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Acid-Catalyzed Aromatizations of Arene Oxides and Arene Hydrates: Are Arene Oxides Homoaromatic?

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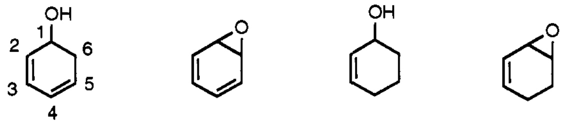
Abstract: Measurements are reported of rates of acid-catalyzed dehydration of water adducts (hydrates) of benzene, naphthalene, anthracene, and phenanthrene. Benzene hydrate (2,4-cyclohexadienol) reacts in aqueous acetic acid buffers and is subject to specific acid catalysis consistent with rate-determining formation of a cyclohexadienyl cation intermediate which is rapidly deprotonated to benzene. The mechanism of dehydration differs from that of simple alcohols for which deprotonation of the carbocation is rate-determining, reflecting the lower stability of an alkene than an arene product. For 9,10-phenanthrene hydrate (9,10-dihydro-9-hydroxyphenanthrene), product studies from solvolysis of 9-phenanthryl carboxylate esters show that an appreciable fraction (20%) of the 9-phenanthrenonium ion intermediate reforms the hydrate in competition with deprotonation. This indicates that deprotonation is partially rate-determining in the dehydration reaction, consistent with the smaller gain in resonance energy accompanying the formation of phenanthrene rather than benzene or naphthalene as products. Relative reactivities of arene hydrates are strongly influenced by benzoannelation: benzene hydrate is 500 times more reactive than 1-hydroxy-1,2-dihydronaphthalene (α-naphthalene hydrate) which is 100 times more reactive than 9,10-phenanthrene hydrate. This reactivity order reflects relative stabilities of carbocation intermediates and hydrate reactants. Comparison of benzene hydrate with benzene oxide shows, surprisingly, that the hydrate is more reactive toward acid despite acid-catalyzed carbon–oxygen bond breaking in simple epoxides occurring 10^6–10^7 times more readily than in structurally related alcohols. For a series of arene oxides and hydrates, oxide/hydrate aromatization rate ratios are inversely related to the resonance energy of the aromatized ring. This behavior is tentatively ascribed to homoaromatic stabilization of the arene oxides.

Introduction

Arene hydrates are water adducts of aromatic molecules which may be prepared by chemical[2-5] or enzymatic synthesis, including microbial oxidation of dihydroaromatic substrates.[6] In the presence of acids, they undergo dehydration and aromatization. In a previous paper, the mechanism of this reaction was investigated for three isomeric hydrates of naphthalene and the reactivities of these substrates were compared with those of aralkyl alcohols undergoing analogous dehydrations to alkenes.[7] In the present paper, this investigation is extended to hydrates of benzene, anthracene, and phenanthrene, and their aromatization reactions are compared with those of arene oxides[8] derived from the same aromatic parent. Structures of the hydrate and oxide of benzene (**1** and **2**) are shown in Chart I.

Chart I



1	**2**	**3**	**4**
190	32	~10^{-3}	1.1 x 10^4

When comparing hydrates and oxides, it seems reasonable to suppose that differences in reactivity might parallel those of alcohols and epoxides derived (by hydration and epoxidation) from the same alkene, for example, 2-cyclohexenol (**3**) and cyclohexene epoxide (**4**). Normally, acid-catalyzed carbon–oxygen bond breaking in an epoxide occurs 10^6–10^7 times more readily than in a structurally related alcohol, as illustrated by the rate constants (M^{-1} s^{-1} at 25 °C in aqueous solutions) shown below **3** and **4**. We were surprised, therefore, to find that acid-catalyzed aromatization of benzene oxide proceeds *less* readily than that of benzene hydrate, even though carbon–oxygen bond breaking should be rate-determining in each case.[7,9-12] Moreover, for a series of oxides and hydrates, ratios of rate constants of aromatization appear to depend on the resonance energy of the ring subject to aromatization. These unexpected findings are described in this paper.

Results

Rate constants for aromatization of a number of arene oxides have been reported,[8-13] but measurements for arene hydrates have

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[1] (a) University College Dublin. (b) The Queen's University of Belfast.

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[7] Boyd, D. R.; McMordie, R. A. S.; Sharma, N. D.; More O'Ferrall, R. A.; Kelly, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 7822.

[8] Boyd, D. R.; Jerina, D. M. In *Small Ring Heterocycles—Part III Oxiranes, Arene oxides, Oxaziridines, Dioxetanes, Thietanes, Thietes and Thiazetes*; Hassner, A., Ed.; John Wiley: New York, 1985; 197.

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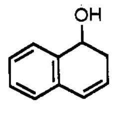
been confined to derivatives of naphthalene (e.g. **5** and **6**).[7] The hydrate of benzene (2,4-cyclohexadienol, **1**) was synthesized following the procedure of Stavascik and Rickborn[2] therefore, and the hydrates of phenanthrene (**7**, **8**, and **9**) and anthracene (**10** and **11**) were prepared by literature methods or as previously described for naphthalene.[3,4] Details of preparations of new compounds are given elsewhere.[3,4] Arene oxides **12**–**16** are structurally related to these hydrates.



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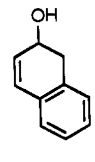

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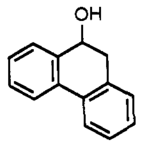

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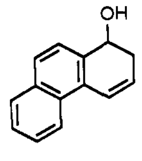

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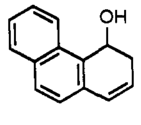

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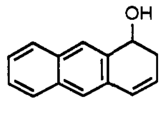

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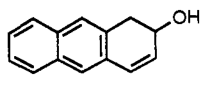

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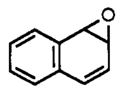

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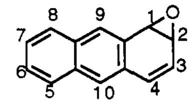

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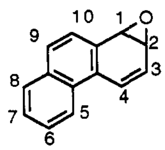

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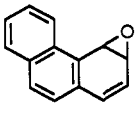

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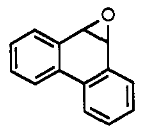

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Kinetic measurements indicated that benzene hydrate aromatizes in aqueous acetic acid buffers at 25 °C. Figure 1 shows a "repetitive scan" of the change in the UV spectrum of the accompanying reaction, with the characteristic spectrum of benzene appearing in the weakly absorbing product. Measurements in acetic acid buffers with buffer ratios of [AcOH]/[AcO$^-$] = 5/1 and 1/1 in the range of 0.03–0.3 M acetic acid showed no buffer catalysis and gave a rate constant of 190 M^{-1} s^{-1} for H$^+$ based on measurements of first-order rate constants shown in Table I.

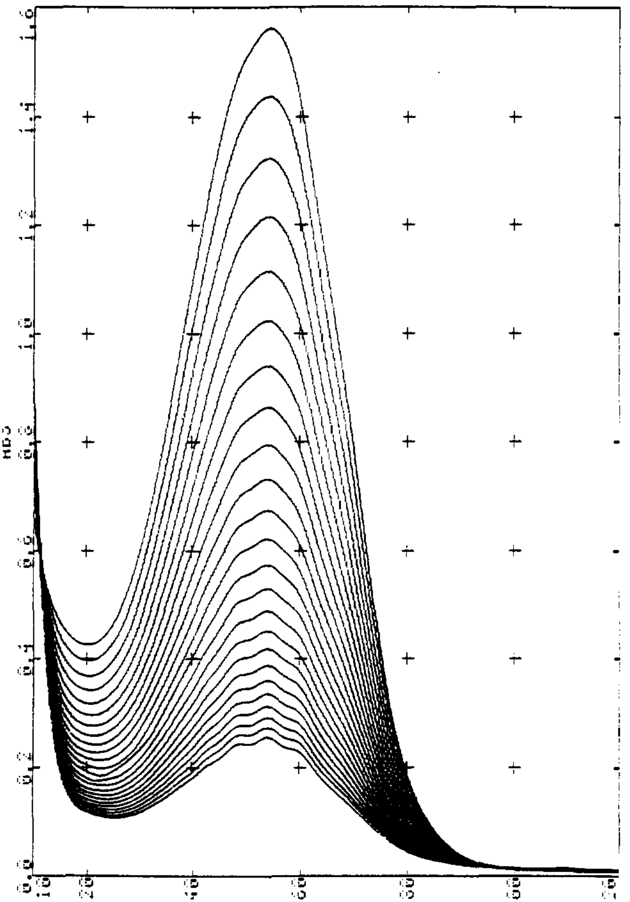

Figure 1. Repetitive scans of UV spectra for the reaction of benzene hydrate in an aqueous acetic acid buffer (pH = 5.6).

Table I. First-Order Rate Constants for Dehyration of Benzene Hydrate (**1**) in Aqueous Acetic Acid Buffers at 25 °C[a]

[AcOH]/[AcO$^-$] = 1.0, pH 4.80		[AcOH]/[AcO$^-$] = 5.0, pH 4.04	
[AcOH]/M	10^3k_{obs}/s^{-1}	[AcOH]/M	10^3k_{obs}/s^{-1}
0.03	2.91	0.03	16.9
0.06	2.85	0.06	17.5
0.09	3.00	0.06	17.5
0.15	3.16	0.12	17.8
0.30	3.21	0.15	17.1
		0.21	17.4
		0.30	17.4

[a] Ionic strength of 0.3 M in NaCl.

Rate constants for aromatization of other hydrates were measured in dilute solutions of HCl or HClO$_4$. However, phenanthrene hydrate **7** was sufficiently unreactive that measurements were extended to more concentrated solutions of perchloric acid and the second-order rate constant k_H was extrapolated to dilute solutions from a plot of log k_2 (where k_2 is the second-order rate coefficient $k_{obs}/[H^+]$) versus the acidity function X[14] (log $k_2 = -m^*X +$ log k_H). Measured first-order rate constants (10^3 k_{obs}/s^{-1}, 25 °C) at different concentrations of HClO$_4$ (M) were as follows: 1.89, 0.43 M; 2.81, 0.574 M; 3.98, 0.718 M; 4.94, 0.808 M; 7.36 0.97 M; 9.06, 1.123 M. The plot gave $k_H = 3.2 \times 10^{-3}$ M^{-1} s^{-1} and an approximate value of m^* = 1.4.

No kinetic measurements appear to have been reported for 1,2-anthracene oxide (**13**), and reaction of this substrate was studied in acetic acid and cacodylic acid buffers. The following buffer independent rate constants (k_{obs}/s^{-1}, 25 °C) at different pHs were obtained: 0.054, pH 3.62; 0.0316, pH 4.05; 0.0170, pH 4.52; 0.0157, pH 4.68; 0.0100, pH 4.82; 4.84 × 10^{-3}, pH 5.52; 4.40 × 10^{-3}, pH 6.32; 3.28 × 10^{-3}, pH 6.64. They were fitted to eq 1 with $k_o = 3.5 \times 10^{-3}$ s^{-1} and k_H = 300 M^{-1} s^{-1} representing

$$k_{obs} = k_o + k_H[H^+] \tag{1}$$

first- and second-order rate constants for water and acid-catalyzed reactions, respectively. Oxide **13** undergoes ring-opening to form a mixture of 1-anthrol and 2-anthrol, and the measured rate constants may be factored into contributions for 1- and 2-carbon–

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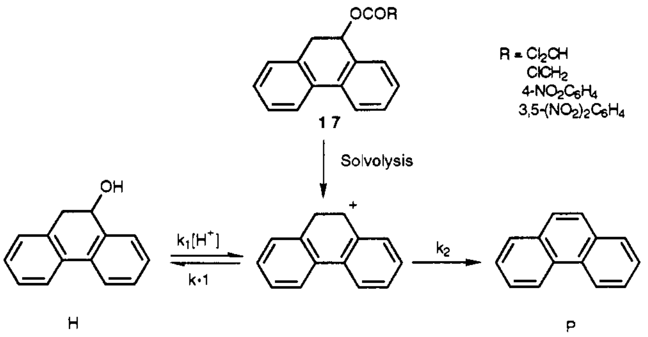
(14) Cox, R. A.; Yates, K. *J. Am. Chem. Soc.* **1978**, *100*, 3861. Cox, R. A.; Yates, K. *Can. J. Chem.* **1981**, *59*, 3861. Bagno, A.; Scorrano, G.; More O'Ferrall, R. A. *Rev. Chem. Intermed.* **1987**, *7*, 313.

Table II. Solvolysis of 9-Hydroxy-9,10-dihydrophenanthryl Carboxylate Esters (ArOOCR) in 20% CH_3CN:80% H_2O (v/v) at 25 °C: Rate Constants and Percent Phenanthrene Formed

R in ArCOOR	pK_a(RCOOH)	$10^4k/s^{-1}$	% phenanthrene[a]
Cl_2CH	1.29	54.6[b]	83[c]
3,5-$(NO_2)_2C_6H_3$	2.82	4.17	79
$ClCH_2$	2.86	1.97	68
4-$NO_2C_6H_4$	3.42	0.56	86

[a] Second product presumed to be phenanthrene hydrate. [b] Rate constant unaffected by 0.01 M H^+. [c] Product ratios unaffected by 0.01 M H^+ or 0.1 M $NaOOCCH_3$.

Scheme I



oxygen bond breaking according to the proportions of products obtained. Measurements of product ratios in $CHCl_3$ in the presence of CF_3COOH gave 97% 1-anthrol and 3% 2-anthrol. These values are unlikely to differ substantially from those in aqueous acid media (measurements in which were limited by solubility), and they lead to a reliable value of $k_H = 290\ M^{-1}\ s^{-1}$ for formation of 1-anthrol and an approximate value of $k_H \simeq 8\ M^{-1}\ s^{-1}$ for formation of 2-anthrol.

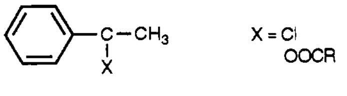
Product Partitioning of Phenanthrenonium Ion. For the reaction of naphthalene hydrates, it has been established[7] that in contrast to dehydration of simple alcohols, deprotonation of the carbocation formed from acid-catalyzed carbon–oxygen bond breaking occurs in a rapid step reflecting the stability of the aromatic product (see below). There is little doubt that the same must be true of most of the arene hydrates studied here. However, in the case of the 9,10-phenanthrene hydrate, the gain in resonance energy of the aromatized product is relatively low and the possibility that deprotonation may be partly rate-determining needs to be considered.

Evidence bearing on this point comes from the reported formation of 9,10-dihydrodiols in addition to 9-phenanthrol in the reaction of phenanthrene oxide **16** with acids,[10] which indicates that attack of water at the carbocation center of the α-hydroxy phenanthrenonium ion intermediate formed in the reaction competes with deprotonation (or an NIH shift)[8] to form 9-phenanthrol.

Relative rates of deprotonation and attack of water at the carbocation center in the dehydration of phenanthrene hydrate **7** itself were determined by generating the 9-phenanthrenonium ion solvolytically and measuring the ratio of phenanthrene to phenanthrene hydrate formed under conditions where the latter does not react further, i.e., in the absence of acid. Solvolyses of phenanthryl carboxylate esters **17** occur at convenient rates for study, and results of measurements of rate constants and product ratios, based on absorbance measurements for reactants and products in 20% v/v CH_3CN:H_2O for a series of esters, are shown in Table II.

Pathways for reaction and partitioning of the phenanthryl esters are shown in Scheme I. According to this scheme, the product ratio of phenanthrene (P) to hydrate (H), [P]/[H], yields the rate constant ratio (k_2/k_{-1}) for deprotonation and reaction of the carbocation to form a hydrate. This ratio may be used to correct the measured rate constant for dehydration $k_H = k_1k_2/(k_{-1} + k_2)$ to yield the desired rate constant for carbocation formation as $k_1 = k_H(1 + [H]/[P])$.

This analysis assumes that the carboxylate counter ion in the solvolysis reaction exerts no influence on the product ratio. Jencks and Richard have shown for the solvolysis of ring-substituted α-phenethyl chlorides and carboxylate esters **18** that this is true if the α-phenethyl carbocation intermediate is sufficiently long-lived for the counter ion to diffuse away before it reacts.[15] For short-lived carbocations, a carboxylate counter ion may increase the fraction of elimination product by 6-fold compared with that for dehydration of the alcohol or solvolysis of the corresponding alkyl chloride.



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Jencks and Richard observed borderline behavior with respect to carbocation–carboxylate ion lifetimes for a *p*-methylphenethyl substrate but found the *p*-methoxyphenethyl carbocation to be sufficiently long-lived to show no dependence of the product ratio on its precursor.[15] It is likely that the behavior of the phenanthrenonium ion is closer to that of the *p*-methoxy- than that of the *p*-methylphenethyl cation. This ion should be significantly more stable than the *p*-methylphenethyl cation both as a consequence of its cyclic character and the presence of an "*o*-phenyl" substituent within the phenanthryl structure, and it is noteworthy that the rate constant for dehydration in 1:1 CF_3CH_2OH:H_2O at 25 °C ($10^{-2} \times M^{-1}\ s^{-1}$) is intermediate in value between those for *p*-methoxyphenethyl alcohol ($1.1 \times 10^{-1}\ M^{-1}\ s^{-1}$) and *p*-methylphenethyl alcohol ($8.4 \times 10^{-4}\ M^{-1}\ s^{-1}$). Moreover, for solvolysis in 1:1 TFE:H_2O, the rate constant for phenanthryl *p*-nitrobenzoate ($3.3 \times 10^{-5}\ s^{-1}$, estimated from the value in H_2O) is comparable with the value of $10^{-4}\ s^{-1}$ calculable from data for *p*-methoxyphenethyl benzoate reported by Richard, Rothenberg, and Jencks.[16] Significantly, addition of acetate ions increased the yield of elimination product from reaction of *p*-methylphenethyl chloride[15] but not of phenanthrene from phenanthryl dichloroacetate.

It seems safe to conclude, therefore, that the product ratios observed from solvolysis of phenanthryl carboxylate esters can be used directly to estimate the rate constants for acid-catalyzed carbocation formation from the hydrate based on the measured rate constant for dehydration as indicated in Scheme I. Although there is some variation from leaving group to leaving group (±10% in Table II), this probably represents experimental scatter rather than systematic differences in products. Since formation of 85% phenanthrene in solvolysis of the phenanthrene esters implies that carbocation formation is only marginally slower than dehydration, there can be little doubt that for the other hydrates studied here, for which deprotonation of the carbocation is substantially more exothermic, carbocation formation is fully rate-determining in the dehydration reaction.

Rate Constants for Oxides, Epoxides, and Alcohols. Rate constants for a number of the substrates required for comparison with the arene hydrates were available from the literature. For H^+-catalyzed aromatization of arene oxides, measurements have generally been made at 30 °C compared with 25 °C for the hydrates.[8–13] However, the difference in temperatures corresponds to less than a factor of 2 in ratios of rate constants and, for the purpose of the comparison, represents a small factor within the 10^7-fold variation in the relative rates of these reactions.

Rate constants for carbocation formation from alcohols and epoxides generally have been measured at 25 °C. However, a

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(15) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373.

(16) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361.

value for *tert*-butyl alcohol was extrapolated from data for acid-catalyzed ^{18}O exchange with labeled water at several higher temperatures.[17] The value for cyclohexenol ($\sim 10^{-3}$ M^{-1} s^{-1}) was estimated from a value (3.0×10^{-4} M^{-1} s^{-1}) for *cis*-to-*trans* isomerization of *cis*-5-methyl-2-cyclohexenol at 30 °C in 35% v/v aqueous acetone.[18] It compares with a rate constant for dehydration of cyclohexenol to cyclohexadiene (for which deprotonation of the cyclohexenyl cation is rate-determining) extrapolated from measurements in strong acid solutions of 1.6×10^{-7} M^{-1} s^{-1}.[19]

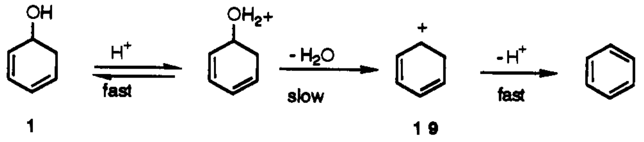
Rate constants for H^+-catalyzed hydrolysis of the epoxides of 2-butene,[20] styrene,[21] cyclohexadiene,[21] and 1,2-dihydronaphthalene[11] were all measured in aqueous solution at 25 °C.

Estimates of ΔG°_f(aq). To analyze effects of structural changes on stabilities of reactants, free energies of formation in aqueous solution had to be evaluated for cyclohexene and cyclohexadiene and their benzo analogues 1,2-dihydro- and 1,2,3,4-tetrahydronaphthalenes. These were taken from the literature or estimated.[22-24] Thus, a value for 1,2-dihydronaphthalene was obtained from measurement of the equilibrium constant for dehydration of tetralol (1-hydroxy-1,2-dihydronaphthalene) and interpolation of the effect of replacing H with a hydroxyl at the benzylic position of tetralin to give tetralol (for which ΔG°_f is known) from comparison with the same change in other hydrocarbons. Details of this will be published elsewhere.

Discussion

The mechanism of acid-catalyzed aromatization of the arene hydrates investigated in this work was presumed to be the same as that for the previously studied naphthalene hydrates and as illustrated for benzene hydrate (**1**) in Scheme II. Preequilibrium protonation of the hydroxyl group is followed by rate-determining formation of a 1,3-cyclohexadienyl cation (**19**) which rapidly deprotonates to form benzene. The mechanism of this reaction differs from that for dehydration of simple alcohols to form alkenes in which deprotonation of the carbocation is rate-determining and dehydration is 10^2–10^3 times slower than carbocation formation. The more rapid deprotonation for the arene hydrates stems from the greater stability of the aromatic product. As shown above, for phenanthrene hydrate, for which the gain in aromatic resonance energy of the product is relatively small, carbocation formation and dehydration occur at comparable rates.

Scheme II



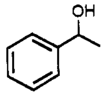
Rate constants for aromatization of the hydrates of benzene (**1**), naphthalene (**5**, **6**), phenanthrene (**7**, **8**, **9**), and anthracene (**10**, **11**) and for dehydration of the alcohols 2-cyclohexenol (**3**), α-phenylethanol (**20**), α-tetralol (**21**), and *tert*-butyl alcohol to alkenes are listed in Table III. Isomeric hydrates, such as those of naphthalene, are distinguished by prefixes α or β depending on whether the hydroxyl group is attached at benzylic carbon atom 5 or the adjacent carbon atom 6 remote from the ring-junction (cf. α- and β-naphthols and tetralols). For the alcohols, since deprotonation of the carbocation is rate-determining, rate constants refer to the 10^2–10^3-fold faster carbocation forming step.

Table III. Comparison of Rate Constants (M^{-1} s^{-1}) for Hydronium Ion-Catalyzed Dehydration and Epoxide Ring-Opening Reactions in Aqueous Solution

aromatic or alkene prodt	hydrate or alcohol[a]	oxide	$k_{hydrate}$[b] (25 °C)	k_{oxide}[c] (30 °C)	$k_{oxide}/k_{hydrate}$
benzene	**1**		190	32	0.08[d]
naphthalene	**5**(α)	1,2	0.35	11[e]	31
naphthalene	**6**(β)	1,2	1.8	99[e]	56
phenanthrene	**8**(α)	1,2	2.50	220	88
phenanthrene	**9**(α)	3,4	7.50	810	108
anthracene	**10**(α)	1,2	0.05	($\sim$10)[f]	($\sim$200)
anthracene	**11**(β)	1,2	0.21	300[f]	1430
phenanthrene	**7**	9,10	4.0×10^{-3} [g]	130	3.8×10^4 [d]
1,2-dihydro-naphthalene	**22**	3,4	6.0×10^{-4} [h]	1250[j]	2.1×10^6
styrene	**20**		3.0×10^{-6} [h]	27[k]	9×10^6
1,3-cyclohexa-diene	**3**		($\sim 10^{-3}$)[h,l]	1.1×10^4 [k]	($\sim 10^7$)
isobutene			1.4×10^{-6} [h,m]	6.0[j]	4.3×10^6

[a] Position of hydroxyl relative to fused benzene ring indicated by α and β. [b] Rate constants (M^{-1} s^{-1}) for carbocation formation at 25 °C. [c] Position of epoxidation matches that of hydration; rate constants (M^{-1} s^{-1}) at 30 °C from ref 10 except as indicated. [d] Statistically corrected for equivalent positions of oxide ring opening. [e] Rate constant for naphthalene oxide (110 M^{-1} s^{-1}) partitioned according to 90:10 product ratio of 1- to 2-naphthols. [f] This work, $T = 25$ °C, rate constants for anthracene oxide partitioned according to 97:3 product ratio of 1:2 anthrols from reaction with CF_3COOH in $CHCl_3$ solution. [g] Dehydration rate constant corrected for 20% reversibility of carbocation formation as described in text. [h] Rate constant for carbocation formation from alcohol. [j] Reference 11, 25 °C. [k] Reference 20, 25 °C. [l] Reference 18, estimated as described in text. [m] Rate constant for carbocation formation from *tert*-butyl alcohol.

Reactivities of the hydrates and alcohols in Table III span a range of 10^8-fold. The earlier comparison of naphthalene hydrates and alcohols showed that differences in reactivity reflect chiefly the stability of the carbocation intermediate. Thus, the nearly 10^5-fold greater reactivity of α-naphthalene hydrate **5** than of the structurally related α-phenylethanol (**20**) derives in part from the cyclic nature of the naphthalenonium cation **22** and in part from the presence of a vinyl substituent ortho to the carbocation center. The influence of the cyclic character of the carbocation is indicated by the 150-fold greater reactivity of α-tetralol (**21**) than α-phenylethanol (**20**).[7]



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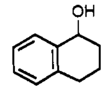

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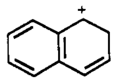

21

Benzoannelation. Relative reactivities of the newly studied hydrates also reflect carbocation stabilities, although this is not immediately apparent. Comparisons between benzene hydrate, α- and β-naphthalene hydrates, and the 9,10-hydrate of phenanthrene may be considered in terms of replacing one of the double bonds of benzene hydrate by a benzene ring, i.e., benzoannelation. Thus, replacement of the double bonds adjacent to and remote from the hydroxyl group gives the α- and β-naphthalene hydrates, respectively, and replacement of both double bonds gives 9,10-phenanthrene hydrate. These compounds react 100-fold, 500-fold, and 50 000-fold, respectively, less rapidly than benzene hydrate.

Clearly, benzoannelation slows dehydration by a large amount. Surprisingly, however, for the apparently related dehydration or solvolysis reactions of allylic substrates, replacement of a double bond by benzene has little effect. Thus, 2-cyclohexenyl chloride in ethanol solvolyzes 2–3 times *less* rapidly than its benzo analogue,[18] and there is a 2-fold rate difference in the opposite direction for carbocation formation from the corresponding alcohols **3**[19] and **22**.

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(17) Dostrovsky, I.; Klein, F. S. *J. Chem. Soc.* **1955**, 791.

(18) Goering, H. L.; Silversmith, E. F. *J. Am. Chem. Soc.* **1955**, *79*, 348.

(19) Rao, S. N.; More O'Ferrall, R. A. Unpublished results.

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(21) Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658.

(22) Guthrie, J. P. *J. Am. Chem. Soc.*, in press and references cited.

(23) Harcourt, M. P.; More O'Ferrall, R. A. *Bull. Soc. Chim. Fr.* **1988**, 407.

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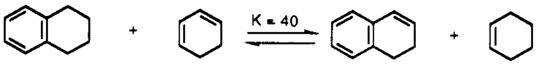
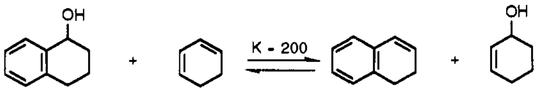
To interpret this contrast in behavior, it is helpful to recognize that benzoannelation affects the stability not only of carbocation forming transition states but also of reactants. Thus, replacement of one double bond in cyclohexadiene by benzene has a significant stabilizing effect on the other. This can be expressed in terms of the isodesmic reaction of eq 2, in which benzoannelation of cyclohexadiene is compared to that of cyclohexene and an approximate equilibrium constant, $K = 40$, in aqueous solution can be evaluated from measurements or estimates of free energies of formation of reactants and products.[22-24]



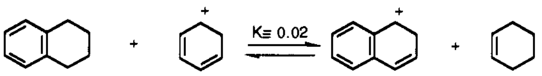
(2)

The full effect of this double-bond stabilization is probably not felt in the comparison of benzene and α-naphthalene hydrates, however, because it may be partly compensated for by a more favorable "geminal" interaction[23] of the hydroxyl group in the reactant with a double bond than with a benzene ring. This is indicated by the large value of the equilibrium constant ($K \simeq 200$) for the isodesmic reaction of eq 3, which can be evaluated from the ratio of measured equilibrium constants for the hydration of dihydronaphthalene[24] and cyclohexadiene.[25] From the further ratio of equilibrium constants for reactions 3 and 2 (200/40), it appears that the geminal interaction of the hydroxyl group in cyclohexenol is ~5-fold more stabilizing than that in α-tetralol. It should be noted, however, that while eq 3 satisfactorily expresses the combined effects of double-bond stabilization and geminal interactions, their dissection is subject to greater uncertainty.[26]



(3)

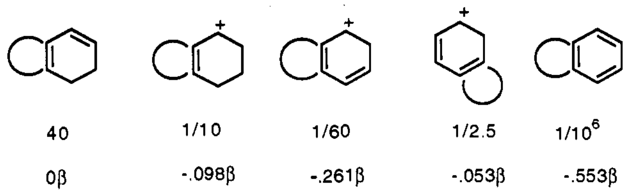
In eq 3, the effects of the double bond and geminal hydroxyl group reinforce one another but in the comparison of benzene hydrate and α-naphthalene hydrate, they are opposed. This means that the net effect on the reactants is probably small, perhaps less than 10-fold, and that most of the 500-fold difference in rates does indeed come from destabilization of the carbocation transition state. This implies assignment of a small value (~1/60) for the equilibrium constant of the isodesmic reaction of eq 4, in which the cationic centers strictly represent carbocation-forming transition states rather than fully formed carbocations.



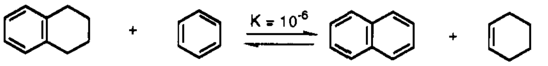
(4)

The contrast between the destabilization represented in eq 4 and the stabilizing effect of benzoannelation upon cyclohexadiene (eq 2) emphasizes that effects of benzoannelation are quite variable. A further example is provided by benzoannelation of the second double bond, i.e., that remote from the carbocation center, in the transition state leading to formation of a cyclohexadienyl cation. This effect is obtainable from the ratio of rate constants for reaction of benzene and β-naphthalene hydrates. Here there is no contribution from a geminal hydroxyl group, and the observed 100-fold rate depression apparently is caused mainly by double-bond stabilization in the reactant. Significantly, the effect of benzoannelation on the transition state leading to a cyclohexenyl cation is intermediate between the corresponding effects upon the two double bonds of the cyclohexadienyl cation transition state. By correcting for the hydroxyl geminal effect in the cyclohexenol reactant (a factor of 5), the 2-fold rate reduction from benzoannelation translates into a ~10-fold destabilization of the cyclohexenyl cation-like transition state.

Chart II



The magnitudes of these effects are summarized in Chart II, with the position of benzoannelation shown by a circle. The differences between them can be rationalized in valence-bond terms by supposing that benzoannelation is unfavorable where it interrupts a strong resonance interaction. This is a familiar feature of polycyclic aromatic hydrocarbons, and eq 5 shows that benzoannelation of benzene itself is unfavorable by 10^6-fold. For a weakly conjugated double bond such as in cyclohexadiene, on the other hand, benzoannelation is favorable (eq 2).

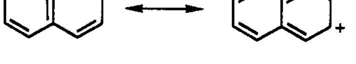


(5)

The relative magnitudes in Chart II can also be accounted for semiquantitatively in terms of MO theory, most simply from considering the energies of nonbonded molecular orbitals. Chart II includes stabilizations in units of β estimated from the PMO treatment,[27] and it can be seen that these roughly correlate with the experimental values.

The PMO treatment and notion of "interrupted resonance" also allow us to interpret relative reactivities of α- and β-polycyclic aromatic hydrates. From the effects of benzoannelation on carbocation transition states in Chart II, the expected rate difference between α- and β-naphthalene hydrates is 60/2.5, i.e., 24-fold in favor of the β-hydrate. That the observed rate difference is only 5-fold appears to be a further reflection of the greater stabilizing effect of the hydroxyl geminal interaction in the β-hydrate reactant than that in the α-hydrate reactant.

This interpretation can be extended to benzoannelated naphthalene hydrates. From Chart II, we noted that effects of benzoannelation upon a carbocation-forming transition state are considerably larger for α-hydrates than β-hydrates. If we suppose that relative stabilities of the α transition states reflect ease of through conjugation in the cyclohexadienyl cation segment of the molecule as expressed by resonance structures **23** and **24**, we can recognize that this conjugation is greatest in benzene hydrate and diminishes as the aromatic character of the participating double bond increases, i.e., in the order benzene > phenanthrene > naphthalene > anthracene hydrate. In Table III, it can be seen that this corresponds with the observed reactivity order for the α-hydrates. For the β-hydrates, the main effect should be upon the reactants and the slower rate of β-anthracene hydrate (**11**) than of β-naphthalene hydrate (**6**) probably reflects greater stabilizations of the double bond in eq 2 by a naphthyl than a phenyl group.



23 **24**

Arene Oxides. The above discussion establishes that the dominant influence upon reactivity in acid-catalyzed carbon–oxygen bond breaking of aralkyl alcohols and arene hydrates is indeed the stability of their carbocation-forming transition states,[7] with a significant but minor role played by reactant stabilities. Understanding the factors controlling the reactivities of these

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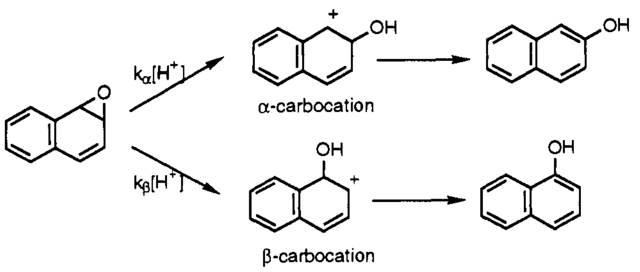
(25) Rao, S. N. Unpublished results.

(26) Thus, there is no evidence of a difference in hydroxyl stabilization in allyl and benzyl alcohols.

(27) Dewar, M. J. S.; Dougherty, R. C. In *The PMO Theory of Organic Chemistry*; Plenum: New York, 1975.

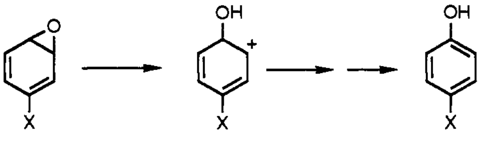
Scheme III



substrates is a prerequisite for comparing them with arene oxides and alkene epoxides, in which the alcohol or hydrate function is replaced by an epoxide ring.

The rate-determining step in epoxide ring opening is carbon–oxygen bond fission of the O-protonated epoxide to yield a carbocation differing from that formed from the hydrates only by the presence of a β-hydroxyl group.[8,10–12,20,28] This hydroxyl group may direct further reaction of the carbocation along new reaction pathways, e.g., through occurrence of an NIH shift,[29,30] but as these follow the rate-determining step, they should not affect relative reactivities which should depend upon carbocation stabilities in the same way as for the hydrates and alcohols.

In principle, epoxide ring opening may also occur via an S_N2 mechanism.[20] However, this is unlikely for substrates yielding tertiary alkyl or secondary benzylic carbocations in the absence of stronger nucleophiles than water as considered here. By analogy with arene hydrates, arene oxides should yield more stable carbocations and be more favorable to an S_N1 mechanism than their aralkyl counterparts. Direct evidence of the carbocation character of epoxide and arene oxide transition states is provided by extensive studies of the influence of structure upon reactivity of epoxides[11,20,28] and measurement of $\rho = -7.2$ for aromatization of 4-substituted-1,2-benzene oxides (eq 6) based on σ^+ constants.[12]

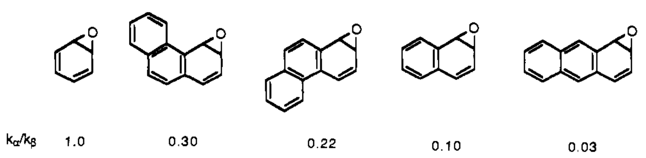


(6)

For unsymmetrical epoxides, carbon–oxygen bond breaking may yield either (or both) of two isomeric carbocations. For the epoxides considered here, which are structurally related to the alcohols listed in Table III, it is assumed that only the more stable cation is formed, matching that formed from the alcohol (apart from the presence of a β-hydroxyl group). For unsymmetrical arene oxides, however, appreciable reaction may occur by both pathways and rate constants must be partitioned according to the product ratios of isomeric phenols, as shown for naphthalene oxide[10] in Scheme III.

These product ratios correspond to ratios of rate constants k_α/k_β leading to the formation of α- and β-carbocations, respectively.[10] As discussed in connection with the α- and β-hydrates above, they reflect the relative stabilities of these ions. For the symmetrical benzene oxide, $k_\alpha/k_\beta = 1$, but this ratio is decreased by benzoannelation adjacent (α) to the carbocation center as a result of the sacrifice of aromatic resonance stabilization in the benzene ring arising from resonance interaction between the remaining double bond and the carbocation center ($\mathbf{23} \leftrightarrow \mathbf{24}$). For the polycyclic arene oxides shown in Chart III, k_α/k_β ratios[10] are inversely related to the aromatic stabilization energy sacrificed in this resonance. As already noted, benzoannelation of the remote (β) double bond of benzene hydrate has little effect on the carbocation transition-state stability.

Chart III



Comparison of Arene Hydrates and Arene Oxides. Rate constants for ring opening of alkene epoxides and dissected rate constants for α- and β-carbon–oxygen bond breaking of arene oxides are listed in Table III alongside corresponding values for the alcohols and hydrates. If, as suggested, both sets of reactions occur with rate-determining formation of a carbocation intermediate, we expect their relative rates to reflect principally the greater reactivity of the carbon–oxygen bond in the strained epoxide ring than that in the alcohol, with a lesser influence from the hydroxyl substituent present in the carbocation formed from the epoxide. They should be relatively insensitive to variations in structure and reactivity of the reactants.

For the alkyl or aralkyl epoxides and alcohols of Table I, this indeed is true. In the four examples listed at the bottom of the table, the reactivity ratio varies by a factor of only five, with the epoxide consistently 10^6–10^7-fold more reactive than the alcohol, although the individual alcohol and epoxide rate constants vary by nearly 1000-fold.

Inclusion of the arene oxides and arene hydrates in table III, as expected, extends the reactivity range of alcohols and epoxides. However, as shown in the last column of the table, the *ratios* of oxide to hydrate rate constants, instead of remaining nearly constant, now change by nearly 10^8-fold. It can be seen that benzene oxide and benzene hydrate at the top of the table and nonaromatic epoxides and alcohols at the bottom represent opposite extremes of behavior with small and large oxide/hydrate rate ratios, respectively. Between these extremes, there is a systematic divergence in the effect of aromatic structure upon the reactivities of the oxides and hydrates. Moving down the table, the reactivity of the hydrates decreases sharply, in line with the unfavorable benzoannelation and decreasing stability of carbocation transition states, whereas the reactivities of the oxides remain relatively unchanged or, for cyclic structures, even increase.

What is the origin of this surprising difference in behavior of aliphatic and aromatic derived reactants? Inclusion of both cyclic and noncyclic aliphatiic substrates shows that it does not arise from the cyclic nature of the arene oxides nor is there much difference between α- and β-substrates.

A clue is provided by the small oxide/hydrate rate ratios at the top of the table. If our argument is correct that with respect to carbocation and reactant stabilities the reactivities of the hydrates are normal, then these indicate that the oxides are unusually unreactive. This low reactivity is most marked for benzene oxide (**2**) which, uniquely, is *less* reactive than its corresponding hydrate **1**, implying that the factor responsible overrides the 10^6-fold advantage from ring strain.

Why then are the arene oxides unreactive? In principle it might be because a stereoelectronic effect inhibits efficient delocalizatiion of positive charge in a bicyclic (**25**) as compared with a monocyclic (**26**) carbocation transition state. However, while such an effect might moderate the 10^5-fold acceleration from the double bond converting cyclohexenol to benzene hydrate, it would not explain the 300-fold reduction in rate from the corresponding double bond converting cyclohexadiene oxide to benzene oxide (Chart I).

One might also imagine that the geometric constraint of the extra carbon–oxygen bond in the transition state for benzene oxide (**25**) increases the adverse inductive effect ($-I$) of the partially charged oxygen ($\delta+$) upon delocalization of the car-

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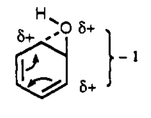
(28) Lamaty, G.; Maleq, R.; Selve, C.; Sivade, A.; Wylde, J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1119.

(29) Jerina, D. M.; Daly, J. W.; Witkop, B. *Biochemistry* **1970**, *9*, 147.

(30) Jerina, D. M.; Daly, J. W.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 6523.



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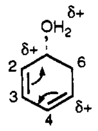
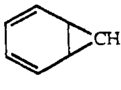


26

bocation charge to C_5 relative to that for hydrate **26**. However, this is unlikely to be a major factor, and neither it nor a stereoelectronic effect account for the systematic dependence of the oxide/hydrate rate ratios upon aromatic structure.

Homoaromaticity. As already noted, the oxide/hydrate rate ratios decrease in moving down Table III. If one considers α- and β-hydrates as forming separate series, with hydrates of symmetrical double bonds such as benzene hydrate and 9,10-phenanthrene hydrate belonging to each, it can be seen that this decrease correlates with decreasing resonance energy of the ring subject to epoxidation or hydration in the order benzene–naphthalene–phenanthrene(1,2 or 3,4)–anthracene–phenanthrene(9,10)–alkene.

A reasonable explanation of this behavior is that the arene oxides are homoaromatic and subject to varying degrees of resonance stabilization, with the largest effect for benzene oxide and no effect for epoxides of alkenes. Hitherto, homoaromaticity has been considered mainly for carbocations and thought unimportant for neutral molecules.[31] However, recent measurements of heats of hydrogenation by Roth and Klarner[32] suggest a resonance energy of 5–8 kcal/mol for norcaradiene **27**, the neutral hydrocarbon analogue of benzene oxide, and these measurements receive support from calculations[33] and a critical discussion.[34] For benzene oxide **28**, Kollmann has pointed to the possibility of a stabilizing interaction of a lone pair of the oxygen atom with the π-orbitals of the arene oxide ring,[35] in which case benzene oxide might be considered a 6-π analogue of the 2π-homoaromatic 7-norbornenyl cation **29**.[36] On the other hand, the evidence of aromaticity for norcaradiene, which has no lone-pair electrons, probably implies that σ–π interactions are dominant.



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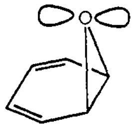

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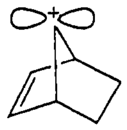

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If homoaromaticity is significant in arene oxides, we can understand how this combines with the influence of carbocation stability and epoxide ring strain to produce the structure–reactivity dependence of oxides and hydrates shown in Table III. Assuming that the ring strain is constant, the rather small variation in rate constants for the arene oxides (~70 fold) implies a compensation between changes in stabilization of a homoaromatic reactant and carbocation transition state. The influence of carbocation stability, as we have seen, is substantially measured by the reactivity of the hydrates. The small rate variation arises because, coincidentally, this shows a similar dependence upon the structure of the parent molecule as does homoaromaticity. This is apparent from inspection of Table III and is qualitatively confirmed by evaluation of NBMO coefficients.

It is worth noting that a similar interplay of cation stability and aromaticity occurs in electrophilic aromatic substitution. The carbocation intermediates from reaction of arene oxides and arene hydrates with acids are formally equivalent to the arenonium ions that would be formed from electrophilic attack on the aromatic product by OH^+. For ring-substituted benzenes, it is well known that the loss in resonance energy accompanying attack of an electrophile depends only weakly on the substituent and that the dominant influence of the substituent is upon the stability of the benzenonium ion intermediate. For polycyclic aromatic hydrocarbons, on the other hand, the resonance energy of the *reactant* dominates the reaction and relative reactivities correlate inversely with the stabilities of the arenonium ions[37] (or the reactivities of the corresponding aromatic hydrates). The intermediate behavior of arene oxides is consistent with their possessing an appreciable resonance energy which, nevertheless, is smaller than that of their parent hydrocarbons.

Although circumstantial evidence for homoaromaticity is strong, confirmation will be required from thermodynamic measurements and further calculations. At this point, it may be appropriate to emphasize the magnitude of the effect and its sensitive detection by kinetic measurements rather than its interpretation. Thus, if 10^6-fold is the normal rate difference between alcohols and epoxides, the 10-fold smaller rate of benzene oxide than that of benzene hydrate implies that the oxide is slowed by 10^7-fold, which corresponds to at least 10 kcal of stabilization energy for benzene oxide.

In conclusion, we note that this stabilization of arene oxides is of interest in connection with studies of the liver enzyme metabolism of aromatic molecules and in particular the involvement of arene oxides and their dihydrodiol derivatives in the well-known carcinogenic action of polycyclic aromatic hydrocarbons. All of the arene oxides considered here (**2** and **12–16**) have been postulated as metabolites, but only naphthalene oxide has been detected directly.[38] The influence of homoaromaticity, in preferentially stabilizing the smaller polycyclic arene oxides, may be a factor in this observation and indeed in the general viability of naphthalene and other arene oxides as intermediates that can be trapped as their dihydrodiols or glutathione adducts.[39] Knowledge of the stabilities of the arene hydrates has also been of importance in the detection and characterization of these species as products from liver enzyme biotransformations of the corresponding dihydroaromatic hydrocarbons.[40]

Experimental Section

NMR measurements were made with Jeol JNM-GX 270MHz FT or JNM-PMX 60MHz continuous wave spectrometers. Reaction kinetics were monitored with Phillips Pye Unicam SP8-400 and Perkin Elmer-Hitachi PE-124 UV–vis spectrophotometers.

Synthesis. Benzene hydrate (1) was prepared by epoxidation of 1,4-cyclohexadiene and reaction of the resulting monoepoxide with methyllithium as described by Stavascik and Rickborn.[2] Benzene was separated by rotary evaporation to yield a product of ~95% purity (NMR). The proton NMR showed multiplets for all hydrogens except the C_1 hydrogen (double triplet) for which decoupling measurements gave $J_{1,2} = 4.58$ and $J_{1,6} = 6.23$ Hz. Details of the spectra are as follows: ^1H NMR ($CDCl_3$) δ 2.5 (m, 2H, CH_2), 3.4 (br s, 1H, OH), 4.2 (dt, 1H, CH), 5.8–6.1 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 63.0 (d), 123.1 (d), 125.4 (d), 125.6 (d), 127.4 (d). Comparison of the ^{13}C spectrum with that of benzene oxide[41,42] and other epoxides[42,43] as expected, offered no evidence of

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(31) (a) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 106. (b) Dewar, M. J. S. *J. Am. Chem. Soc.* **1989**, *111*, 5384.

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homoaromaticity of the benzene oxide. The vinyl ^{1}H peaks (δ 5.8–6.1) are also similar to those of benzene oxide (6.3).[44]

Phenanthrene was epoxidized following the procedure of Krishnan et al.[45] The 9,10-oxide **16** obtained was reduced with $LiAlH_4$ (by analogy with the similar reaction for benzene oxide[44]) to 9,10-phenanthrene hydrate (**7**) which was converted to a number of carboxylic acid esters (**17**). For example, dropwise addition of 10% molar excess of chloroacetic anhydride in pyridine (5 mL) to **7** (200 mg, 1 mmol) in pyridine (5 mL) and quenching with 10% aqueous $NaHCO_3$ after 30 min followed by extraction with $CHCl_3$, washing with $NaHCO_3$ and HCl, drying (Na_2SO_4), and removal of $CHCl_3$ gave 9-(chloroacetoxy)-9,10-dihydrophenanthrene as an oily solid (>99% pure by HPLC): ^{1}H NMR ($CDCl_3$) δ 3.05 (d, 2H, C_{10}, CH_2), 4.0 (s, 2H, CH_2CO), 6.05 (t, 1H, C_9, CHOOCR), 7.0–8.0 (m, 8H, aromatic). The corresponding 9-(dichloroacetoxy)-9,10-dihydrophenanthrene was prepared similarly by stirring the hydrate with dichloroacetyl chloride in pyridine at 0 °C overnight, as were the 4-nitro and 3,5-dinitro benzoyloxy esters using the appropriate acid chlorides. Except for the carboxylate groups, NMR spectra were similar to that for the corresponding dichloroacetate.

Preparation of hydrates of phenanthrene **8** and **9** and anthracene **10** and **11** are described elsewhere.[4] 1,2-Anthracene epoxide was prepared by the previously reported method.[46]

Product Analysis. The reaction of 1,2-anthracene oxide (**13**) with CF_3COOH in $CDCl_3$ solution was monitored by NMR spectrometry, and the product ratio of 1-anthrol to 2-anthrol was determined by GLC using a VG12-250 GC-mass spectrometer equipped with a PDP11/23 plus data system. The GC analysis was performed with a 25-m BP-1 column, and the ratio of 1-anthrol:2-anthrol was taken as equal to the directly measured ratio of peak areas (97:3).

Kinetics. Kinetic measurements were made spectrophotometrically. Stock solutions of substrates (~0.01 M) were normally prepared in acetonitrile or methanol solvents using a microbalance for weighings, and approximately 20 μL was injected into a thermostated cuvette containing 2 mL of aqueous acid to initiate the reaction. Measurements were made at 25 °C. Normally the ionic strength for buffer measurements was maintained as 0.1 M by addition of NaCl, but reactions with H^+ (HCl or $HClO_4$) contained no salt and for the reaction of benzene hydrate in acetic acid buffers, the ionic strength was 0.3 M. Measurements for dehydration of phenanthrene hydrate in aqueous solution were possible despite the low solubility of the phenanthrene product because of its large extinction coefficient. Solvolysis measurements for phenanthrene carboxylate esters **17** (Scheme I) were made in 20% CH_3CN–80% H_2O (v/v) with formation of the phenanthrene product monitored spectrophotometrically. For product analyses, initial and final absorbances A_0 and A_∞ were measured (the latter determined from extrapolation of absorbance measurements over 3 half-lives) and compared with corresponding absorbances following hydrolysis to the hydrate in 0.1 M OH^- (A_0') and reaction with H^+ to effect dehydration (A_∞'). The fraction of phenanthrene in the product mixture of phenanthrene and phenanthrene hydrate from solvolysis was given by $(A_\infty - A_0)/(A_\infty' - A_0')$. In this expression, any contributions from absorption of the carboxylate leaving group were cancelled. Close identities of measured values of A_0 and A_0' (in 0.01 M NaOH) confirmed that ionization (and presumably alkylation of the carboxyl groups) had little effect on the measured absorbances. It was presumed that the partitioning between phenanthrene and hydrate was unchanged from that in water by the presence of 20% acetonitrile.

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