Substituent Effects on Rates and Product Distributions in the Hydrolysis Reactions of Naphthalene Tetrahydro Epoxides. Models for Tetrahydro Epoxides of Polycyclic Aromatic Hydrocarbons

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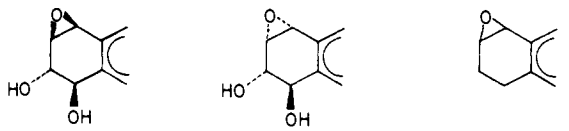
Bay-region diol epoxides derived from polycyclic aromatic hydrocarbons have been implicated as "ultimate carcinogens" responsible for the carcinogenic behavior of certain hydrocarbons.[1] Therefore, their solution chemistry has been of considerable interest. Product studies on the acid-catalyzed hydration of diol epoxides **1** and **2**[2] and tetrahydro epoxides **3**[3] of several polycyclic



1 2 3

a, benzo[*a*]pyrene c, phenanthrene
b, chrysene d, naphthalene

aromatic hydrocarbons have been reported. An especially interesting observation is that whereas the trans-diol epoxides (**2a–c**) undergo predominantly trans hydration, cis-diol epoxides (**1a–c**) and -tetrahydro epoxides (**3a–d**) gave varied cis/trans hydration ratios. Thus, **1a** gives 80% cis hydration, and **1b** only 50% cis hydration.

The varied product distributions are even more striking for acid-catalyzed hydrolysis of the related tetrahydro epoxides (Table I). Whereas benzo[*a*]pyrene tetrahydro epoxide **3a** gives ca. 80% cis hydration, chrysene tetrahydro epoxide **3b** and phenanthrene tetrahydro epoxide **3c** (which also possess the epoxide ring in a bay region) undergo only ca. 14–18% cis hydration. Naphthalene tetrahydro epoxide **3d**, although it does not contain a bay region, gives only 6% cis hydration by the acid-catalyzed process.[4] Throughout the series from naphthalene to benzo[*a*]pyrene, therefore, the amount of cis hydration increases as the ability of the aryl group to stabilize positive charge at the benzyl position increases, as reflected by HMO calculations[5] and the values of k_{H^+} for acid-catalyzed hydrolysis (Table I).

In order to test whether increasing amounts of cis hydration in the acid-catalyzed hydrolysis of cis-diol epoxides and tetrahydro epoxides were due to stabilizing effects of the aryl group on the development of positive charge at the benzyl position, we have synthesized 6-methoxy-1,2,3,4-tetrahydro 1,2-epoxide **4b**[6] (Scheme I) and compared its hydrolysis reactions with those of the related naphthalene tetrahydro epoxide **4a**. We report here that, whereas acid-catalyzed hydrolysis of **4a** yields only 6% of cis hydration,[4] the amount of cis hydration in the corresponding hydrolysis of **4b** is increased to 81%. In addition, the spontaneous reaction of **4b** with solvent gives a very different product distribution than **4a**.

Table I. Second-Order Rate Constants[a] and Relative Amounts of Cis Hydration of the Acid-Catalyzed Hydrolysis Reactions of Tetrahydro Epoxides

compd	k_{H^+}, M^{-1} s^{-1}	% cis hydration
3a[b]	1.2×10^4	80
3c[c]	6.9×10^3	18
3b[b]	1.6×10^3	14
3d[d]	5.0×10^2	6

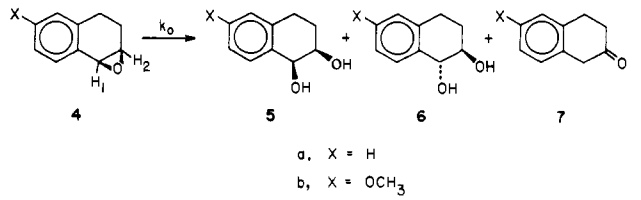
[a] 25 °C. [b] Determined in 25% dioxane–water, 0.1 M $NaClO_4$. [c] Determined in water, 0.1 M $NaClO_4$. [d] Rate constant determined in water, 0.1 M $NaClO_4$. Product data determined in water, 1.0 M $NaClO_4$; ref 4.

Table II. Product Distributions from Acid-Catalyzed and Spontaneous Hydrolysis of Naphthalene Tetrahydro Epoxides 4a and 4b

	acid catalyzed			spontaneous		
compd	cis 5, %	trans 6, %	ketone 7, %	cis 5, %	trans 6, %	ketone 7, %
4a[a]	6	94	0	0	100	0
4b[b]	81	19	<1	17	7	76

[a] Water, 1.0 M $NaClO_4$, ref 4. [b] Water, 0.1 M $NaClO_4$. Products were analyzed by HPLC on a reverse-phase C18 Waters Co. μBondapak column. Diols 5b and 6b were separated by preparative HPLC. The cis-isomer 5b (mp 119–120 °C) was compared with authentic sample (ref 6b). Trans-isomer 6b possessed mp 119–120.5 °C.

Scheme I



4 5 6 7

a, X = H
b, X = OCH_3

At pH <ca. 10, the rates of reaction of **4a** and **4b** in water (μ = 0.1, $NaClO_4$, 25 °C) fit $k_{obsd} = k_{H^+}a_{H^+} + k_0$, where k_{H^+} and k_0 represent specific rate constants for acid-catalyzed and spontaneous hydrolysis processes, respectively. Values of k_{H^+} were determined to be $(5.0 \pm 0.1) \times 10^2$ and $(1.68 \pm 0.03) \times 10^5$ M^{-1} s^{-1} for **4a** and **4b**, respectively, and values of k_0 were measured to be $(1.51 \pm 0.06) \times 10^{-5}$ and $(8.8 \pm 0.2) \times 10^{-3}$ s^{-1}, respectively, for **4a** and **4b**.

Hydrolysis reactions of **4a** and **4b** yield products whose structures are outlined in Scheme I. The product distributions from hydrolysis of **4b** by both the acid-catalyzed and spontaneous pathways differed markedly from those of **4a** as outlined in Table II. Whereas **4a** yielded 94% of trans-diol **6a** from acid-catalyzed hydration,[4] **4b** yielded predominantly (81%) the cis-diol **5b**. Thus, substitution of methoxyl at the 6-position of **4a** has the same effect as the substitution of additional aromatic rings, namely, that cis hydration in the acid-catalyzed reaction is favored.

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(6) (a) The bromohydrin (mp 90.5–92 °C) of 3,4-dihydro-6-methoxynaphthalene[6b] was prepared by treatment of the olefin with *N*-bromoacetamide in 75% tetrahydrofuran–water solution. Treatment of this bromohydrin with powdered KOH in tetrahydrofuran yielded **4b**, mp 34.5–35.5 °C: (b) Clark-Lewis, J. W.; Nair, V. *Aust. J. Chem.* **1967**, *20*, 2151.

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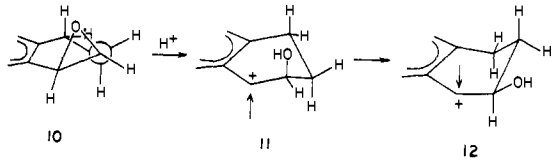
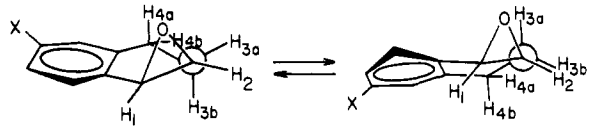
Scheme II



10 11 12

Inspection of molecular models leads to the prediction that **4a** and **4b** can exist in two possible conformations, a staggered conformation **8** and an eclipsed conformation **9**. The 250-MHz



8 9

spectra of **4a** and **4b** were recorded, and the resonances due to the six hydrogens of the reduced ring (labeled H_1-H_{4b} in **8** and **9**) were separated and essentially first order in nature. From decoupling experiments, resonances were assigned and coupling constants determined.[7a] The small couplings $J_{2,3a}$ (2.8-3.0 Hz) and $J_{2,3b}$ (0.8-1.0 Hz) for both **4a** and **4b** are consistent with structure **8**, in which H_2 is staggered between H_{3a} and H_{3b}, but not with structure **9**. In **9**, a larger coupling would be expected due to the dihedral angle of ca. 0° for H_2-H_{3b}.[7b]

A rationale for the product distributions from acid-catalyzed hydrolyses of **4a** and **4b** is outlined in Scheme II.[8] Ionization of **4a** and **4b** from their ground-state conformations via A1 mechanisms lead to intermediate benzyl cations **11**.[9] Unsubstituted cyclohexenyl cations are known to undergo preferential pseudoaxial attack by solvent at a rate faster than conformational isomerization of the ion,[10] and therefore the unstabilized ion **11a** derived from **4a** might be expected to undergo a similar attack by solvent to yield the trans-diol **4a**. For more stabilized ions such as that derived from **4b**, however, conformational isomerization of the initially formed ion might be expected to compete with solvent attack of **11b**. Product would then be derived from the more stable ion **12b**, which should undergo stereoselective axial attack by solvent to give preferential cis hydration. Therefore, as the ability of the aryl group to stabilize positive charge at the benzyl position increases, cis hydration will be favored.

The predominant trans hydration throughout the trans-diol epoxide series (2a-2c) has been rationalized by assuming that ionization occurs from the favored ground-state conformation with the hydroxyl groups equatorial, leading directly to the more stable cation with the newly formed hydroxyl group in an axial position.[8] Axial collapse of solvent with this intermediate leads to trans hydration.

The mechanisms of the spontaneous reactions are discussed in detail in the following paper.[11]

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Registry No. 3a, 36504-68-4; **3b**, 67694-88-6; **3c**, 56179-80-7; **3d**, 2461-34-9; **4b**, 82167-70-2; **5b**, 16821-34-4; **6b**, 65272-94-8; **7b**, 24722-22-2; 3,4-dihydro-6-methoxynaphthalene, 52178-91-3; 3,4-dihydro-6-methoxynaphthalene bromohydrin, 82167-71-3.

(11) Gillilan, R. E.; Pohl, T. M.; Whalen, D. L. *J. Am. Chem. Soc.*, the following paper in this issue.

"α" and "β" Deuterium Isotope Effects in the Hydrolysis of Naphthalene Tetrahydro Epoxides: Rate-Limiting Hydrogen Migration in the Spontaneous Hydrolysis of 6-Methoxy-1,2,3,4-tetrahydronaphthalene Oxide

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The mechanism by which an epoxide undergoes hydrolysis is a function of the pH of the solution. In addition to hydronium ion and hydroxide ion catalyzed hydrolyses, many epoxides undergo spontaneous reactions with solvent within certain pH limits.[1] The products from the spontaneous reaction of simple epoxides are usually diols or carbonyl compounds, formed in ratios dependent on the structure of the epoxide.[2-6] Spontaneous reactions of arene oxides usually yield phenolic products.[7]

The mechanism proposed for the spontaneous reaction of benzene oxide is outlined in Scheme I and involves the intermediacy of a zwitterionic species **2**. Formation of the intermediate **2** was proposed to be the rate-limiting step due to the lack of a significant kinetic deuterium isotope effect on the migrating hydrogen.[7b] The isomerization of aryl and vinyl epoxides to ketones via spontaneous reaction with solvent is formally similar to the spontaneous isomerization of arene oxides to phenols and presumably also occurs with 1,2-hydrogen migration.[8] In this paper, we report that 6-methoxy-1,2,3,4-tetrahydronaphthalene oxide **5b** (Scheme II) undergoes a spontaneous reaction to yield mostly (ca. 76%) 6-methoxy-2-tetralone **8b**, *and that this reaction proceeds with rate-limiting hydrogen migration.*

The rates of reaction of **5a** and **5b** (at pH <10) were fit to $k_{obsd} = k_{H^+}a_{H^+} + k_0$. Values of k_{H^+} and k_0 are provided in the previous paper,[9] along with product distributions from both acid-catalyzed

(7) (a) The 250-MHz spectra of **4a** and **4b** in $CDCl_3$ solutions were recorded. Coupling constants (Hz) assigned for **4a** were as follows: $J_{1,2} = 4.4$, $J_{2,3a} = 3.0$, $J_{2,3b} = 0.8$, $J_{2,4b} = 1.3$, $J_{3a,3b} = 14.6$, $J_{3a,4a} = 6.5$, $J_{3a,4b} = 1.6$, $J_{3b,4a} = 13.4$, $J_{3b,4b} = 5.8$, $J_{4a,4b} = 15.7$. Coupling constants (Hz) assigned for **4b** were as follows: $J_{1,2} = 4.4$, $J_{2,3a} = 2.8$, $J_{2,3b} = 1.0$, $J_{2,4b} = 1.5$, $J_{3a,3b} = 14.3$, $J_{3a,4a} = 6.6$, $J_{3a,4b} = 1.5$, $J_{3b,4a} = 13.1$, $J_{3b,4b} = 5.5$, $J_{4a,4b} = 15.5$. Assignments were made with the aid of decoupling experiments. (b) Couplings between eclipsed hydrogens in compounds with conformations similar to **9** are ca. 5.0 Hz: Yagi, H.; Thakker, D. H.; Lehr, R. E.; Jerina, D. M. *J. Org. Chem.* **1979**, *44*, 3439.

(8) This mechanism has been proposed to explain product distributions from bay-region diol epoxides of polycyclic aromatic hydrocarbons: Sayer, J. M.; Yagi, H.; Silverton, J. V.; Friedman, S. L.; Whalen, D. L.; Jerina, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 1972.

(9) Evidence for an A1 mechanism in the acid-catalyzed hydrolysis of **4a** has been provided by the fact that in solutions containing chloride ion, the product distribution is different than when chloride ion is absent despite the fact that there is no kinetic dependence on chloride ion at sufficiently low pH. Therefore, an intermediate must be trapped by chloride ion subsequent to the rate-limiting step (ref 4).

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(8) The isomerization of 1,3-cyclopentadiene oxide to 3-cyclopentenone occurs via hydride migration; ref 5.

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