*a*]anthracen-1(2*H*)-one (Aldrich), 1,2-dihydrobenz[*a*]anthracen-4(3*H*)-one,[34,36] and 5,6,8,9-tetrahydrobenz-[*a*]anthracen-11(10*H*)-one (Aldrich), respectively, by addition of methyl Grignard to the ketone, dehydration of the resulting carbinol, and dehydrogenation to the fully aromatic hydrocarbon. Typically, 16.5 mL of 3 M methylmagnesium bromide was added dropwise over 30 min to a solution of ketone (10 mmol) in anhydrous ether (50 mL) at 0 °C. After standard workup, the carbinol was dissolved in warm benzene (50 mL) containing *p*-toluenesulfonic acid monohydrate (100 mg). The benzene solution was kept at 50 °C for 15 min. Workup provided a mixture of the exo- and endocyclic double-bonded compounds, which were redissolved in benzene (100 mL) containing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3–6 g). After heating at reflux for 3 h and standard workup, the product was chromatographed on silica gel that was eluted with 20% benzene in hexane. Each hydrocarbon gave MS (CI, NH_3) *m/z* 243 (MH^+). 1-MBA (34% yield): NMR δ 9.38 (s, H_{12}), 8.38 (s, H_7), 3.28 (s, CH_3). 4-MBA (80% yield): NMR δ 9.16 (s, H_{12}), 8.71 (d, H_1, J = 8.3 Hz), 8.35 (s, H_7), 2.74 (s, CH_3). 11-MBA (66% yield): NMR δ 9.34 (s, H_{12}), 8.89 (d, H_1, J = 8.2 Hz), 8.37 (s, H_7), 2.95 (s, CH_3).

K-Region cis Dihydrodiols. The hydrocarbons 1-, 4-, 7-, 11-, and 12-MBA were converted to osmate esters, which were decomposed to cis dihydrodiols with sodium bisulfite by standard procedures.[37,38] In a typical synthesis, a solution of the hydrocarbon (0.95 g, 3.9 mmol) and osmium tetroxide (1 g, 3.9 mmol) in pyridine (15–20 mL, distilled from calcium hydride) was stirred at room temperature for 1 week. After addition of aqueous sodium bisulfite and standard workup, the crude product was chromatographed on a silica gel column (15 × 2.5 cm), eluted initially with chloroform to remove the unreacted hydrocarbon followed by elution with 2% methanol in chloroform, to provide the pure cis dihydrodiol in 65–85% yield: MS (CI, NH_3) *m/z* 294 (MH_4N^+, ~20), 276 ($MH_4N^+ - H_2O$, ~20), 259 ($MH^+ - H_2O$, 100), except for the cis dihydrodiol of 1-MBA for which the base peak was *m/z* 294. Diagnostic NMR signals for all cis dihydrodiols used in the present study are provided in the supplementary material.

K-Region trans Dihydrodiols. Diagnostic NMR signals ($CDCl_3$ and CD_3CN) for all trans dihydrodiols used in the present study are provided in the supplementary material. For 1-, 4-, and 11-MBA, the trans dihydrodiols were isolated and characterized from hydrolysis products of the corresponding arene oxides on the basis of their HPLC separation from and UV spectra nearly identical with that of the cis isomer as well as their NMR spectra. The trans dihydrodiols of 7- and 12-MBA were synthesized by initial oxidation of the cis dihydrodiols to K-region quinones with pyridinium chlorochromate.[39,40] This reagent was selected since it limits the extent of cleavage of the K-region bond to form dialdehydes.[41] Typically, pyridinium chlorochromate (1 g) was added portionwise over 1 h to a stirred mixture of cis dihydrodiol (0.3 g) and sodium acetate (0.3 g) in dichloromethane (50 mL) at room temperature. After filtration through a pad of silica gel, NMR spectra indicated complete conversion to a ca. 2:1 mixture of quinone and dialdehyde. Crystallization from acetone provided pure quinones: MS (CI, NH_3) *m/z* 290 (MH_4N^+), 273 (MH^+). 5,6-quinone of 7-MBA: NMR (THF-d_8) δ 8.57 (s, H_{12}), 3.05 (s, CH_3). 5,6-quinone of 12-MBA: NMR ($CDCl_3$) δ 8.62 (s, H_7), 3.02 (s, CH_3). Reduction of the quinones to trans dihydrodiols with potassium borohydride was as described.[41] In the case of 12-MBA, only the trans dihydrodiol ($\epsilon_{266\,nm}$ = 43 000) after elution from silica gel with 2% methanol in chloroform was produced, whereas both the cis and trans dihydrodiols (ca. 2:1) were formed on reduction of the 5,6-quinone of 7-MBA. The MS (CI, NH_3) for the trans dihydrodiols were quite similar to those of their cis isomers where comparisons were made.

Resolution of the trans dihydrodiols of 12-MBA was achieved both by separation of their diastereomeric diesters with (−)-MOA and by chiral HPLC (see hydrolysis of optically active 12-MBA-O). The diesters were separated on a Du Pont Zorbax SIL column (0.94 × 25 cm) eluted with 5.5% ether in cyclohexane at a flow rate of 6 mL/min as oils: MS (CI, NH_3) *m/z* 686 (MH_4N^+). k'_{early} = 1.72 for the 5*R*,6*R* diastereomer with $[\alpha]_D$ −167°. Free dihydrodiol (elutes late on chiral HPLC) has $[\alpha]_D$ 89°. k'_{late} = 1.96 for the 5*S*,6*S* diastereomer with $[\alpha]_D$ 29°. Free dihydrodiol (elutes early on chiral HPLC) has $[\alpha]_D$ −94°. Concentrations (*c* 0.7, THF) for rotations are based on the value of $\epsilon_{266\,nm}$ for the trans dihydrodiol. NMR spectra (C_6D_6) of both diastereomers showed the 12-CH_3 at δ 2.62, H_7 at δ 7.99, and $H_{5/6}$ at δ 6.41/6.57 with $J_{5,6}$ = 5.1 Hz. The pair of $-OCH_AH_BCO_2-$ groups in the early-eluting diastereomer appeared as a two-proton singlet at δ 3.73 and a pair of doublets at δ 3.67 and 3.74 with J_{gem} = 16.3 Hz; the late-eluting diastereomer showed four doublets centered at δ 3.64, 3.67, 3.80, and 3.83 with J_{gem} = 16.2, 17.0, 17.0, and 16.2 Hz, respectively. Correlation of physical properties[41] for the less polar diastereomer (more negative $[\alpha]_D$ for diastereomer leading to (+) dihydrodiol with less magnetic nonequivalence for H_AH_B) suggests 5*R*,6*R* absolute configuration. Definitive assignment of absolute configuration was achieved through comparison of CD spectra of the resolved trans dihydrodiols of 12-MBA and the previously assigned trans dihydrodiols of BA.[42] The shapes of these CD spectra are determined by the skew sense of their "biphenyl-like" chromophores, which in turn is determined by the conformation of the dihydrodiols, which can be solvent-dependent. NMR spectra (CD_3OD) of the trans 5,6-dihydrodiols of BA ($H_{5/6}$ at δ 4.66/4.74, $J_{5/6}$ = 8.8 Hz) and 12-MBA ($H_{5/6}$ at δ 4.47/4.54, $J_{5/6}$ = 9.3 Hz) indicate nearly identical conformations. CD spectra (CH_3OH) of the (+)-trans 5,6-dihydrodiols from the two hydrocarbons show strong positive bands in the region of 235–240 nm, indicating 5*R*,6*R* absolute configuration for both. Although this correlation had been made earlier,[43] the conclusion was suspect since the NMR and CD spectra were compared in different solvents. Recently, the CD spectrum of the (5*S*,6*S*)-dihydrodiol as its diester with *p*-(*N*,*N*-dimethylamino)benzoic acid has been described.[44] Although an exciton interaction between the ester groups was suggested, the spectrum did not show the requisite, symmetric bands. As the reported spectrum is nearly identical with that of the same diester of the trans (9*S*,10*S*)-dihydrodiol of phenanthrene,[42] the conclusion[44] regarding absolute configuration turns out to be correct.

Since the cis and trans dihydrodiols of 7-MBA were not easily separable on silica-based HPLC due to extreme peak broadening for the

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cis isomer, the mixture was esterified with (−)-MOA. HPLC on a Du Pont Zorbax SIL column (0.94 × 25 cm) eluted with 8% ether in hexane provided a good separation of the cis from the trans diastereomers. The cis diastereomers (k'_{early} = 2.07, k'_{late} = 2.43) were not pursued, as they were more easily separated as their (−)-MTPA diesters (see chiral 7-MBA-O synthesis). The trans diastereomers as oils: MS (EI) m/z 668 (M^+). k'_{early} = 3.48 for 5*R*,6*R* diastereomer with $[\alpha]_D$ −288°. Free dihydrodiol (elutes early on chiral HPLC) has $[\alpha]_D$ −292°. k'_{late} = 3.78 for 5*S*,6*S* diastereomer with $[\alpha]_D$ +90°. Free dihydrodiol (elutes late on chiral HPLC) has $[\alpha]_D$ 264°. Rotations (*c* 0.5) are in THF for the dihydrodiols and methanol for the diastereomers (signs unchanged in THF). The late-eluting diastereomer and resulting dihydrodiol contained ca. 5–7% of the other stereoisomer. For chiral HPLC conditions, see hydrolysis of optically active 7-MBA-O. NMR spectra (benzene-d_6) for both diastereomers showed the 7-CH_3 δ 2.68, H_{12} at 8.08, and H_5 at ca. 6.56 with $J_{5,6}$ = 3.4 Hz. The signal for H_6 was shifted downfield and obscured in the aromatic multiplet. The pair of $-OCH_AH_BCO_2-$ groups in the early-eluting diastereomer appeared as a 2 H singlet at δ 3.55 and a pair of doublets at δ 3.61 and 3.70, whereas the late-eluting diastereomer showed two pairs of doublets at δ 3.46 and 3.66 and at δ 3.60 and 3.72, all with J_{gem} = 16.3 Hz. Correlation[41] of elution order, degree of magnetic nonequivalence for the $-OCH_AH_BCO_2-$ groups, and rotations for the diastereomers and free dihydrodiols (note axial hydroxyl groups) all indicate the assigned absolute configurations. In addition, the strong, negative CD band at ca. 240 nm for the 7-MBA (−) dihydrodiol has been utilized to assign 5*R*,6*R* absolute configuration to this enantiomer[45] by correlation of its CD spectrum with that of 7-BrBA, which was reduced to the (+)-trans (5*R*,6*R*)-dihydrodiol of BA.[42]

Dihydrodiol Monomethyl Ethers. Acid-catalyzed methanolysis of arene oxides produced cis and trans pairs of regioisomeric methanol adducts (dihydrodiol monomethyl ethers). The four stereoisomers from each arene oxide were readily separated by HPLC (supplementary material). Partial methylation of all cis and selected trans dihydrodiols (CH_3I and NaH in THF)[25,27] provided reference standards with which cis and trans methanol adducts were readily distinguished. A combination of NMR techniques and chemical methods described elsewhere[25] were utilized to distinguish between methanol adducts at C_5 versus C_6.

K-Region Phenols. Diagnostic NMR signals for all K-region phenols (and their *O*-methyl ethers) produced as solvolysis products of the corresponding arene oxides are provided in the supplementary material. K-Region phenols of BA were prepared as described.[46] For 1-, 4-, 7-, and 11-MBA, the corresponding cis dihydrodiols (10–20 mg) were allowed to dehydrate in 1:1 trifluoroacetic acid–dichloromethane (10 mL) for 1 h at room temperature. In the cases of 4- and 7-MBA, single isomers were produced (HRMS (m/z) calcd for $C_{19}H_{14}O$ 258.1045, found 258.1041 and 258.1040, respectively). Comparison of the NMR spectra of 5- and 6-HO-BA indicates that a hydrogen peri to the phenolic hydroxyl group will be shifted downfield ca. 0.4–0.6 ppm. A similar observation had been made for the isomeric phenols of benzo[*a*]pyrene.[47] In the 4-MBA case, the signal for H_7 appears at δ 8.8, indicating the isomer to be 6-HO-4-MBA. In the case of 7-MBA, the signal for H_4 of the phenol is not easily identified, as it is in the aromatic multiplet. However, this phenol was readily characterized as 5-HO-7-MBA by comparison of its *O*-methyl ether (produced by treatment of the phenol with diazomethane in ether) with the sole product (5-CH_3O-7-MBA) formed on dehydration of *trans*-5-methoxy-6-hydroxy-7-MBA with BF_3 etherate: NMR ($CDCl_3$) δ 2.97 (7-CH_3), 4.09 (5-OCH_3), 7.18 (H_6), 7.4–7.8 (aromatic, 7 H), 8.75 (d, J = 7.9 Hz, H_1), 8.95 (H_{12}); HRMS (m/z) calcd for $C_{20}H_{16}O$ 272.1201, found 272.1191. Although 5-CH_3O-7-MBA has been reported,[48] NMR data were not given.

Structures of the positionally isomeric K-region phenols as well as their *O*-methyl ethers from 1-, 11-, and 12-MBA were easily assigned on the basis of the downfield shift of H_7 when the oxygen substituent was at C_6. For both 1- and 11-MBA, a pair of isomeric K-region phenols were obtained on dehydration of the cis dihydrodiols. Due to chemical instability, they were O-methylated by treatment with 5 mL of 0.25 M diazomethane in ether for 10 min. The isomeric methyl ethers were separated on an Axxiom silica gel column (1 × 25 cm) eluted with 1% dichloromethane in hexane. 5-CH_3O-1-MBA: 50%; k' = 4.06; HRMS calcd for $C_{20}H_{16}O$ 272.1201, found 272.1186. 6-CH_3O-1-MBA: 50%; k' = 4.28; HRMS calcd for $C_{20}H_{16}O$ 272.1201, found 272.1203. 5-CH_3O-11-MBA: 79%; k' = 5.26; HRMS calcd for $C_{20}H_{16}O$ 272.1201, found 272.1191. 6-CH_3O-11-MBA: 21%; k' = 5.51; HRMS calcd for $C_{20}H_{16}O$ 272.1201, found 272.1196. Phenols of 12-MBA were prepared by isomerization of 12-MBA-O (2 mg) in 1 mM ethanesulfonic acid in acetonitrile (10 mL). After O methylation with diazomethane, the methyl ethers were separated on the Axxiom column eluted with 8% dichloromethane in hexane. 5-CH_3O-12-MBA: 90%; k' = 2.62; HRMS calcd for $C_{20}H_{16}O$ 272.1201, found 272.1206. 6-CH_3O-12-MBA: 10%, k' = 2.79, HRMS calcd for $C_{20}H_{16}O$ 272.1201, found 272.1196. The isomeric K-region phenol methyl ethers were smoothly O-demethylated on treatment with 50% trifluoroacetic acid in dichloromethane at room temperature for 7 h, except for those of 12-MBA where the phenols proved to be unstable.

K-Region Arene Oxides. The orthoester procedure,[49] in which cis dihydrodiols are converted to arene oxides, was used for preparation of all arene oxides in overall yields of ca. 40%. All arene oxides showed the expected MS (CI,NH_3) MH^+, and their NMR spectra are given in the supplementary material.

For chiral oxides of 7-MBA, the diastereomeric (−)-MTPA diesters of the cis dihydrodiol were separated on a Rainin-Microsorb silica gel column (1 × 25 cm) eluted with 1:1 dichloromethane and hexane at a flow rate of 10 mL/min. Isolated yields were 53% for each diastereomer. k'_{early} = 0.77 for 5*S*,6*R* diastereomer with $[\alpha]_D$ −74°. Free dihydrodiol (late, 21.70 min on chiral HPLC) has $[\alpha]_D$ −135°. k'_{late} = 1.19 for 5*R*,6*S* diastereomer with $[\alpha]_D$ −22°. Free dihydrodiol (early, 20.57 min on chiral HPLC) has $[\alpha]_D$ 127°. The NMR ($CDCl_3$) signal for H_6 was obscured in the aromatic multiplet for both diastereomers while H_5 appeared at δ 6.53 and 6.45 with $J_{5,6}$ = 2.1 Hz for early and late, respectively. Rotations are in methanol (*c* 1), and chiral HPLC was as described below for hydrolysis. The (+)-cis (5*R*,6*S*)-dihydrodiol has a strong, positive CD band at 240 nm as does the (+)-trans-(5*S*,6*S*)-dihydrodiol. Since steric hindrance due to the 7-CH_3 group requires the 6-OH group in both the cis and trans dihydrodiols to be axial, the skew sense of their chromophores must be the same, and both must have 6*S* substituents. The same assignment for the cis dihydrodiols had been made earlier,[50] but supporting data were not presented.

(+)-(5*S*,6*R*)-oxide from the (−)-cis dihydrodiol: $[\alpha]_D$ +142°, late, 30.55 min on chiral HPLC. (−)-(5*R*,6*S*)-oxide from the (+)-cis dihydrodiol: $[\alpha]_D$ −134°, early, 29.21 min on chiral HPLC. Rotations (*c* 1) are in THF, and the chiral column was eluted at 1 mL/min with 0.7% ethanol and 0.3% acetonitrile in hexane. The weak, positive CD bands at 260 and 320 nm for (+)-7-MBA (5*S*,6*R*)-oxide and (+)-BA (5*S*,6*R*)-oxide[26] had been previously used as a basis of configurational assignment.[51] Absolute configurations of the 7-MBA oxide and trans dihydrodiol were cross-correlated by addition of methoxide (4 M NaO-CH_3 in methanol, 7 h, room temperature) to the (+)-(5*S*,6*R*)-oxide to provide samples of (5*R*)-methoxy-(6*R*)-hydroxy adduct (35%, early on silica) and (5*S*)-hydroxy-(6*S*)-methoxy adduct (65%, late on silica). Enantiomers of these adducts (prepared by O methylation of optically active dihydrodiol) are separable on the chiral HPLC column eluted with 6% ethanol and 3% acetonitrile in hexane at 2 mL/min. The *trans*-5-methoxy-6-hydroxy adducts elute at 10.78 (5*R*,6*R*) and at 11.57 (5*S*,6*S*) min, and the *trans*-5-hydroxy-6-methoxy (late enantiomers on silica) at 11.67 (5*R*,6*R*) and 12.76 (5*S*,6*S*) min. The methanol adducts from the (+)-(5*S*,6*R*)-oxide chromatographed with the early 5-methoxy enantiomer and late 6-methoxy enantiomer, respectively, as was required.

For chiral oxides of 12-MBA, the diastereomeric (−)-*O*-methylmandelate diesters of the cis dihydrodiol were separated on a Du Pont Zorbax SIL column (0.94 × 25 cm) eluted with 10% ethyl acetate in hexane. Notably, diesters with either (−)-MOA or (−)-MTPA failed to provide adequate separations. Isolated yields were 85% for each diastereomer with MS (CI, NH_3) m/z 590 (MH_4N^+). k'_{early} = 3.34 for 5*S*,6*R* diastereomer with $[\alpha]_D$ −144°. Free dihydrodiol (early, 20.20 min on chiral HPLC) has $[\alpha]_D$ 61°. k'_{late} = 4.44 for 5*R*,6*S* diastereomer with $[\alpha]_D$ −57°. Free dihydrodiol (late, 21.40 min on chiral HPLC) $[\alpha]_D$ −60°. The NMR ($CDCl_3$) signals for $H_{5/6}$ were at δ 6.09 and 6.42 and at δ 6.03 and 6.23 as singlets for the early- and late-eluting diastereomers, respectively. Temperature-dependent NMR studies indicated that more than two conformations of the diastereomers were in equilibrium near room temperature. Rotations are in THF (*c* 1, similar values in methanol), and chiral HPLC was as described below for hydrolysis. The (−)-cis (5*R*,6*S*)-dihydrodiol has a weak, negative CD band at 230 nm. Yang et al.[52] have assigned absolute configurations to these cis di-

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hydrodiols on the basis of an exciton chirality CD spectrum of their 7-bromo derivatives as diesters with *p*-(*N*,*N*-dimethylamino)benzoic acid. (+)-(5*S*,6*R*)-Oxide from the (+)-cis dihydrodiol: $[\alpha]_D$ 137°, early, 11.10 min on chiral HPLC. (−)-(5*R*,6*S*)-Oxide from the (−)-cis dihydrodiol: $[\alpha]_D$ −130°, late, 11.60 min on chiral HPLC. Rotations (*c* 0.5) are in THF, and the chiral column was eluted at 2 mL/min with 0.7% ethanol and 0.3% acetonitrile in hexane. The (+)-(5*S*,6*R*)-oxide has a weak, positive CD band at 245 and a weak negative band at 270 nm. An initial tentative assignment of configuration for the arene oxide enantiomers[51] was later corrected[44] to the assignments given here, and the arene oxide enantiomers were correlated with the trans dihydrodiol enantiomers as above for 7-MBA-O.

Products of Solvolysis. Yields of Methanolysis Products in Acid. A solution of arene oxide (1–10 mg) in acetonitrile (1–3 mL) was added to 1 mM ethanesulfonic acid in methanol (30 mL) under nitrogen at room temperature. The solution was stirred for 6–8 half-lives, and reaction was terminated by the addition of ethyl acetate and water (100 mL each). Prompt workup and analysis (NMR, $CDCl_3$) precluded product decomposition. Products consisted of phenols resulting from isomerization as well as pairs of regioisomeric cis and trans methanol adducts. The amount of K-region phenols formed was determined by integration of the signals for the H_5 or H_6 protons. Since these protons are ortho to the phenolic hydroxyl groups, their signals are upfield from the aromatic multiplet of the product mixture. In the case of 6-HO-4-MBA-O and 5-HO-7-MBA, the signals for H_5 and H_6, respectively, due to deshielding by the adjacent methyl group, lie within the aromatic multiplet of the product mixture. Thus, the signals for H_1 and H_{12} were utilized. For the regioisomeric pairs of cis and trans methanol adducts, integration of the signals for H_5 and H_6 (ring carbinol or ether) allowed quantitation. Relative intensities of the methyl ether signals provided additional confirmation of adduct ratios as did peak areas for these adducts on HPLC (267–270 nm). Details of the NMR spectra (phenols) and chromatographic conditions (adducts) are provided in the supplementary material. Results are in Table IV.

Hydrolysis of Optically Active Arene Oxides. Reactions were run in 1 L of 10% dioxane in water (v/v) containing 0.1 M $NaClO_4$ at 25 °C. For acid-catalyzed hydrolysis, pH was adjusted to ca. 4.3 with $HClO_4$ while 1 mM Tris–perchlorate buffer was used at pH ca. 9.0 for reactions in the spontaneous region. Solutions of 1–2 mg of >98% optically pure arene oxide in 1 mL of dioxane were added dropwise over 1 min to the stirred solvent. The (+)-5*S*,6*R* enantiomers were used for BA-O, 7-MBA-O, and 12-MBA-O, and the (−)-5*R*,6*S* enantiomer was used for 7,12-DMBA. After 6–8 half-lives (from 4 min for 7,12-DMBA to 30 min for BA-O in acid and from 3.3 h for 7,12-DMBA to 48 h for BA-O and 7-MBA-O at pH 9.0; see Table I), the solutions were adjusted to pH 7, saturated with salt, and extracted twice with 70 mL of dichloromethane. The combined organic phase was dried with sodium sulfate and concentrated for analysis. Products were identified by comparison of retention time on HPLC and UV spectra with standards. Ratios of cis to trans dihydrodiols were determined at the indicated wavelengths. Other products were not quantified, as no attempts were made to ensure stability of phenols. Enantiomer ratios for trans dihydrodiols, which arise by inversion at C_5 or C_6, are given in Table III. Enantiomer ratios for cis dihydrodiols were within 1% of those of the starting arene oxides as expected.

a. Benz[*a*]anthracene 5,6-Oxide. Analytical HPLC (270 nm) was done on a Perkin-Elmer HS-3 C_{18} column eluted at 1.7 mL/min with 15% methanol and 25% acetonitrile in water for 15 min followed by a linear gradient to 20% methanol and 40% acetonitrile at 25 min: cis dihydrodiol, 12.3 min; trans dihydrodiol, 13.1 min; 5,6-quinone, 21 min; and 5/6-phenols, 26 min. The ratio of trans to cis dihydrodiols was 1:1 and >99:1 for the acid and spontaneous reactions, respectively. The trans (3.13 min) and cis dihydrodiols (4.88 min) were isolated with a Perkin-Elmer HS-3 silica column eluted with 1.5% methanol and 15% ethyl acetate in hexane at 2.0 mL/min. Enantiomer compositions of the trans dihydrodiols were determined[42] by analysis of their (−)-MOA diesters. The cis dihydrodiol isolated from the acid reaction was 100% 5*S*,6*R*, which gives the more polar or later eluting diester with (−)-MTPA.[26]

b. 7,12-Dimethylbenz[*a*]anthracene 5,6-Oxide. Analytical HPLC (270 nm) was done on a Perkin-Elmer HS-3 C_{18} column eluted with 70% methanol in water for 7 min, followed by a linear gradient to 100% methanol over 6 min at a flow rate of 1 mL/min: trans dihydrodiol, 1.7 min and cis dihydrodiol, 4.3 min. The ratio of trans to cis dihydrodiols was 83:17 and >98:2 for the acid and spontaneous reactions, respectively. Dihydrodiols were preparatively isolated on a Du Pont Zorbax SIL column (0.95 × 25 cm) eluted with 5% methanol and 15% ethyl acetate in hexane at a flow rate of 9.6 mL/min: cis, 4.2 min and trans, 6.7 min. Enantiomer compositions were determined by converting the dihydrodiols to their diesters with (−)-MTPA chloride (75 mg of acid chloride in 0.2 mL of pyridine at room temperature overnight, standard workup). The trans diastereomers were separated on a Perkin-Elmer HS-3 silica column eluted with 40% dichloromethane in hexane at a flow rate of 2.0 mL/min: (5*R*,6*R*)-diester, 5.0 min and (5*S*,6*S*)-diester, 6.1 min. Assignment is based on order of elution for diesters prepared from the known enantiomers.[41] The cis diastereomers[27,53] were separated under the same conditions except that 35% dichloromethane in hexane was utilized: (5*S*,6*R*)-diester, 3.4 min and (5*R*,6*S*)-diester, 4.0 min. Both reactions gave cis dihydrodiol that was greater than 97% (5*R*,6*S*)-enantiomer.

c. 7- and 12-Methylbenz[*a*]anthracene 5,6-Oxides. The chiral HPLC column was eluted at 2.0 mL/min with hexane containing 10% of a 2:1 mixture of ethanol and acetonitrile, and effluent was monitored at 267 nm. Standards for products from 7-MBA-O chromatographed as follows: 5-hydroxy (11.34 min), cis (5*R*,6*S*)-dihydrodiol (20.80 min), cis (5*S*,6*R*)-dihydrodiol (22.19 min), trans (5*R*,6*R*)-dihydrodiol (28.52 min), and trans (5*S*,6*S*)-dihydrodiol (30.13 min). For the acid reaction, the ratio of cis to trans dihydrodiol was 48:52. Standards for products from 12-MBA-O chromatographed as follows: trans (5*S*,6*S*)-dihydrodiol (11.68 min), trans (5*R*,6*R*)-dihydrodiol (12.97 min), cis (5*S*,6*R*)-dihydrodiol (20.20 min), and cis (5*R*,6*S*)-dihydrodiol (21.40 min). For the acid reaction, the ratio of cis to trans dihydrodiol was 15:85. No cis dihydrodiol was detected in the spontaneous reaction of either arene oxide.

Yields of Hydrolysis Products in Acid. BA-O and its methyl-substituted derivatives were allowed to react at pH 3.0 for 10 min in 1 L of 1:9 dioxane–water essentially as described above for optically active compounds. Prompt workup followed by immediate determination of the NMR spectrum (CD_3CN for all but 7-MBA-O where $CDCl_3$ was used) of the product mixture allowed quantitation of all products, including labile phenols. Analysis of NMR spectra was as described above for methanolysis products except that dihydrodiols were quantified by integration of peak areas for carbinol signals. Results are given in Table III. Details of the NMR spectra are provided in the supplementary material.

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Supplementary Material Available: Figures showing pH–rate profiles for the hydrolysis of 12-MBA-O, 7-MBA-O, and 7,12-DMBA-O in 1:9 dioxane–water in the presence of 0.5 M NaCl or 0.1 M $NaClO_4$ at 25 °C, five tables that contain selected NMR data for K-region cis and trans dihydrodiols, arene oxides, phenols, phenol *O*-methyl ethers, and HPLC conditions for separation of mono- and di-*O*-methyl ethers of dihydrodiols, geometries of benzyl cation, 2-naphthylmethylene cation, toluene, and 2-methylnaphthalene, which are given at the STO-3G, 3-21G, and 6-31G* basis levels, and geometries of both conformational isomers a and b of the C_5 and C_6 carbocations derived from BA-O, 1-MBA-O, and 12-MBA-O at the STO-3G level (16 pages). Ordering information is given on any current masthead page.

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