(5) For electronic calculations of the phenyl cations see C. G. Swain, J. E. Sheats, D. C. Gorenstein, and K. G. Harbison, *J. Am. Chem. Soc.*, **97**, 791 (1975), and E. M. Evleth and P. M. Horowitz, *ibid.*, **93**, 5636 (1971)
(6) G. D. Miller, Ph.D. Dissertation, Florida State University, 1975.
(7) At small LAB angles (like 5°), the forward direction in the cm frame corresponds approximately to scattering with LAB energies smaller than that of the center-of-mass (CM), while the backward direction corresponds to scattering with LAB energies greater than that of the CM.

R. C. Horvat, G. D. Miller, S. A. Safron*
Department of Chemistry, Florida State University
Tallahassee, Florida 32306
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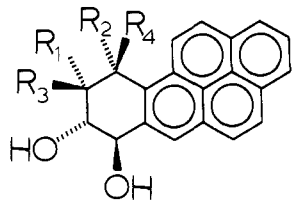
Hydrolysis of *syn*- and *anti*-Benzo[*a*]pyrene Diol Epoxides: Stereochemistry, Kinetics, and the Effect of an Intramolecular Hydrogen Bond on the Rate of *syn*-Diol Epoxide Solvolysis

Sir:

A 9,10-oxide of *trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene has recently been implicated as a major activated metabolite in benzo[*a*]pyrene mutagenesis and carcinogenesis.[1,2] Both the *anti*-diol epoxide, **1**, and the *syn*-diol epoxide, **2**, have been synthesized.[2a,3] Although both compounds proved to be mutagenic to mammalian cells, the anti-stereoisomer, **1**, is exceptionally powerful;[2d,3] however, **2**, was more mutagenic than **1** to *Salmonella typhimurium*.[2b,c] Moreover, liver microsomal metabolism of benzo[*a*]pyrene-7,8-*trans*-dihydrodiol gave products identical on high pressure liquid chromatography with those obtained from the hydrolysis of **1**, but not of **2**.[2d]



	R_1	R_2	R_3	R_4
1:	-O-		H	H
2:	H	H	-O-	
3:	OH	OH	H	H
4:	H	H	OH	OH
5:	OH	H	H	OH
6:	H	OH	OH	H

We have investigated the aqueous solvolysis of **1** and **2** as models for the reaction of these epoxides with other weak nucleophiles in aqueous systems. We report now that ring opening of both isomers proceeds with relatively similar rates and with remarkable cis stereoselectivity at pH 5.0. In addition, oxide **2** proved more sensitive to dihydrogen phosphate general acid catalysis than **1**.

Solvolysis of both **1** and **2** was carried out at pH 5.0 in 1:1 (v/v) dioxane-water, 0.10 M in KCl at 37 °C. Acetylation of the reaction products[5] followed by thin layer chromatography[6] of the crude acetates afforded the 7,8,9,10-tetraacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenes in good yield.[7] NMR spectroscopy (270 MHz)[8] of the tetraacetates derived from the *anti*-diol epoxide, **1**, indicated the formation of the *trans,cis,cis*-**5**, and the *trans,cis,trans*-**3**, stereoisomers in the ratio of 3:2. These products presumably arise from addition of water at C-10 in both cis and trans directions. Regiospecific attack at C-10 is supported by the failure to detect the trans-trans-trans-isomer, **6**, expected to arise from trans-specific attack at C-9, and is consistent with the previous observations

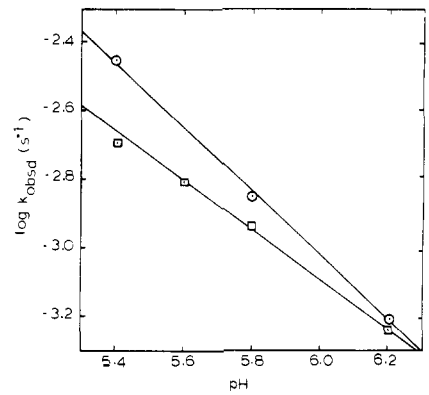


Figure 1. pH-Rate profiles of the reactions of 7α,8β-dihydroxy-9β,10-epoxy-(**1**,○) and 7α,8β-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**2**, ⊡) in 1:1 dioxane-water at 34.8 °C, 0.0950 M in KCl and 0.0034 M in phosphate. Points are experimental; lines are theoretical.

of attack of sulfur nucleophiles at C-10.[3a,b] The NMR spectrum (90 MHz) of the tetraacetates derived from the *syn* diol epoxide, **2**, showed the presence of only the 9,10-cis adduct, tetraacetyl-**4**.[10]

The kinetic measurements were carried out in a solvent system of similar composition as the product studies above (1:1 (v/v) dioxane-water, 0.095 M in KCl and 0.003 42 M in phosphate).[11] The reactions were run in a spectrophotometer in order to monitor the appearance and disappearance of the characteristic λ_{max}'s of product dihydrodiols and the starting epoxide.[12]

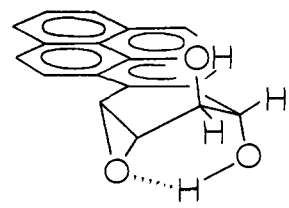
First-order rate constants were calculated from the change of absorbance at 278.8 nm.[13] The pH dependence of these reactions is illustrated in Figure 1. Diol epoxide **1** exhibits a linear log $k_{obsd,1}$ vs. pH plot with a slope = −1.0. This is normally associated with acid catalysis; i.e., $k_{obsd,1} = k_{h,1}a_H$, where a_H is the hydrogen ion activity as determined by glass electrode and $k_{H,1}$ is the specific acid catalyzed rate constant, here equal to 910 M^{-1} s^{-1}.[14]

Diol epoxide **2** failed to conform to this pattern, since the slope of the log $k_{obsd,2}$ vs. pH plot is −0.7, instead of −1.0. This deviation can be rationalized by adding a term for general acid catalysis by dihydrogen phosphate anion to the expression for $k_{obsd,2}$, i.e.,

$$k_{obsd,2} = k_{H,2}a_H + k_{H_2PO_4^-}[H_2PO_4^-] \qquad (1)$$

Substituting $F_{PO_4}a_H/(K_a + a_H)$ for $[H_2PO_4^-]$ in eq (1), dividing through by a_H, and plotting $k_{obsd,2}/a_H$ vs. $F_{PO_4}/a_H(K_a + a_H)$ produces a linear array of points with slope = $k_{H_2PO_4^-}$ = 0.32 M^{-1} s^{-1} and intercept = $k_{H,2}$ = 300 M^{-1} s.

These results are in accord with present ideas concerning the structures of diol epoxides **1** and **2** in solution.[3,15] The lower $k_{H,2}$ value may reflect a decrease in the pK_b of the oxirane oxygen caused by an internal hydrogen bond between C_7-OH and the oxirane oxygen in **2**.[3,15] *anti*-Diol epoxide, **1**, cannot form such a bond. Likewise, hydrogen bond-induced polarity in the epoxide moiety of **2** may enhance participation of the dihydrogen phosphate anion in the ring opening process.[16]



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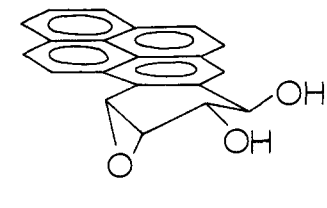

1

The difference between the 9,10-cis/trans ratios of the hydrolysis products from diol epoxides **1** and **2** resists a simple explanation. Nevertheless, these reactions do provide models for the reactions of **1** and **2** with other weak nulceophiles in aqueous systems. In particular, on the basis of our results, it would be reasonable to expect both cis and trans adducts of metabolically produced *anti*-diol epoxide, **1**, with the nucleophilic sites on cellular DNA. Furthermore, while the intramolecular hydrogen bond in **2** greatly facilitates the addition of nucleophiles in the *tert*-butyl alcohol solvent system,[3a] S_N1 reactivity of the two diol epoxide stereoisomers, **1** and **2**, in aqueous solvents seems to be very similar. Also, in the naphthalene system, sulfur nucleophile addition rates in aqueous ethanol were very similar for the *syn*- and *anti*-3,4-diol 1,2-oxides.[3a] Thus, the suggestion[2d] that the observed lower mutagenic activity of **2** may be a consequence of the fact that this isomer is so "highly reactive that it hydrolyzes rapidly before it can reach and react with DNA" would appear untenable.

Finally, it should be noted that epoxide rearrangement to afford *trans*-7,8-dihydroxy-9-keto-7,8,9,10-tetrahydrobenzo[*a*]pyrene could not be detected. This is consistent with the known tendency of aryl epoxides to hydrolyze rather than rearrange in aqueous solvents.[17] The K-region arene oxides which furnish large amounts of rearranged products (i.e., phenols) during aqueous solvolysis represent a special case for the reasons discussed previously.[4]

Acknowledgments. This work was supported by Grants CA-07175 and CRTY-5002 from the National Cancer Institute, National Institutes of Health, and Grant BC-132 from the American Cancer Society (R.G.H.). C. H. is an American Cancer Society Professor of Oncology.

References and Notes

(1) P. Sims, P. L. Grover, A. Swaisland, K. Pal, and A. Hewer, *Nature (London)*, **252**, 326 (1974).
(2) Anti-diol epoxide, **1**, is also named (±)-7α,8β-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene. The syn-diol epoxide, **2**, is also named (±)7α,8β,-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene. (b) C. Malaveille, H. Bartsch, P. Grover, and P. Sims, *Biochem. Biophys. Res. Commun.*, **66**, 693 (1975). (c) P. G. Wislocki, A. W. Wood, R. L. Chang, W. Levin, H. Yagi, O. Hernandez, D. M. Jerina, and A. H. Conney, *ibid.*, **68**, 1006 (1976). (d) E. Huberman, L. Sachs, S. K. Yang, and H. V. Gelboin, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 607 (1976). (e) R. F. Newbold and P. Brookes, *Nature (London)*, **261**, 52 (1976).
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(4) J. W. Keller and C. Heidelberger, *J. Am. Chem. Soc.*, **98**, 2328 (1976).
(5) The acetylation procedure consisted of first removing the hydrolysis solvent under vacuum, then extracting the reaction products from the salts with THF and adding the THF solution (about 1 ml) to a mixture of 10 ml of acetic anhydride and 1 ml of pyridine, which had been previously refluxed for 10 min. After sitting overnight at room temperature under nitrogen, the mixture was mixed with equal volumes of benzene and water and was separated, and the organic phase was reduced to dryness under vacuum.
(6) Thin layer chromatography was performed on Kodak silica gel sheets with dichloromethane–1% diethyl ether as the eluting solvent. The developed chromatograms were cut into pieces and extracted with diethyl ether, and the optical density of the extracts was measured at 280 nm; 80–90% of the total OD units recovered from the sheets coincided with the tetraacetate spots.
(7) The tetraacetates showed mass spectral molecular ions at *m/e* 488 and base peaks at 488 − CH_3CO_2H. The ultraviolet spectra showed λ_{max}'s at 248, 263, 278, 310, 336, and 348 nm in 95% EtOH.
(8) We thank Professor H. W. Whitlock for performing this NMR experiment.
(9) In subsequent experiments, we were able to separate $(Ac)_4$-**3** and -**5** by thin layer chromatography. NMR($CDCl_3$) $(Ac)_4$-**3** (R_f 0.25) δ 2.06 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 5.64 (q, 1 H, $J_{7,8}$ = 3.5, $J_{8,9}$ = 2.3 Hz, H-8), 5.95 (q, 1 H, $J_{9,10}$ = 4.9, $J_{8,9}$ = 2.3 Hz, H-9), 6.66 (d, 1 H, $J_{7,8}$ = 3.5 Hz, H-7), 7–8.5 (m, H-10 and aromatic H's); $(Ac)_4$-**5** (R_f 0.30) δ 2.03 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 2.29 (s, 3 H, OAc), 5.79 (q, 1 H, $J_{8,9}$ = 2.25, $J_{7,8}$ = 8.90 Hz, H-8), 5.84 (q, 1 H, $J_{9,10}$ = 3.75, $J_{8,9}$ = 2.25 Hz, H-9), 6.80 (d, 1 H, $J_{7,8}$ = 8.9 HZ, H-7), 7–8.5 (m, 9 H, H-10 and aromatic H's).
(10) NMR ($CDCl_3$) of Ac_4-**4**: δ 2.04 (s, 6 H, 2 OAc's), 2.06 (s, 3 H, OAc), 2.29 (s, 3 H, OAc), 5.60 (q, 1 H, J = 3.4, 11 Hz, H-9), 6.09 (q, 1 H, J = 11,8 Hz, H-8), 6.76 (d, 1 H, J = 8 Hz, H-7), 7.47 (d, 1 H, J = 3.4 Hz, H-10), 8.0–8.5, 8 H, aromatic H's).
(11) This buffer system was made by titrating a solution of 1: dioxane–water, 0.0950 M in KCl and 0.0034 M in K_2HPO_4 with 1:1 dioxane–water, 0.0950 M in KCl and 0.50 M in HCl at 35 °C. The pK_a was 5.9. Thus, buffers with an ionic strength of 0.106 M could be made up with less than 2% difference in the ionic strength between pH 5.2 and pH 9.
(12) Both oxides **1** and **2** exhibited UV maxima at 280.0 nm which shifted to 278.6 nm during hydrolysis. Isosbestic points were observed at 279.5 nm.
(13) R. C. Williams and J. W. Taylor, *J. Chem. Educ.*, **47**, 129 (1970).
(14) General acid catalysis by dihydrogen phosphate anion in the solvolysis of **1** cannot be totally excluded by these preliminary experiments. However, $k_{H_2PO_4^-,1}$ is certainly less than 0.05 M^{-1} s^{-1}.
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John W. Keller,* Charles Heidelberger
McArdle Laboratory for Cancer Research
University of Wisconsin
Madison, Wisconsin 53706

Fred A. Beland, Ronald G. Harvey
Ben May Laboratory for Cancer Research
University of Chicago
Chicago, Illinois
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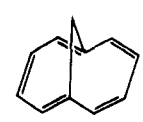
Construction of the 1,5-Methano[10]annulene (Bicyclo[5.3.1]undeca-1,3,5,7,9-pentaene) System

Sir:

Vogel and his associates accomplished the first synthesis of 1,6-methano[10]annulene (**1**) in 1964[1] and have built the elegantly organized chemistry of bridged cyclic π-electron systems.[2] This development has naturally aroused interest in 1,5- (instead of 1,6-)methano[10]annulene (**2**) and its chemistry, initially for the apparent structural similarity of the two systems. Indeed numerous attempts at the synthesis of **2** have been made.[3] Our own interest in **2** originated from two main experimental facts: (i) the lability exhibited by two (nonbridged) [10]annulenes[4] appears more pronounced than that intuitively conceived from the stability of **1** and (ii) the apparent existence of a nonnegligible 1,6-interaction calculated by several theoretical treatments[5] seems to be manifested in the photoelectron[5a] and ultraviolet spectra of **1**.[6,7] To further examine to what extent the transannular interaction, if it exists, perturbs the monocyclic 10 π-electron system of **1**, we have selected **2** where such an interaction would very likely vanish (cf. azulene and naphthalene[8,9]). It is obvious, however, that the evaluation of the electronic structure of **2** in comparison with **1** requires a careful examination of the geometry of the two compounds, since Allinger and Sprague[10] have recently predicted that the σ system constraints of **2** would force ring dihedral angles to differ up to 54° from planarity; thus **2** would have complete bond alternation and lack so-called aromaticity. We have now achieved the first construction of this system in a remarkably simple manner and wish to present its spectral and chemical properties in preliminary form.



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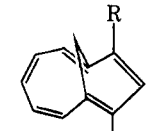

2, R = R′ = H
11, R = H; R′ = CO_2CH_3
14, R = H; R′ = OCH_3
15, R = H; R′ = $OSi(CH_3)_2t$-C_4H_9
16, R = H; R′ = $OPO(OC_2H_5)_2$
17, R = OCH_3; R′ = CO_2CH_3
18, R = Cl; R′ = CO_2CH_3
19, R = H; R′ = Cl

The present scheme owes its success to a one-step synthesis of the proper ring system containing four carbon–carbon