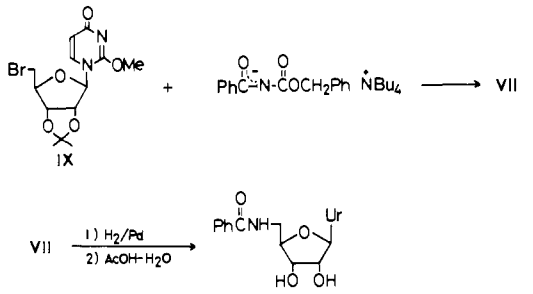
Scheme III



deoxy-5′-benzoylamino-2′,3′-*O*-isopropylideneuridine (X) in a 75% yield. The X was treated with 20% acetic acid under reflux for 4 h to give 5′-deoxy-5′-benzoylaminouridine in an 80% yield as amorphous solid.

The reaction sequence disclosed herein may provide a potential method for the synthesis of acylaminosugars and acylaminonucleosides.[10]

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(2) Recently the direct conversion of hydroxyl groups of sugars and nucleosides into an azide group has been reported. B. Castro, Y. Chapleur, B. Gross, and C. Selve, *Tetrahedron Lett.*, 5001 (1972); T. Hata, Y. Yamamoto, and M. Sekine, *Chemistry Lett.*, 977 (1975).

(3) All products, except for 5′-deoxy-5′-phthaloylaminouridine, were isolated by preparative layer chromatography (Merck PF_{254}). Structures of reaction products described herein were confirmed by elemental analyses and/or spectral data (^1H NMR, UV, mass). Zamojski et al. have reported phthaloylamination of sugar derivatives by the use of I, II, and III. A. Zamojski, W. A. Szarek, and J. K. N. Jones, *Carbohyd. Res.*, **23**, 460 (1972). The protection of aglycone is necessary to avoid anhydronucleoside formation; see M. Wada and O. Mitsunobu, *Tetrahedron Lett.*, 1279 (1972), and references therein.

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(9) The IX was prepared from V by the use of the Verheyden-Moffatt procedure. J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **37**, 2289 (1972).

(10) This work was assisted financially by the Ministry of Education, Japan.

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Specific Effects of Chloride Ion on Epoxide Hydrolysis. The pH-Dependence of the Rates and Mechanisms for the Hydrolysis of Indene Oxide

Sir:

The metabolism of aromatic hydrocarbons is thought to proceed via the intermediacy of arene oxides,[1] and the carcinogenic effects of certain hydrocarbons have been attributed to the covalent binding of the intermediate epoxide to cellular reagents.[2] Recent reports suggest that the principal causative agent in the carcinogenicity of benzo[*a*]pyrene might be a dihydrodiol epoxide in which the epoxide group is located at a benzylic position.[3] A more detailed knowledge of the hydrolysis mechanisms and nucleophilic reactions of non-arene oxides (such as benzylic epoxides) is therefore desirable.

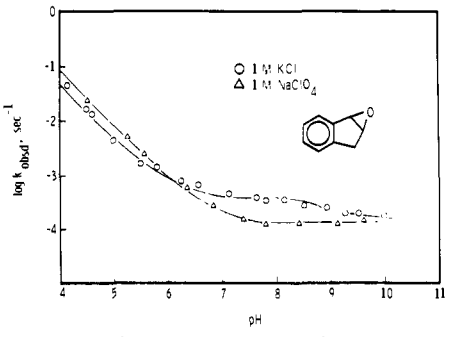
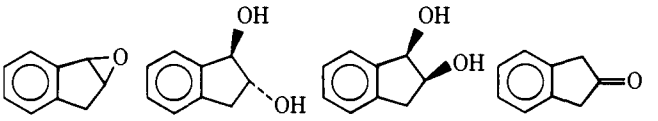


Figure 1. Plots of log k_{obsd} vs. pH for the hydrolysis of indene oxide in 1 M $NaClO_4$ and 1 M KCl solutions at 25 °C.

The rates and mechanisms for hydrolysis of various arene and non-arene oxides have been studied as a function of pH. It is common practice to carry out the hydrolysis studies of a given epoxide in solutions held at a constant ionic strength by addition of an electrolyte, and potassium chloride is often the electrolyte chosen.[4] In this paper we wish to report the specific effects of added chloride ion on the hydrolysis of indene oxide, and to caution against the use of nucleophilic reagents such as potassium chloride to maintain constant ionic strength in solutions used for hydrolysis of epoxides highly susceptible to nucleophilic reagents.

Various reports of the stereochemistry of the products from the hydrolysis of indene oxide (**1**) have appeared. Several publications have stated that trans and cis diols **2** and **3** from the hydrolysis of **1** are formed in ratios that depend on pH, reaction times, and reaction conditions.[5] A more recent publication appeared in which the authors obtained the same ratio (69:31) of **3** and **2** from the hydrolysis of **1** in both 0.1 and 1.0 N sulfuric acid at room temperature, and demonstrated that some of the differences in the product distributions reported previously were not due to differences in acid concentration, but rather to secondary transformations of the diol products under reaction conditions.[6]



1 **2** **3** **4**

Because of discrepancies in the published data on the hydrolysis of **1** at pH >1, and due to the importance of understanding the mechanisms of epoxide hydrolyses, we undertook a study of the kinetics and stereochemical outcome of the hydrolysis of **1** as a function of pH. Our results reveal that the product distributions and mechanisms for the hydrolysis of **1** at pH 4–10 are indeed pH dependent, and are reported here.

The rate expression for the hydrolysis of **1** in buffered aqueous 1 M $NaClO_4$ solutions, in which the rates were extrapolated to zero buffer concentration, is given by eq 1.[7] The

$$k_{obsd} = k_{H^+}a_{H^+} + k_0 \qquad (1)$$

values for the rate constants k_{H^+} and k_0 are 8.9×10^2 M^{-1} s^{-1} and 1.3×10^{-4} s^{-1}, respectively. The pH–rate profile for the hydrolysis of **1** in 1 M $NaClO_4$ solutions is given in Figure 1. Two distinct regions in the pH–rate profile between pH 4 and 10 are apparent, one region at pH ca. 6 in which $k_{H^+}a_{H^+} > k_0$, and a plateau at pH ca. 7.5, where $k_0 > k_{H^+}a_{H^+}$. From analysis of eq 1 (or the pH–rate profile), it is clear that there are two distinct mechanisms for the hydrolysis of indene oxide in 1 M $NaClO_4$. At pH 2 the acid-catalyzed mechanism predominates, and yields 30% of **2** and 70% of **3**. At pH 8.3, however, $k_0 \gg k_{H^+}a_{H^+}$, and the product mixture from hy-

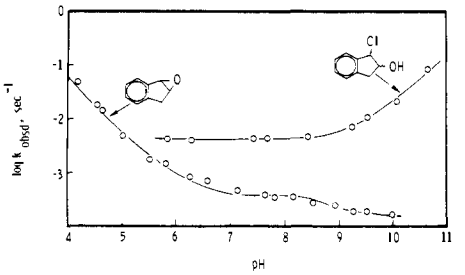
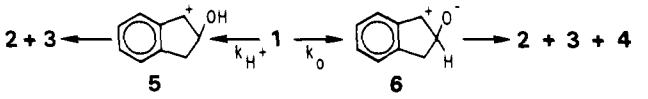


Figure 2. Plots of log k_{obsd} vs. pH for the hydrolysis of indene oxide and indene chlorohydrin in 1 M KCl solutions at 25 °C.

Scheme I



drolysis of **1** contained 37% of **2**, 2% of **3**, and 38% of **4**.[8] Possible mechanisms for hydrolysis of **1** by the k_{H^+} and k_0 processes are outlined in Scheme I.[9] Of significance is the fact that the k_0 process gives rise to 38% of **4**, which is most likely formed by "NIH shift-related" mechanism.[4e]

The pH-rate profile for the hydrolysis of **1** in 1 M KCl solutions was more complicated than the profile in 1 M $NaClO_4$ solutions, and is also given in Figure 1. A distinguishing feature is the presence of an inflection point at pH ca. 8.5 in the KCl profile. The lack of a similar inflection point in the $NaClO_4$ profile indicates that chloride ion introduces a specific effect in the hydrolysis of **1**.

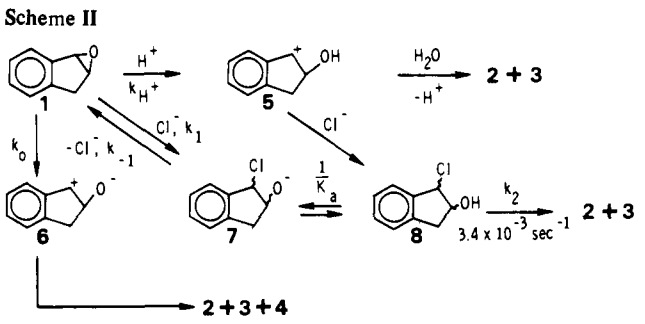
Analysis of the kinetic data for the hydrolysis of **1** at pH 4–5 in 1 M KCl solution revealed that in addition to the acid-catalyzed hydrolysis of **1**, a secondary reaction occurred with a rate constant of 3.4×10^{-3} s^{-1}. The material that gave rise to the secondary reaction was isolated from the hydrolysis of **1** in 0.25 M HCl solution that was also 3 M in KCl. This material possessed an NMR spectrum that was consistent with that expected from a mixture of cis and trans chlorohydrins **8**. A mixture of these same chlorohydrins was prepared by addition of HCl to **1** in dioxane,[10] and therefore intermediate **5** must collapse with chloride ion to yield **8** when the hydrolysis of **1** is carried out in the presence of significant amounts of chloride ion at low pH.

The pH-rate profile for the solvolysis of the chlorohydrin mixture **8** is given in Figure 2.[11] The rate for hydrolysis of **8** is independent of pH at <ca. 8.5, and therefore hydrolysis of **8** in this region must occur via the benzyl cation **5**. At pH >ca. 8.5, the solvolysis rate increases with a rate proportional to $1/a_{H^+}$, and a secondary, slower reaction with a rate equal to that for hydrolysis of **1** is observed. Thus, epoxide **1** must be forming from **8** at high pH.

The product mixture from the hydrolysis of **1** in 3 M KCl solution at pH ca. 1.5, after complete reaction of the intermediate chlorohydrin **8**, consisted of 25% of **2** and 75% of **3**. Therefore, the product mixture from solvolysis of the chlorohydrin mixture **8** is very similar to that from the hydrolysis of **1** in the absence of chloride ion. At pH 8, in the presence of 1 M KCl, hydrolysis of **1** yielded a product mixture in which the ratio of **2**:**3** was 32:68. This ratio is vastly different from that obtained in the hydrolysis of **1** in $NaClO_4$ solution (or in the absence of salt) at pH 8.3, and suggests that chlorohydrin **8** is also an intermediate in the hydrolysis of **1** at pH 8 in 1 M KCl solution.

A mechanistic scheme that provides an explanation for the pH-rate profile observed in 1 M KCl solution, and also for the product ratios observed throughout the pH range, is given in Scheme II. Steady state approximations for intermediates **7** and **8** provides the kinetic expression given in eq 2. The data

Scheme II



were fit to eq 2, and yielded values of $k_{H^+} = 5.5 \times 10^2$ M^{-1} s^{-1}, $k_1[Cl^-] = 2.6 \times 10^{-4}$ s^{-1}, k_0 = ca. 1.6×10^{-4} s^{-1}, and $k_{-1}K_a/k_2$ = ca. $10^{-8.6}$.[7] The pH-rate profile can be divided

$$k_{obsd} = k_{H^+}a_{H^+} + \frac{k_1[Cl^-]}{1 + \frac{k_{-1}K_a}{k_2 a_{H^+}}} + k_0 \qquad (2)$$

into three distinct regions, each with a different rate-determining step.

A. pH Range 4–6. In this region, the hydrolysis of **1** is acid catalyzed via the k_{H^+} process. Intermediate **5** is captured in part by Cl^- to yield **8**, which undergoes solvolysis (k_2) to give a mixture of **2** and **3** similar to that obtained by direct collapse of solvent with **5** in the absence of chloride ion.

B. pH Range 7–8.5. The rate-limiting steps in the hydrolysis of **1** in this pH range are nucleophilic addition of Cl^- to **1** (k_1) and spontaneous reaction of **1** with solvent (k_0).[9] In 1 M KCl solution, $k_1[Cl^-] \approx 2k_0$. In this pH range, however, **7** rapidly protonates to form **8**, which then solvolyzes (k_2) to give **2** and **3** in the ratio of ca. 25:75.

C. pH Range 9.5–10. At pH > ca. 9.5, the pH-dependent equilibrium between epoxide **1** and chlorohydrin **8** shifts sufficiently in favor of epoxide such that $k_0[\mathbf{1}] > k_2[\mathbf{8}]$. The rate-limiting step in this range therefore becomes the k_0 process. The product mixture from hydrolysis of **1** in 1 M KCl at pH 10.5 contained 29% of **2**, 3% of 3, and 19% of **4**.[8] The change in product distribution at pH 10.5 from that at pH 8 in 1 M KCl verified the change in rate determining step between these pH values.

In conclusion, specific effects induced by chloride ion on indene oxide hydrolysis have been demonstrated. Care should therefore be taken to ensure that specific effects are not introduced when epoxide hydrolysis is carried out in solutions containing chloride or other nucleophilic ions.[12] The use of a nonnucleophilic salt like $NaClO_4$ to maintain constant ionic strengths is to be preferred over the use of a nucleophilic salt such as KCl.[13]

Acknowledgment. This investigation was supported by Public Health Service Research Grant No. CA-17278 from the National Cancer Institute, and by the American Cancer Society, Maryland Section.

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Chem. Soc., **98**, 114 (1976); (d) D. L. Whalen, *ibid.*, **95**, 3432 (1973); (e) D. L. Whalen and A. M. Ross, *ibid.*, **96**, 3678 (1974); (f) P. Y. Bruice, T. C. Bruice, H. G. Selander, H. Yagi, and D. M. Jerina, *ibid.*, **96**, 6814 (1974); (g) P. Y. Bruice, T. C. Bruice, P. M. Dansette, H. G. Selander, H. Yagi, and D. M. Jerina, *ibid.*, **98**, 2965 (1976); (h) J. W. Keller and C. Heidelberger, *ibid.*, **98**, 2328 (1976).

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(7) The concentration of H^+ was calculated by assuming that it is equal to the hydrogen ion activity measured by the glass electrode. The reactions were monitored spectrophotometrically at 225–235 nm in the thermostated cell compartment of a Cary 16K spectrophotometer.

(8) Product analyses were carried out with the aid of a Radiometer pH-stat. 2-Indanone (4) was unstable at pH >10 in spectrophotometric concentrations. In a control experiment in which a known amount of 2-indanone was allowed to stir at pH 8.3 under the conditions for hydrolysis of **1**, only 61% of the ketone was recovered. Product mixtures were analyzed by gas chromatography on a 5% DC-550 column (5 ft, ⅛ in.) with silylated solid support.

(9) The detailed mechanism for the hydrolysis of **1** via the k_0 process has not been determined. The mechanism presented in Scheme II is consistent with that found for rearrangement of arene oxides, ref 4a–c.

(10) H. Bodot, J. Jullien, and E. Leblanc, *Bull. Soc. Chim. Fr.*, 41 (1962).

(11) Both cis and trans chlorohydrins **8** have similar solvolysis rates in 80% dioxane–water, ref 10. No attempt was made in this study to determine the relative reactivities of the cis and trans isomers at pH >8, although the trans isomer is presumably more reactive than the cis isomer.

(12) Phenanthrene 9,10-oxide exhibits a pH–rate profile (ref 4f,g) in 1 M KCl that resembles the profile of indene oxide. It was suggested that a change of mechanism from general acid catalysis by water to nucleophilic addition of water to phenanthrene 9,10-oxide was responsible for the inflection point observed, ref 4g. We have determined the pH–rate profiles for phenanthrene 9,10-oxide in both KCl and $NaClO_4$ solutions, and have concluded that the inflection point at pH 7.2 reported in 1 M KCl solution is due to a specific effect of chloride ion, D. L. Whalen, A. M. Ross, and D. M. Jerina, unpublished results.

(13) Some difficulties are encountered in measuring the pH of concentrated perchlorate solutions, D. B. Dennison, G. A. Gettys, D. G. Kubler, and D. Shepard, *J. Org. Chem.*, 41, 2344 (1976).

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1,1-Dimethyl-λ⁵-phosphabenzene and 1,1-Dimethyl-λ⁵-arsabenzene

Sir:

Despite rather extensive investigation of the chemistry of λ⁵-phosphabenzenes **1**,[1,2] the question whether these structures possess appreciable aromatic stabilization (**1′**) or whether they are better represented as delocalized ylides (**1″**, **1‴**, **1⁗**) remains open. The basicity of the ring-unsubstituted 1,1-diphenyl-λ⁵-phosphabenzene **1a**, prepared by a rather laborious route, suggests an ylide type of bonding.[3] Unfortunately, data are limited and no NMR spectra have appeared for **1a**. Most of the investigations have focused on the more readily available 1,1-disubstituted-2,4,6-triaryl-λ⁵-phosphabenzenes **2**.[1] The chemistry and spectra of **2** have usually been discussed in terms of an aromatic model.[1,2] Since the heavy substitution of **2** may mask the properties of the parent ring system, a reinvestigation of the ring-unsubstituted-λ⁵-phosphabenzenes seems warranted. We now wish to report on a facile synthesis of 1,1-dimethyl-λ⁵-phosphabenzene, **1b**, and on a similar synthesis of the first λ⁵-arsabenzene **3**.[3]

The readily available 1-methyl-2,4-phosphacyclohexadiene, **4**[4] may be quaternarized with methyl iodide to give 50% of the phosphonium salt **5**, mp 198–199°C dec. ^{1}H NMR[5] (Me_2SO-d_6) δ 7.1 (ddd, J = 35, 12, 5.5 Hz, 1 H), 6.6–6.0 (m, 3 H), 3.3 (dd, J = 17, 4 Hz, 2 H), 2.0 (d, J = 15 Hz, 6 H). Addition of this salt to Me_2SO containing excess dimsyl anion produced the desired 1,1-dimethyl-λ⁵-phosphabenzene, **1b**. The proton NMR spectrum illustrated in Figure 1 shows signals for H_3 (H_5) centered at δ 6.70 (J_{PH} = 34 Hz), for H_4 as a triplet at δ 4.62 (J = 7.5 Hz), for H_2 (H_6) as doublet of doublets at δ 3.98 (J = 17, 11 Hz), and for the methyl groups as a doublet at δ 1.5 (J = 13.5 Hz). ^{13}C NMR (Me_2SO) δ 139.2 (s for C_3, C_5), 94.0 (d, J = 22 Hz for C_4), 67.5 (d, J = 94 Hz for C_2, C_6), 24.7 (d, J = 57 Hz for CH_3). Treating **1b** with acid leads back to the phosphonium salt **5**. Four P-ring protons of **5** readily exchange for deuterium in Me_2SO-d_6 containing D_2O and base. The H NMR signals for the protons at H_2, H_4, and H_6 completely disappear while the peaks for H_3 (a 35 Hz doublet at δ 7.1) and for H_5 (a 22 Hz doublet at δ 6.1) and for the methyl groups remain undiminished. The facile interconversion of **1** and **5** is similar to that reported by Märkl for **1a**.[3]

In a completely analogous manner 1-methyl-2,4-arsacyclohexadiene, **6**,[4] can be quaternarized to salt **7**, mp 195–197 °C. ^{1}H NMR (Me_2SO-d_6) δ 7.0 (dm, J = 12 Hz, 1 H), 6.6 (d, J = 12 Hz, 1 H), 6.2 (m, 2 H), 3.4 (d, J = 3 Hz, 2 H), 2.2 (s,

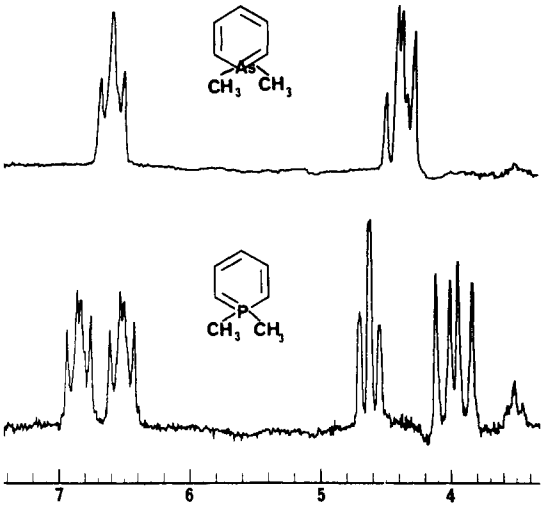
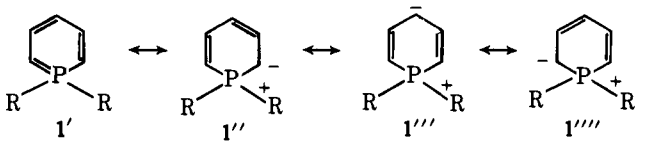
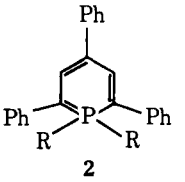


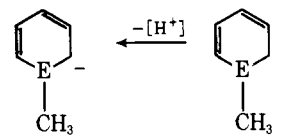
Figure 1. The lower field portion of the H NMR spectra of 1,1-dimethyl-λ⁵-arsabenzene, **3** (above), and 1,1-dimethyl-λ⁵-phosphabenzene, **1b** (below). Peak positions are indicated downfield (δ) from internal Me_4Si.



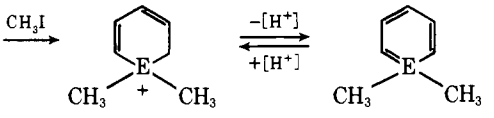
a, R = C_6H_5
b, R = CH_3



2



8, E = P
9, E = As
4, E = P
6, E = As



5, E = P
7, E = As
1b, E = P
3, E = As