Carbon-13 Nuclear Magnetic Resonance Study of Nucleophilic Additions to Benzo[a]pyrene 4,5-Oxide and of Its Acid-Catalyzed Rearrangement

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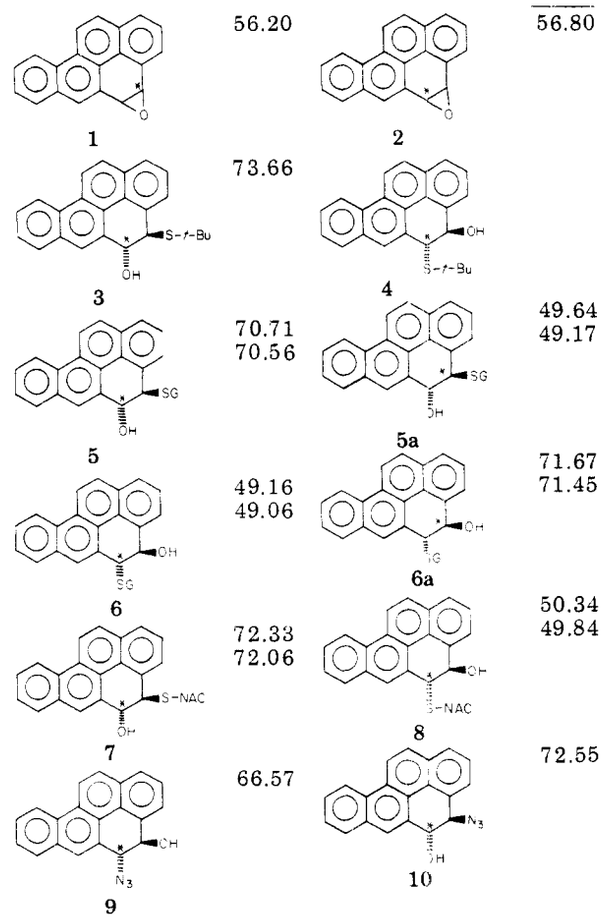
Nucleophilic additions to benzo[a]pyrene 4,5-oxide labeled in position 4 or 5 with carbon-13 were studied by ^{13}C NMR spectroscopy. Under neutral or basic conditions, only soft nucleophiles such as *tert*-butylmercaptan, glutathione, *N*-acetylcysteine, and azide are able to add to the oxirane ring to give the trans adducts. No preferential attack at position 4 or 5 is observed. With chiral nucleophiles, such as glutathione and *N*-acetylcysteine, all four diastereomers are observed by ^{13}C NMR spectroscopy. Under acidic conditions with methanesulfonic acid in aqueous dioxane, benzo[a]pyrene 4,5-oxide preferentially undergoes the NIH shift to form the 4-phenol and 5-phenol in a 60:40 ratio. In methanol, the two phenols are obtained in a 60:40 ratio along with the four possible hydroxy ethers. However, if HCl in dioxane is used, the trans dihydro diol and two chlorohydrins are formed in addition to the two phenols. Likewise, these same products form if methanesulfonic acid is used as the acid in the presence of LiCl. Chloride appears to be especially effective as a nucleophile in trapping the carbocation from acid-catalyzed ring opening of benzo[a]pyrene 4,5-oxide. The acid-catalyzed dehydration of trans-4,5-dihydrobenzo[a]pyrene-4,5-diol also gives a 60:40 ratio of the 4-phenol and the 5-phenol. The lack of significant selectivity observed in nucleophilic addition reactions and acid-catalyzed rearrangement of benzo[a]pyrene 4,5-oxide as well as in the acid-catalyzed dehydration of the trans diol are consistent with the identical Dewar reactivity numbers for the 4- and 5-positions.

Metabolic transformation of polycyclic aromatic hydrocarbons results in the formation of a variety of oxidized species, including arene oxides, phenols, and quinones. The ability of arene oxides to exhibit mutagenic[3,4] and carcinogenic[3,5] activity has resulted in an extensive study of both K-region and non-K-region arene oxides. Several attempts have been made to correlate the chemical properties of arene oxides with theoretical parameters. For example, Jerina and co-workers have obtained the relative reactivities of a variety of arene oxides by calculating the difference in delocalization energy (ΔE_{deloc}) between the arene oxide and the ring-opened zwitterion.[6] On the basis of these calculations, they have proposed that arene oxides located in a "Bay region" should be unusually reactive. In addition, these calculations lead to the prediction of high reactivity for diol epoxides, such as benzo[a]pyrene-7,8-diol 9,10-epoxide, which currently are viewed as the ultimate carcinogens of polycyclic hydrocarbons. Harvey and co-workers have used Dewar reactivity numbers,[7] N_t, to calculate regioselectivity of attack of nucleophiles on arene oxides and have observed rather good agreement between theory and experimental results.[8] These two methods are related in that both ΔE_{deloc} and N_t are calculated from nonbonding MO coefficients. Recently, Harvey and co-workers have tabulated a large amount of experimental data and have evaluated these data by using N_t calculations.[9] There is a good correlation between predicted and

Table I. Structure and Carbon Chemical Shifts of Labeled BAP 4,5-Oxide and Derivatives



(1) (a) Taken in part from the Ph.D. thesis of M.D.H., submitted to the Graduate School of the University of New Mexico in partial fulfillment of the requirements for the Ph.D. degree, 1979. (b) Address correspondence to D.L.V.J., Department of Biochemistry, University of New Mexico School of Medicine, Albuquerque, N.M. 87131. (c) This work was supported by NIH Grant CA 16871 and by a Research Career Development Award (CA 70939) to D.L.V.J., both grants from the National Cancer Institute, and by NSF Grant MPS 75-06111.

(2) Abbreviations: BAP, benzo[a]pyrene; BAP 4,5-oxide, benzo[a]-pyrene 4,5-oxide; BAP-4,5-diol, *trans*-4,5-dihydrobenzo[a]pyrene-4,5-diol; BAP-4-ol, benzo[a]pyrene-4-ol; BAP-5-ol, benzo[a]pyrene-5-ol; GSH, glutathione; NACSH, *N*-acetylcysteine.

(3) P. Sims and P. L. Grover, *Adv. Cancer Res.*, **20**, 165 (1974).

(4) J. McCann, E. Choi, E. Yamasaki, and B. Ames, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 5135 (1975).

(5) W. Levin, A. W. Wood, H. Yagi, P. M. Dansette, D. M. Jerina, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 243 (1976).

(6) D. M. Jerina, R. E. Lehr, H. Yagi, O. Hernandez, P. M. Dansette, P. G. Wislocki, A. W. Wood, R. L. Chang, W. Levin, and A. H. Conney, "In Vitro Metabolic Activation in Mutagenesis Testing", Elsevier/North-Holland Biomedical Press, Amsterdam, 1976, p 159.

(7) M. J. S. Dewar in "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969.

(8) F. A. Beland and R. G. Harvey, *J. Am. Chem. Soc.*, **98**, 4963 (1976).

(9) P. P. Fu, R. G. Harvey, and F. A. Beland, *Tetrahedron*, **34**, 857 (1978).

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observed products in the isomerization of arene oxides to phenols and the dehydration of arene dihydro diols to phenols. Correlations for nucleophile additions to arene oxides are less certain owing to limited data. Benzo[a]pyrene 4,5-oxide (BAP 4,5-oxide[2]) does not appear to follow the correlation. The N_t values for the 4- and 5-positions are identical, leading one to expect that the rearrangement of BAP 4,5-oxide via the NIH shift[10] should give similar amounts of BAP-4-ol and BAP-5-ol. Yang et al.[11] reported that the acid-catalyzed rearrangement of BAP 4,5-oxide gave only BAP-5-ol. Grover et al.[12] reported that this rearrangement gave only BAP-4-ol. Likewise, the dehydration of BAP-4,5-diol was reported to give only BAP-5-ol by Yang et al. and only BAP-4-ol by Grover et al.

As part of a program aimed at evaluating the reactivity–selectivity properties of carcinogenic electrophiles, we report here on some nucleophilic additions to benzo[a]pyrene 4,5-oxide under both acidic and basic conditions and also a reinvestigation of the acid-catalyzed rearrangement of BAP 4,5-oxide. BAP 4,5-oxide labeled with ^{13}C in either position 4 or position 5 (**1** and **2**) was used, and products were analyzed by ^{13}C NMR spectroscopy.

Experimental Section

The synthesis of BAP 4,5-oxide labeled with ^{13}C (90% enriched) in position 4 or 5 and the synthesis of some of the BAP derivatives used in this study for obtaining carbon chemical shifts will be described elsewhere.[13] Tables I and II give the structures and carbon chemical shifts of the compounds described in this study. All chemical shifts are expressed as parts per million downfield from Me_4Si.

Reaction of *tert*-Butylmercaptan with BAP 4,5-Oxide. BAP-5-^{13}C 4,5-oxide (**2**; 5.0 mg, 0.019 mmol) was dissolved in 1.75 mL of freshly distilled dioxane. The solution was stirred while 1.75 mL of water was added which resulted in a suspension of the arene oxide. *tert*-Butylmercaptan (4.2 μL, 0.038 mmol) was added to the stirring suspension followed by the addition of 0.1 mL (0.1 mmol) of 1 M NaOH. The mixture was flushed with N_2 and stirred for 3 h at 55 °C. The pale red solution was cooled and treated with water and ethyl ether. The ether phase was washed several times with water and then dried over anhydrous $MgSO_4$. After removal of the solvent by rotary evaporation, the residue was dissolved in $CDCl_3$ for ^{13}C NMR analysis.

Reaction of Glutathione with BAP 4,5-Oxide. BAP-4-^{13}C 4,5-oxide (**1**; 4.5 mg, 0.017 mmol) was allowed to react with glutathione (10 mg, 0.033 mmol) in a manner similar to the above procedure. The workup was also similar except that the products were in the aqueous phase. The aqueous phase was dried by rotary evaporation, and the residue was dissolved in D_2O for ^{13}C NMR analysis. The reaction was repeated for BAP-5-^{13}C 4,5-oxide (**2**).

Reaction of *N*-Acetylcysteine with BAP 4,5-Oxide. In a manner similar to that described for the reaction of BAP 4,5-oxide with glutathione, BAP-5-^{13}C 4,5-oxide (**2**; 5.0 mg, 0.019 mmol) was allowed to react with *N*-acetylcysteine (6 mg, 0.038 mmol). ^{13}C NMR analysis was carried out in D_2O.

Reaction of Sodium Azide with BAP 4,5-Oxide. Sodium azide (0.2 mL of a 0.15 M solution, 0.030 mmol) was added to a suspension of BAP-5-^{13}C 4,5-oxide (**2**; 4.0 mg, 0.015 mmol) in 3 mL of 50% aqueous dioxane. The reaction mixture was treated in a manner similar to the above procedures, and the crude products were dissolved in acetone-d_6 for ^{13}C NMR analysis.

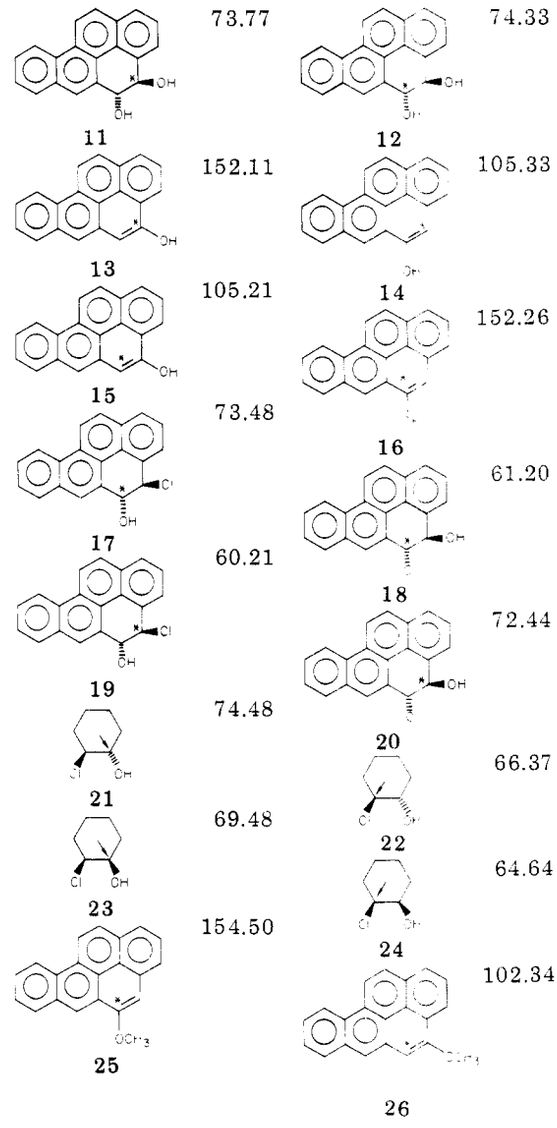
Methanesulfonic-Acid-Catalyzed Rearrangement of BAP 4,5-Oxide. The following general procedure was used for the study of the acid-catalyzed rearrangement of BAP 4,5-oxide. BAP-4-^{13}C 4,5-oxide (**1**; 3 mg, 0.01 mmol) or BAP-5-^{13}C 4,5-oxide (**2**; 3.0 mg, 0.01 mmol) was dissolved in 10 mL of the appropriate solvent. Methanesulfonic acid (0.03 mmol) was added, and the resulting solution was stirred for 1 h at room temperature. NaOH (0.03 mmol) was added, and the solvent was removed on a rotary evaporator. The residue was dissolved in acetone-d_6 for ^{13}C NMR analysis.

HCl-Catalyzed Rearrangement of BAP 4,5-Oxide. To a solution of BAP-4-^{13}C 4,5-oxide (**1**; 3.9 mg, 0.015 mmol) in 10 mL of dioxane was added 0.2 mL of 1 N HCl. The solution was stirred for 3 h under N_2, and the solvent was removed on a rotary evaporator. The residue was dissolved in acetone-d_6 for ^{13}C NMR analysis. In an analogous manner, BAP-5-^{13}C 4,5-oxide (**2**) was allowed to react with HCl in dioxane containing varying amounts of water.

Formation of Chlorohydrins of BAP 4,5-Oxide. To a solution of BAP-5-^{13}C 4,5-oxide (3.0 mg, 0.012 mmol) in 10 mL of dioxane was added 0.2 mL of 1 N HCl and 0.3 mL of water containing LiCl (9 mg, 1.3 mmol). The same reaction was run in 10 mL of dioxane containing 0.5 mL of water, 9 mg of LiCl, and 0.22 mg (0.23 mmol) of methanesulfonic acid. After removal of solvent by rotary evaporation, the residue was dissolved in acetone-d_6 for ^{13}C NMR analysis.

Acid-Catalyzed Dehydration of BAP-4,5-diol. BAP-4,5-diol-5-^{13}C (**12**; 2.0 mg, 0.007 mmol) was dissolved in 10 mL of the appropriate solvent. Methanesulfonic acid (1.5 mmol) was added, and the resulting solution was refluxed for 12 h. The solution

Table II. Structures and Carbon Chemical Shifts of Products from the Acid-Catalyzed Reactions of BAP 4,5-Oxide



(10) D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974).
(11) S. K. Yang, P. P. Roller, and H. V. Gelboin, *Biochemistry*, **16**, 3680 (1977).
(12) P. L. Grover, A. Hewer, and P. Sims, *Biochem. Pharmacol.*, **21**, 2713 (1972).
(13) M. D. Hylarides, G. H. Daub, and D. L. Vander Jagt, submitted for publication.

was cooled by addition of 5 g of ice and was extracted with ether. The ether extract was washed with water and dried over $MgSO_4$. After removal of the ether, the residue was dissolved in acetone-d_6 for ^{13}C NMR analysis.

Synthesis of Chlorohydrins of Cyclohexene. The trans chlorohydrin was prepared as follows:[14]

A 125-mL pear-shaped flask equipped with a magnetic stirrer and a thermometer was charged with a solution of 0.50 g (6.06 mmol) of cyclohexene in 60 mL of methylene chloride and 20 mL of 0.5 M $NaHCO_3$. The vigorously stirred mixture was cooled to 2 °C in an ice–water bath, and 1.23 g (6.06 mmol) of 85% *m*-chloroperbenzoic acid was added in small portions over a 20-min period. After the addition of the peracid, the reaction mixture was allowed to warm to ambient temperature and then stirred for 3 h. The organic layer was washed with 10% Na_2SO_3 and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 0.55 g of a pale yellow oil. This oil was dissolved in 200 mL of anhydrous ether containing 0.99 g (6.10 mmol) of anhydrous $FeCl_3$. After 3 min of stirring, the reaction mixture was washed twice with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give 0.56 g (68%) of a pale yellow oil which was analyzed by ^{13}C NMR spectroscopy.

The cis chlorohydrin was prepared as follows:

A 125-mL Erlenmeyer flask equipped with a magnetic stirrer and condenser was charged with 2.68 g (70.8 mmol) of $NaBH_4$ and 60 mL of absolute ethanol. To this stirred mixture was added 2.10 g (15.8 mmol) of 2-chlorocyclohexanone in one portion, which caused an exothermic reaction. The resulting mixture was stirred under an atmosphere of dry N_2 for 45 min. After dilution with water, the aqueous layer was extracted with ether. The organic layers were combined, and the solvent was removed under reduced pressure to give a colorless oil which was dissolved in ether, washed with 5% HCl and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 2.03 g (95%) of a colorless oil which was analyzed by ^{13}C NMR spectroscopy.

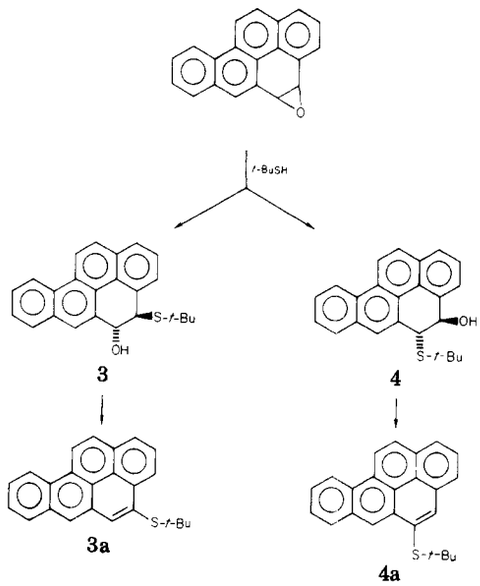
^{13}C NMR Analysis of the Products. ^{13}C NMR spectra of the products formed in the nucleophilic addition reactions or the acid-catalyzed rearrangement of BAP 4,5-oxide and in the dehydration of BAP-4,5-diol were recorded either with a Varian XL-100 CW-FT spectrometer (Nicolet TT 100 FT system) or with a Varian FT-80 spectrometer on FT mode with proton decoupling. The amounts of the various products formed in the reactions described were estimated by recording standard spectra for known mixtures of the various ^{13}C-enriched compounds. The peak heights were measured and used as reference values. The same instrument settings were then used to record the spectra of the reactions' products, and the product ratios were determined from the peak heights. This method is not highly accurate. Thus, reported ratios are not better than ±10%. Generally 50–100 000 transients were obtained with a 20° flip angle and 0.5-s acquisition time. Under conditions where identical workup procedures were used, chemical shifts were reproducible to 0.05 ppm.

Results

Nucleophilic Addition to BAP 4,5-Oxide under Neutral or Basic Conditions. Reactions of BAP 4,5-Oxide with Sulfur Nucleophiles. Beland and Harvey[8] have shown that the reaction of BAP 4,5-oxide with *tert*-butylmercaptan under basic conditions produces both of the isomeric addition products (Scheme I). The subsequent conversion of these products to the corresponding aromatic products by dehydration (Scheme I) followed by analysis by preparative gas chromatography and NMR spectroscopy indicated that **3a** and **4a** were formed in equal amounts. NMR studies of the mixture of **3** and **4** before dehydration to **3a** and **4a** confirmed that no migration occurred during dehydration.[8]

The reaction of BAP-5-^{13}C 4,5-oxide (**2**) with *tert*-butylmercaptan was carried out in aqueous dioxane under conditions similar to those reported by Beland and Harvey. ^{13}C NMR analysis showed two products with chemical

Scheme I



shifts of 73.66 and 49.88 ppm. The product with the chemical shift of 73.66 ppm was assigned to **3** (Table I) on the basis of the similarity of this chemical shift to that of the similarly labeled trans diol **12** (Table II). The product with the chemical shift of 49.88 ppm was assigned to structure **4** (Table I). It was observed previously that conversion of an alcohol to a thioether resulted in an upfield change in chemical shift of about 25 ppm, consistent with this assignment. The ^{13}C NMR spectrum of the mixture of labeled **3** and **4** showed similar peak heights for the two products. Consequently, based upon the results of Beland and Harvey, it was concluded that compounds such as **3** and **4** could be quantified by direct comparison of their ^{13}C NMR peak intensities.

The reaction of BAP-5-^{13}C 4,5-oxide (**2**) was repeated with glutathione in place of *tert*-butylmercaptan. Four products were observed with chemical shifts of 70.71, 70.56, 49.16, and 49.06 ppm. The two downfield chemical shifts were assigned to product **5** resulting from attack by glutathione at position 4. The two products are interpreted to be the two diastereomers since glutathione is a chiral nucleophile. The two upfield chemical shifts were assigned to product **6**. The ^{13}C NMR spectrum suggests that all four diastereomers are present in approximately equal amounts, consistent with the nonselective attack observed by Beland and Harvey for *tert*-butylmercaptan.

A further test of the assumption that peak intensities can be used to quantify the products resulting from nucleophilic addition of sulfur nucleophiles to BAP 4,5-oxide was made by repeating with BAP-4-^{13}C 4,5-oxide (**1**) the reaction with glutathione. Again, four products were observed with chemical shifts of 71.67, 71.45, 49.64, and 49.17 which were assigned to products **6a** and **5a**. ^{13}C NMR analysis again suggested no selectivity in the reaction. Since the products from these two reactions with glutathione are identical except for the location of the labeled carbon, the consistent observation of similar peak intensities suggests that use of peak intensities for quantifying the products is valid for these studies.

If the observation of four products from the reaction of **1** and **2** with glutathione was correctly interpreted to mean that four diastereomers were observed by ^{13}C NMR analysis, then similar results might be expected if another chiral nucleophile were used in place of glutathione. The reaction of BAP-5-^{13}C 4,5-oxide (**2**) with *N*-acetylcysteine gave four products in similar amounts which showed

(14) J. Kagan, B. E. Firth, N. Y. Shih, and C. G. Boyajian, *J. Org. Chem.*, **42**, 343 (1977).

chemical shifts of 72.33, 72.06, 50.34, and 49.84 ppm. These were assigned to products **7** and **8**. Thus, the results of these studies are self-consistent and also are consistent with the results reported by Beland and Harvey[8] that sulfur nucleophiles add to BAP 4,5-oxide in a nonselective manner which is in agreement with predictions based upon Dewar reactivity numbers.[7,9]

Reactions of BAP 4,5-Oxide with Nitrogen Nucleophiles. Attempts to prepare the addition products with nitrogen nucleophiles under similar conditions to those used with sulfur nucleophiles in aqueous dioxane failed with *n*-propylamine, aniline, and alanine. However, the polarizable nucleophile azide was able to react. The reaction of BAP-5-^{13}C 4,5-oxide (**2**) with azide gave two products of similar peak intensities at 66.57 and 72.55 ppm. These were assigned to products **9** and **10**. The chemical shift of 72.55 ppm is consistent with the labeled carbon bonded to a hydroxyl group since similar chemical shifts are observed in **3**, **5**, **7**, **11**, and **12**. Since azide is achiral, only two peaks would be expected. The number of products observed from addition of either sulfur or nitrogen nucleophiles suggests that only trans addition occurs.

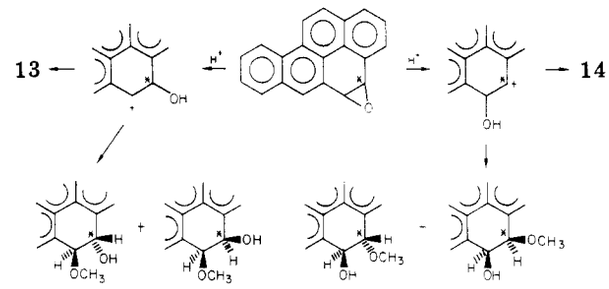
In summary, BAP 4,5-oxide will react only with soft, polarizable nucleophiles under S_N2 conditions. There is no preference for attack at position 4 compared to position 5.

Acid-Catalyzed Rearrangement of BAP 4,5-Oxide in Dioxane. The rearrangement of arene oxides to phenols via the NIH shift can occur by an acid-catalyzed or by a pH-independent pathway. For K-region arene oxides, the acid-catalyzed pathway is the only significant pathway.[15] The rearrangement of BAP-4-^{13}C 4,5-oxide in dioxane, catalyzed by methanesulfonic acid, gave two products with chemical shifts of 105.33 and 152.11 ppm. These were interpreted to be BAP-5-ol-4-^{13}C (**14**) and BAP-4-ol-4-^{13}C (**13**). The assignment of chemical shift 105.33 to **14** was confirmed by using authentic **14**. The assignment of chemical shift 152.11 to **13** is consistent with the chemical shift for a phenolic carbon. The closely related compound, BAP-5-ol-5-^{13}C (**16**), shows a chemical shift of 152.26 ppm. A known mixture of **14** and **16** was analyzed in order to obtain the relative peak intensities of a labeled phenolic carbon compared to a labeled α-carbon. On this basis, the ratio of products **13** and **14** formed in the acid-catalyzed rearrangement of **1** was determined to be about 60:40, indicating essentially no selectivity. These results are consistent with the identical N_t values calculated for the 4- and 5-carbons of BAP-4,5 oxide.[9]

The ability of water to trap the carbocation from acid-catalyzed ring-opening of BAP 4,5-oxide was probed by examining the rearrangement of BAP-4-^{13}C 4,5-oxide (**1**) in 50:1 dioxane/water catalyzed by methanesulfonic acid, in a manner similar to the previous study in pure dioxane. Only the phenols were observed, with chemical shifts of 105.33 (**14**) and 152.11 (**13**) ppm. No trans dihydro diol **11** was observed with the known chemical shift of 73.77 ppm from studies with authentic **11**. The reaction was repeated with 20:1 dioxane/water. This time a detectable amount (ca. 10%) of trans dihydro diol was observed. Thus, if the water concentration is sufficiently high, nucleophilic attack by water will compete with the NIH shift.

Acid-Catalyzed Rearrangement of BAP 4,5-Oxide in Methanol. The rearrangement of BAP-4-^{13}C 4,5-oxide (**1**) in methanol also gave a 60:40 ratio of the two phenols **13** and **14**. The rearrangement of BAP-5-^{13}C 4,5-oxide (**2**) likewise gave a 60:40 ratio of products with chemical shifts of 105.21 and 152.26 ppm. These were interpreted to be BAP-4-ol-5-^{13}C (**15**) and BAP-5-ol-5-^{13}C (**16**). Thus the use of BAP 4,5-oxide labeled either in position 4 or in position 5 gives consistent results when quantified by use of a mixture of authentic **14** and **16**.

Scheme II



The acid-catalyzed reaction in methanol, however, also produced four additional products with chemical shifts of 70.14, 71.59, 81.46, and 82.45 ppm. These are assigned to the cis and trans hydroxy ether products generated by capture of the intermediate carbocations by methanol (Scheme II). The two upfield products were assigned to the cis and trans products from attack by methanol at position 5 based upon the similarity of these chemical shifts to those for BAP-4,5-diol (Table II). The other two chemical shifts were assigned to the cis and trans products from attack by methanol at position 4. The conversion of an alcohol to a methyl ether has been shown to result in a downfield chemical shift of about 10 ppm, consistent with these assignments.[16]

Quantification of the amount of total phenols relative to total hydroxy ether products was achieved by TLC analysis of the reaction mixture, using silica gel plates and benzene/ethyl acetate (1:1). The phenolic products can be separated from the hydroxy ether products with this system. The phenols were measured by using UV–vis spectroscopy and known extinction coefficients.[17] The hydroxy ether products were measured by assuming that the extinction coefficients for BAP-4,5-diol could be used. On this basis, the total amount of hydroxy ether products was about equal to the amount of phenolic products. The main point, however, is that the two phenols are produced in nearly equal amounts, both in methanol and in dioxane.

HCl-Catalyzed Rearrangement of BAP 4,5-Oxide. The acid-catalyzed rearrangement of BAP-4-^{13}C 4,5-oxide was repeated in 50:1 dioxane/water with HCl rather than methanesulfonic acid. The 4-phenol (**13**) and 5-phenol (**14**) were observed in a 60:40 ratio along with trans dihydro diol **11** and two unidentified products with chemical shifts of 72.44 and 60.21 ppm. The reaction was repeated with BAP-5-^{13}C 4,5-oxide. Again the 4-phenol (**15**) and 5-phenol (**16**) were observed along with trans dihydro diol **12** at 74.33 ppm, identified from authentic **12**, and two new products with chemical shifts of 73.48 and 61.20 ppm.

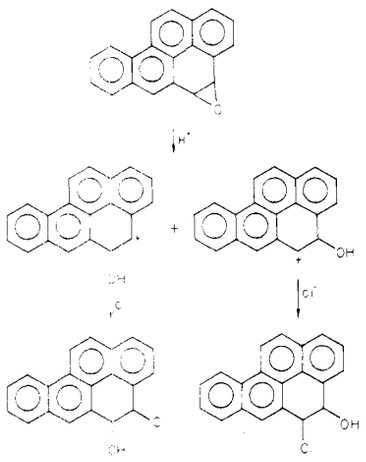
The reaction was repeated with BAP-5-^{13}C 4,5-oxide and 20:1 dioxane/water. The same products were observed except that the amount of trans dihydro diol had increased relative to the amounts of the two unidentified products. At this point, the possible formation of chlorohydrins (**17**, **18**, **19**, **20**) as precursors for the trans dihydro diols was considered (Scheme III).

Chlorohydrin Formation from the Rearrangement of BAP 4,5-Oxide Catalyzed by Acid in the Presence

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

(16) T. A. Lyle, G. H. Daub, and D. L. Vander Jagt, unpublished data.
(17) H. O. House, *J. Org. Chem.*, **21**, 1306 (1956).

Scheme III



of LiCl. If the rearrangement of BAP-5-^{13}C 4,5-oxide was carried out as above with HCl and 9 mg of LiCl was present in the 20:1 dioxane/water, the amounts of the two products presumed to be the trans chlorohydrins **17** and **18** at chemical shifts 73.48 and 61.20 ppm increased relative to the amount of diol. Likewise if the same reaction conditions were used except that methanesulfonic acid replaced the HCl, chlorohydrins were observed if LiCl was present. Additional support for the idea that the trans dihydro diol is formed primarily from the chlorohydrins came from the observation that if water is added to a ^{13}C NMR sample containing chlorohydrins **17** and **18** or **19** and **20**, the chlorohydrins disappear and trans dihydro diol **12** or **11** appears. This observation along with the observation that only a small amount of trans dihydro diol is formed in the absence of chloride ion in the methanesulfonic-acid-catalyzed rearrangement of BAP 4,5-oxide in dioxane/water suggests that chloride is an exceptional nucleophile for trapping the carbocation in competition with the NIH shift. If the same reaction is carried out in the presence of 10 mg (0.12 mmol) of *tert*-butylmercaptan, no products from thiol attack are observed.

The chlorohydrins from the acid-catalyzed rearrangement of BAP 4,5-oxide conceivably could be cis or trans. However, if chloride traps a free carbocation (Scheme III) one might expect to see all four products. Since only two products were observed, it was assumed that chloride probably attacked trans and that the carbocations really are only incipient ions rather than the free ions pictured in Scheme III. A more definitive assignment of these structures was made by preparing a series of cis and trans model chlorohydrins. Cyclohexene was converted into cyclohexene epoxide by reaction with *m*-chloroperbenzoic acid. Treatment of cyclohexene epoxide with $FeCl_3$ gave the trans chlorohydrin. Natural-abundance ^{13}C NMR spectroscopy in $CDCl_3$ (proton decoupled) showed chemical shifts of 74.48, 66.37, 34.64, 32.83, 24.95, and 23.40 ppm. Chemical shifts of carbon bonded to oxygen are generally downfield from carbon bonded to chlorine. Consequently, chemical shift 74.48 ppm was assigned to **21** and chemical shift 66.37 ppm was assigned to **22**. Cis chlorohydrin was prepared by reducing 2-chlorocyclohexanone with $NaBH_4$. ^{13}C NMR spectroscopy of the product showed major peaks at 69.48, 64.64, 30.96, 29.35, 20.98, and 20.89 ppm and minor peaks corresponding to the trans chlorohydrin. Chemical shift 69.48 ppm was assigned to **23** and chemical shift 64.64 ppm was assigned to **24**. The difference in chemical shift between carbon–oxygen in **21** and carbon–chlorine in **22** is about 8 ppm compared to a difference of about 5 ppm in the cis isomer. The two chlorohydrins **17** and **18** formed from BAP-5-^{13}C 4,5-oxide and the two chlorohydrins **19** and **20** formed from BAP-4-^{13}C 4,5-oxide show large (ca. 12 ppm) differences in carbon–oxygen vs. carbon–chlorine chemical shifts, consistent with the trans structures which were assigned.

Acid-Catalyzed Dehydration of BAP-4,5-diol. The dehydration of BAP-4,5-diol-5-^{13}C (**12**) was carried out by refluxing **12** in methanol in the presence of methanesulfonic acid. Two products were observed by ^{13}C NMR spectroscopy with chemical shifts of 154.50 and 102.34 ppm. Neither of these products correspond to phenols **15** or **16**. The product with chemical shift 154.50 ppm was identified as 5-methoxy-BAP-5-^{13}C (**25**) by synthesis of authentic **25** from BAP-5-ol-5-^{13}C (**16**) and methyl iodide. The product with chemical shift 102.34 ppm is assumed, therefore, to be 4-methoxy-BAP-5-^{13}C (**26**). Interestingly, methylation does not result in as large a change in the carbon chemical shift as is observed when alcohols are converted into methyl ethers.[16] If one assumes that the standard spectra of **14** and **16** which were used to estimate the amount of phenols formed in the acid-catalyzed rearrangement of **1** or **2** can also be used to estimate the quantities of **25** and **26**, then these two methoxy products are produced in approximately equal amounts.

The acid-catalyzed dehydration of BAP-4,5-diol-5-^{13}C (**12**) was repeated with dioxane instead of methanol. Only phenols **15** and **16** are observed, in a 60:40 ratio. Consequently, it appears that both the acid-catalyzed rearrangement of BAP 4,5-oxide and the acid-catalyzed dehydration of BAP-4,5-diol show essentially nonselective product distribution in agreement with theoretical predictions.

Discussion

The high regioselectivity reported for the acid-catalyzed rearrangement of BAP 4,5-oxide[11,12] would seem surprising in view of the similar Dewar reactivity numbers for positions 4 and 5 of BAP 4,5-oxide. This is especially so when one considers that a large number of arene oxides show a good correlation between Dewar reactivity numbers and predicted products from acid-catalyzed ring opening.[9] The present study was a reinvestigation of this reaction using ^{13}C-labeled BAP 4,5-oxide. The acid-catalyzed rearrangement was observed to give a 60:40 ratio of 4-phenol to 5-phenol, consistent with the Dewar reactivity numbers. Harvey et al.[18] in a study of K-region oxides observed that the cis diol diacetate of BAP-4,5-diol gave a 60:40 mixture of 4-acetoxy-BAP and 5-acetoxy-BAP upon treatment with acid. These assignments were made, tentatively, on the basis of proton NMR analysis. When they treated BAP 4,5-oxide with 70% aqueous acetic acid followed by acetylation with acetic anhydride and pyridine, they obtained the same 60:40 ratio of the two acetoxy derivatives. The present study agrees completely with their observations.

Similarly, high selectivity has been reported for the acid-catalyzed rearrangement of BAP-4,5-diol.[11,12] The present study of the rearrangement of BAP-4,5-diol in dioxane catalyzed by methanesulfonic acid suggests that the same 60:40 ratio of 4-phenol and 5-phenol is obtained, similar to the case for the acid-catalyzed rearrangement of BAP 4,5-oxide. Thakker et al.[19] reported that heating BAP-4,5-diol in 6 N HCl produced approximately equal amounts of the two phenols. This conclusion was tentative, however, because the two phenols could not be separated

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until they were acetylated. The present results agree with this observation of Thakker et al. No significant stereoselectivity is observed.

The acid-catalyzed reaction of BAP-4,5-diol in methanol gave the two methoxy derivatives **25** and **26**. However, the acid-catalyzed rearrangement of BAP 4,5-oxide in methanol gave the phenols and the four hydroxy ether adducts (Scheme II). Since reflux conditions are required to carry out the reaction with BAP-4,5-diol, it is conceivable that the reaction initially produces phenols and hydroxy ether adducts which subsequently give rise to the two methoxy compounds **25** and **26**. Phenols of BAP are known to be converted into the methoxy derivatives by heating in acidic methanol.[20]

Hydration of the carbocation from the acid-catalyzed ring opening of BAP 4,5-oxide was observed if the concentration of water was sufficiently high. Thus, use of 20:1 dioxane/water produced measurable amounts of trans dihydro diol in addition to the two phenols. If less water was present, only the phenols were formed. These studies used methanesulfonic acid. However, if HCl was used instead of methanesulfonic acid, trans dihydro diol in addition to the phenols was formed even in 100:1 dioxane/water along with two chlorohydrins. Likewise, if LiCl was present with methanesulfonic acid, all of these products were formed even when the water concentration was low. Chlorohydrins were always present unless the sample workup was altered to include an aqueous washing step, in which case the chlorohydrins disappeared. Generally, loss of chlorohydrins resulted in the formation of increased amounts of trans dihydro diol, although the phenols may also be increased somewhat. Clearly, chloride is an exceptionally good nucleophile in trapping the carbocation generated from BAP 4,5-oxide under acidic conditions. Since only trans products are observed, it appears that trapping of the carbocation by water or chloride must involve some type of concerted process rather than the trapping of an essentially free carbocation. However, this statement is only tentative. The conclusion that only trans chlorhydrins form is based only upon the observation of two products rather than four products by ^{13}C NMR and the observation that trans dihydro diol is formed from these two products. The chlorohydrins were never isolated. They were only observed in the NMR analysis.

Although the formation of chlorohydrins as intermediates as reported here represents the first demonstration of their existence in solvolytic reactions of arene oxides, they have been proposed previously from kinetic studies. Whalen, Jerina, and co-workers observed specific chloride effects in their pH–rate studies of the solvolysis of phenanthrene 9,10-oxide.[22] In this study, however, the product composition which included the 9-phenol and cis and trans dihydro diols did not change in the presence of chloride. It was suggested by these workers that the intermediate trans chlorohydrin could solvolyze to the same carbocation formed by acid-catalyzed or spontaneous ring opening and then subsequently give the same distribution of products as are formed in the absence of chloride. Unlike BAP 4,5-oxide, phenanthrene 9,10-oxide shows a significant spontaneous ring opening. It appears that chloride may be generally reactive toward arene oxides. Clearly, caution should be used in using chloride to adjust the ionic strength of a given solution which is to be used for reactivity studies.

Registry No. 1, 71719-12-5; 2, 71719-13-6; 3, 71719-14-7; **3a**, 60692-95-7; 4, 71719-15-8; **4a**, 60692-96-8; 5, isomer 1, 71719-16-9; 5, isomer 2, 71771-92-1; **5a**, isomer 1, 71719-17-0; **5a**, isomer 2, 71869-28-8; 6, isomer 1, 71719-18-1; 6, isomer 2, 71771-93-2; **6a**, isomer 1, 71719-19-2; **6a**, isomer 2, 71771-94-3; 7, isomer 1, 71719-20-5; 7, isomer 2, 71771-95-4; 8, isomer 1, 71719-21-6; 8, isomer 2, 71771-96-5; 9, 71719-22-7; 10, 71719-23-8; 11, 71719-24-9; 12, 71719-25-0; 13, 71719-26-1; 14, 71719-27-2; 15, 71719-28-3; 16, 71719-29-4; 17, 71719-30-7; 18, 71719-31-8; 19, 71719-32-9; 20, 71719-33-0; 21, 71719-34-1; 22, 71719-35-2; 23, 71719-36-3; 24, 71719-37-4; 25, 71719-38-5; 26, 71719-39-6; BAP 4,5-oxide, 37574-47-3; *tert*-butylmercaptan, 75-66-1; glutathione, 70-18-8; *N*-acetylcysteine, 616-91-1; sodium azide, 26628-22-8; methanesulfonic acid, 75-75-2; cyclohexene, 110-83-8; 2-chlorocyclohexanone, 822-87-7.

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An Approach to the Linear Representation of Reaction Mechanisms

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The objectives to be achieved by a satisfactory linear notation for the symbolization of reaction mechanisms are discussed. A scheme is proposed, based on simple valence-bond representations of the elementary processes, which is designed to be suitable for computer storage and search, yet is reducible in simple cases to a few symbols which can be easily related to the conventional diagrammatic representation of a reaction mechanism.

A number of proposals have been made recently for the notation of reaction mechanisms in a systematic manner, with a view to improving on the proliferating nonsystematic usage of symbols modeled on Ingold's original S_N1 and S_N2 abbreviations and with a number of other objectives.[1-3] These include an easier indexing and computer retrieval of related reactions, the clear illustration of interreaction relationships, and the use of symbolization as a pedagogical tool. The present proposals sprang from a critical consideration of the proposals of Guthrie.[2] This has resulted in an extended scheme, addressed more di-

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