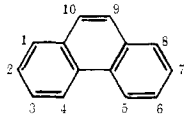
Comparative Mechanisms of Reaction of K-Region and Non-K-Region Arene Oxides of Phenanthrene

Sir:

Substantial evidence has implicated metabolically formed arene oxides as causative agents responsible for the toxic, mutagenic, and carcinogenic activity of many aromatic hydrocarbons.[1] Essentially all polycyclic aromatic hydrocarbons that have been found to be carcinogenic have a common structural feature called a K-region, the prototype of which is the 9,10-bond in phenanthrene.[2] It is, therefore, important to elucidate the comparative mechanisms of reaction of K-region and non-K-region oxides. Herein is described the solvolytic chemistry of I and II (where the oxide is at a non-K-region),[3] and III (where the oxide is at the K-region).[4] These compounds represent the three primary metabolites of phenanthrene.



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

Disappearance of I (240 nm) and II (265 nm) and appearance of products (275 nm) were followed spectrophotometrically at 30° in aqueous dioxane (50% v/v) at μ = 0.1 (KCl). Because of the slow rate of reaction of III, it was investigated in dioxane–water only in the acidic pH range. The pH–rate profiles thus obtained are given in the insert to Figure 1. The pseudo-first-order rate constants provide the rate law of eq 1 where

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

a_H is the hydrogen ion activity determined at the glass electrode and k_H^I = 17 M^{-1} sec^{-1}, k_0^I = 1.15 × 10^{-4} sec^{-1}, k_H^{II} = 38 M^{-1} sec^{-1}, k_0^{II} = 1.50 × 10^{-4} sec^{-1}, and k_H^{III} = 4.6 M^{-1} sec^{-1}. The rearrangement of all other non-K-region oxides investigated (benzene oxide and 1,2-naphthalene oxide in water,[5] 1,4-dimethylbenzene oxide[6] and 8,9-indane oxide[7] in 50% dioxane–water) has also been associated with this rate law. Product analyses for I and II were determined *via* high pressure liquid–liquid chromatography employing authentic samples of 1-, 2-, 3-, and 4-phenanthrol (pK_a's, 11.04, 11.04, 11.00, and 11.82, respectively, in 50% dioxane–water, μ = 0.1, T = 30°) for identification. The reaction path through k_H^I provides 76% 1-phenanthrol and 24% 2-phenanthrol, and that through k_0^I 97% 1-phenanthrol and 3% 2-phenanthrol. The yields associated with the k_H^{II} pathway are 73% 4-phenanthrol and 27% 3-phenanthrol and for k_0^{II} 82% 4-phenanthrol and 18% 3-phenanthrol. The epoxide ring opens preferentially to give an initial vinylogous benzylic cation. Aromatization of naphthalene 1,2-oxide predominately to 1-naphthol[8] also follows this rule.

Appearance of products (250 or 270 nm) from the rearrangement of III was followed at 30°, in H_2O at μ = 1.0 (KCl). Above pH 7, reactions were performed under argon atmosphere. The pH–rate profile thus obtained is shown in Figure 1. The theoretical line passing through the experimental points was generated from the empirical eq 2 where k_H = 100, k_0 = 2.1 × 10^{-4}, k_p = 2.5 × 10^{-5}, k_b = 7.0 × 10^{-18}, and pK_{app} = 7.2. Product analyses were carried out spectrophotometrically employing extinction coefficients of authentic 9-phenanthrol (pK_a = 9.08 in H_2O, μ = 1.0 and 11.05 in 50% dioxane–water, μ = 0.1, both at 30°, λ_{max} 251 nm, ϵ 3.5 × 10^4 M^{-1} cm^{-1}) and *trans*-9,10-dihydroxy-9,10-dihydrophenanthrene (λ_{max} 267 nm, ϵ 1.9 × 10^4 M^{-1} cm^{-1}). Below pH 6 (the pH range where eq 2 corresponds to the k_H and k_0 pathways of eq 1) 9-phenanthrol is the sole product, and above pH 9 (the pH range where product formation is dictated by the k_p and k_b terms of eq 2) only the vicinal dihydrodiol is obtained. At intermediate pH's varying amounts of both products may be observed. The trans diol VI (stereochemistry confirmed by tlc) obtained by allowing III to react under basic conditions was acidified with concentrated HCl, heated to 70°, and its rearrangement to 9-phenanthrol monitored at 250 nm (k_{obsd} = 6.0 × 10^{-4} sec^{-1} at H_0 ~0.4). The rearranged product had λ_{max} 251 nm and pK_a = 9.0. The arrows in the figure indicate points at which both III and 9,10-dideuterio-9,10-phenanthrene oxide were investigated. Lack of a primary kinetic isotope effect in the acidic and first plateau pH region is in agreement with previous results[9] indicating that aromatization of arene oxides takes place *via* rate-limiting epoxide ring opening to provide a resonance stabilized carbonium ion followed by the NIH shift. These results suggest the mechanism of Scheme I for reaction of III. The decrease in k_{obsd} occurring at pH ~7 leading to a second plateau requires the formation of a stable intermediate. While dihydrodiol V is an attractive candidate for this intermediate, structural information is as yet unavailable due to its transient nature. The second plateau results from HO^- attack (k_6) on III in equilibrium with V, and the first-order dependence on [HO^-] observed at high pH is the result of HO^- attack directly on V (k_5). In Scheme I it is not known if HO^- attacks the oxide (III) directly or reacts with carbonium ion IV. If the latter occurs, a kinetically equivalent mechanism is obtained for which $k_4'/k_{-4}' > 2 \times 10^{10}$ and $k_6' > 5 \times 10^5$ M^{-1} sec^{-1}.

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

The observed reaction of III with HO^- to give VI and the product of distal attack V differentiates this K-region arene oxide from most non-K-region arene oxides. For

(1) For pertinent references see reviews by (a) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, **28**, 1129 (1972); (b) D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974).

(2) (a) C. A. Coulson, *Advan. Cancer Res.*, **1**, 1 (1953); (b) A. Pullman and B. Pullman, *ibid.*, **3**, 117 (1955); (c) W. C. Herndon, *Trans. N. Y. Acad. Sci.*, **36**, 200 (1974).

(3) H. Yagi and D. M. Jerina, *J. Amer. Chem. Soc.*, **95**, 243 (1973).

(4) P. Dansette and D. M. Jerina, *J. Amer. Chem. Soc.*, **96**, 1224 (1974).

(5) G. J. Kasperek and T. C. Bruice, *J. Amer. Chem. Soc.*, **94**, 198 (1972).

(6) G. J. Kasperek, T. C. Bruice, H. Yagi, N. Kaubisch, and D. M. Jerina, *J. Amer. Chem. Soc.*, **94**, 7876 (1972).

(7) G. J. Kasperek, P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Amer. Chem. Soc.*, **95**, 6041 (1973).

(8) D. R. Boyd, J. W. Daly, and D. M. Jerina, *Biochemistry*, **11**, 1961 (1972).

(9) G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Chem. Commun.*, 784 (1972).

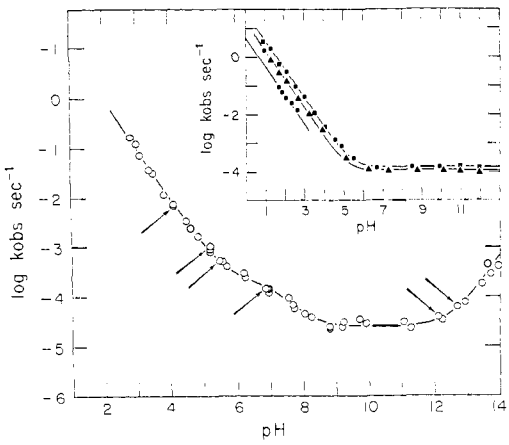
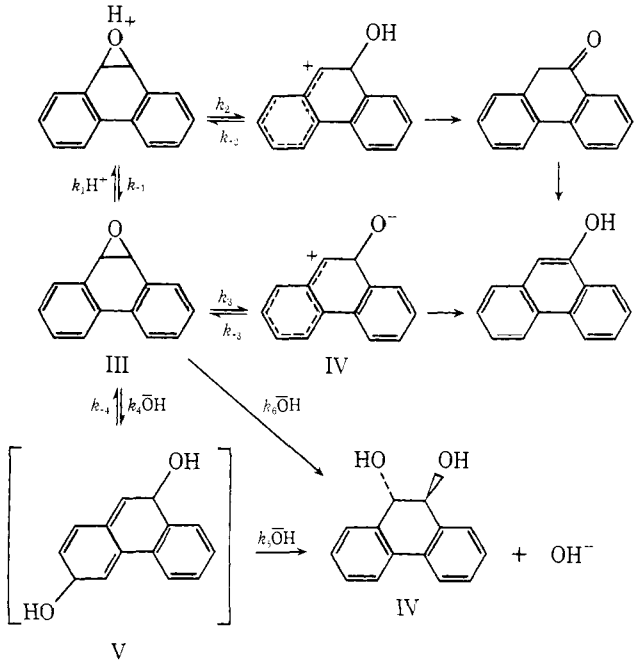


Figure 1. pH–rate profile for the rearrangement of 9,10-phenanthrene oxide (H_2O, μ = 1.0, 30°). Arrows point to duplicate determinations for 9,10-dideuterio-9-10-phenanthrene oxide. Insert to figure: pH–rate profiles for the rearrangement of 3,4-phenanthrene oxide (■), 1,2-phenanthrene oxide (▲), and 9,10-phenanthrene oxide (●). (50% dioxane–water, μ = 0.1, 30°).

Scheme I



$$k_2K_1 = 1.0 \times 10^2 M^{-1}\ \text{sec}^{-1}$$
$$k_3 = 2.1 \times 10^{-4}\ \text{sec}^{-1}$$
$$k_4/k_{-4} = 4.26 \times 10^6$$
$$k_5 = 4.73 \times 10^{-4} M^{-1}\ \text{sec}^{-1}$$
$$k_6 = 1.07 \times 10^2 M^{-1}\ \text{sec}^{-1}$$
$$K_w = 1.48 \times 10^{-14}$$

example, benzene oxides and 1,2-naphthalene oxide do not react with HO^-.[5-7,9] Phenols are their products of rearrangement regardless of pH; the corresponding *trans*-dihydrodiols are obtained only *via* enzymatic hydration.[10] In addition III, unlike the non-K-region arene oxides,[11] has been found to react rapidly with primary and secondary amines. Mercaptide ions have been shown to provide enhanced rates of disappearance of benzene oxide from aqueous solution (Brønsted β = 0.2),[12] but their reaction with III is even more marked. The stereochemistry for the addition of nucleophiles to arene oxides is generally trans.[11] The question of nucleophilic attack on III *vs.* IV and a detailed account of the reaction of III with amines, mercaptide ions, proteins, and nucleic acids will be presented in the full paper.

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(10) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *Biochemistry*, **9**, 147 (1970).

(11) A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo, and G. A. Berchtold, *J. Amer. Chem. Soc.*, in press.

(12) D. M. E. Reuben and T. C. Bruice, *J. Chem. Soc., Chem. Commun.*, 113 (1974).

Paula Yurkanis Bruice, Thomas C. Bruice*
Department of Chemistry, University of California, Santa Barbara Santa Barbara, California 93106

Hans G. Selander, Haruhiko Yagi, Donald M. Jerina*
Laboratory of Chemistry, National Institutes of Health Bethesda, Maryland 20014

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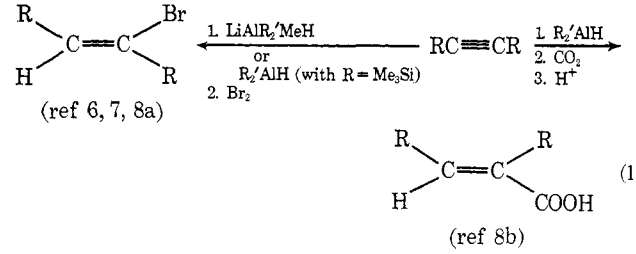
Stereospecific Hydralumination of Alkenes and the Stereochemistry of Reactions at Alkyl Carbon–Aluminum Bonds[1]

Sir:

The stereospecific cis[2-5] or trans[4,6] hydralumination of alkynes, coupled with substitution and insertion reactions on the resulting vinylic aluminum adducts that occur with retention of configuration, is an important synthetic route to stereoregulated alkenes and their derivatives[6-9] (eq 1).



(1)

Extension of such stereospecific hydraluminations and subsequent derivatizations to alkenes has been beset, up to the present, with two difficulties: (a) hydraluminations of alkenes, especially of the vicinally disubstituted ethylenic type, proceed at much slower rates;[10] and (b) more discouragingly, nmr studies have shown that, in

(1) Part XXIX of the series, "Organometallic Compounds of Group III," devoted to carbometalation and hydrometalation, *cf.* J. J. Eisch and S.-G. Rhee, *J. Organometal. Chem.*, in press, for the previous part.

(2) G. Wilke and H. Müller, *Justus Liebigs Ann. Chem.*, **629**, 222 (1960).

(3) J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, **88**, 2213 (1966).

(4) J. J. Eisch and M. W. Foxton, *J. Organometal. Chem.*, **11**, P50 (1968); *J. Org. Chem.*, **36**, 3520 (1971).

(5) J. J. Eisch and R. Amtmann, *J. Org. Chem.*, **37**, 3410 (1972).

(6) G. Zweifel and R. B. Steele, *J. Amer. Chem. Soc.*, **89**, 5085 (1967).

(7) G. Zweifel and C. C. Whitney, *J. Amer. Chem. Soc.*, **89**, 2753 (1967).

(8) (a) J. J. Eisch and G. Gupta, unpublished work; (b) J. J. Eisch and M. W. Foxton, *J. Organometal. Chem.*, **11**, P7 (1968).

(9) *Cf.* H. Lehmkuhl, K. Ziegler, and H.-G. Gellert in "Houben-Weyl Methoden der Organischen Chemie," Vol. XIII/4, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1970, pp 204–258.

(10) (a) K. Ziegler, H.-G. Gellert, H. Martin, K. Nagel, and J. Schneider, *Justus Liebigs Ann. Chem.*, **589**, 91 (1954); (b) G. Hata, *Chem. Commun.*, 7 (1968).