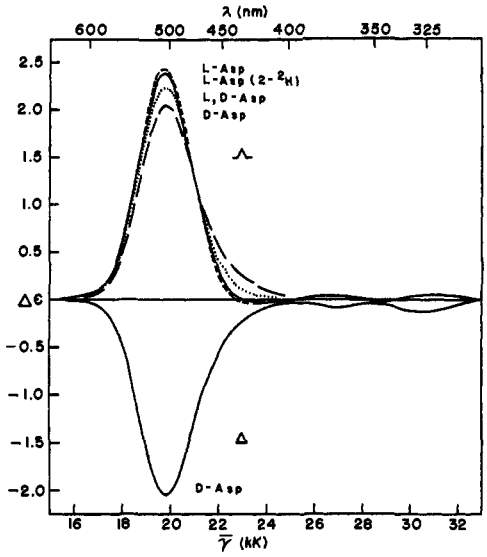

Figure 2. Circular dichroism spectra of various isomers of $Co(en)_2(asp)^{2+}$. For spectra shown with positive maxima at 507 nm: (- - - -) Λ(L) isomer before deuteration, (——) same isomer after deuteration, (· · · ·) Λ(L,D) isomer, (— — —) Λ(D) isomer.

tion had been obtained, the CD spectra should have been indistinguishable (assuming isotope effects to be negligible). However, that partial retention of configuration has been obtained can be seen from the following argument. In Figure 2 is also shown the spectrum obtained for Δ-$Co(en)_2$(L-Asp)$^{2+}$.[4] The mirror image of this isomer is Λ-$Co(en)_2$(D-Asp)$^{2+}$. Its CD spectrum can be obtained by mirroring the spectrum of the Δ isomer through the $\Delta\epsilon = 0$ axis and is shown in Figure 2. The spectrum thus generated would be that obtained if the L-aspartic acid had *inverted* in configuration during the deuteration (Λ(L) → Λ(D)). If total racemization had occurred (Λ(L) → Λ(D,L)), a CD spectrum representing an average between that of Λ-$Co(en)_2$(L-Asp)$^{2+}$ and Λ-$Co(en)_2$(D-Asp)$^{2+}$ would have been obtained, Figure 2. As can be seen in the figure, this spectrum has a lower $\Delta\epsilon$ than the spectrum obtained after deuteration of the Λ(L) isomer. Thus, partial retention of configuration is strongly indicated. The degree of racemization can be calculated from the relative $\Delta\epsilon$ values for the maxima at 507 nm to be 20% (90% L- and 10% D-amino acid).

In order to check these observations the aspartic acid was removed from the complex by reduction with $NaBH_4$[8] to give labile Co(II). Ion-exchange chromatography was used to separate the aspartic acid from the residual products. Although only a 30% yield was obtained, this was sufficient for characterization of the amino acid. The pmr spectrum of the aspartic acid thus obtained, Figure 3, shows that the amino acid is still deuterated at the α carbon since the methine triplet of the nondeuterated acid located between 5 and 4 ppm is absent. It is important to note that the reduction method employed does not appreciably exchange hydrogen (deuterium) at the α carbon which strongly suggests that the configuration about that carbon is retained during this process. The ORD spectrum obtained for the α carbon deuterated amino acid revealed that 77 ± 2% retention of configuration had been obtained. This sets a lower limit to the value of 90% calculated from analysis of the CD spectra of the deuterated and nondeuterated diastereoisomer.

(8) We are grateful to Professor A. Sargeson for suggesting the use of $NaBH_4$ in this step.

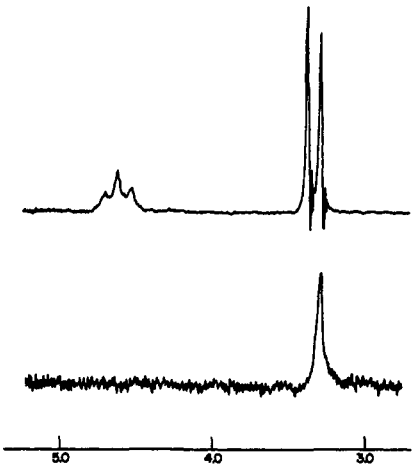

Figure 3. The pmr spectrum of the aspartic acid isolated from the reduction of $Co(en)_2([2\text{-}^2H]asp)^{2+}$ (lower) and of undeuterated aspartic acid (upper).

In contrast it is of interest to note that proton exchange and mutarotation rates for the corresponding alanine and valine complexes were essentially the same.[5] However, the conditions (*e.g.*, pD's >11) were not the same as those employed in this study. It is conceivable that in the aspartic acid complex the presence of a basic component on the side chain may lead to the preference of a particular diastereomeric form for the intermediate. The proposed mechanism for the deuteration involves the formation of a carbanion intermediate stabilized by resonance with the enolate form.[3c] This would bring about racemization unless the ^2H_2O molecule attacked the α carbon preferentially from one side. Such a situation could arise if the side chain interacted preferentially with the complex. A similar "three-point attachment" theory has been employed to account for the dissymmetric action of enzymes on substrates lacking chiral centers. The possibility of such an interaction in this and similar complexes has been discussed previously.[3e,4] To further investigate this hypothesis we are studying the deuteration of various other chelated amino acids.

Acknowledgments. We gratefully acknowledge support for this research through grants from the National Institutes of Health (GM 18983-01), National Science Foundation (GP-34490X), and the Petroleum Research Fund, administered by the American Chemical Society. J. I. L. is also grateful for a National Institutes of Health Special Fellowship, 1972–1973, for study at the Harvard Medical School.

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Buffer Catalysis in Epoxide Hydrolyses

Sir:

Interest in epoxide hydrolyses has recently been stimulated by the discovery that epoxides are interme-

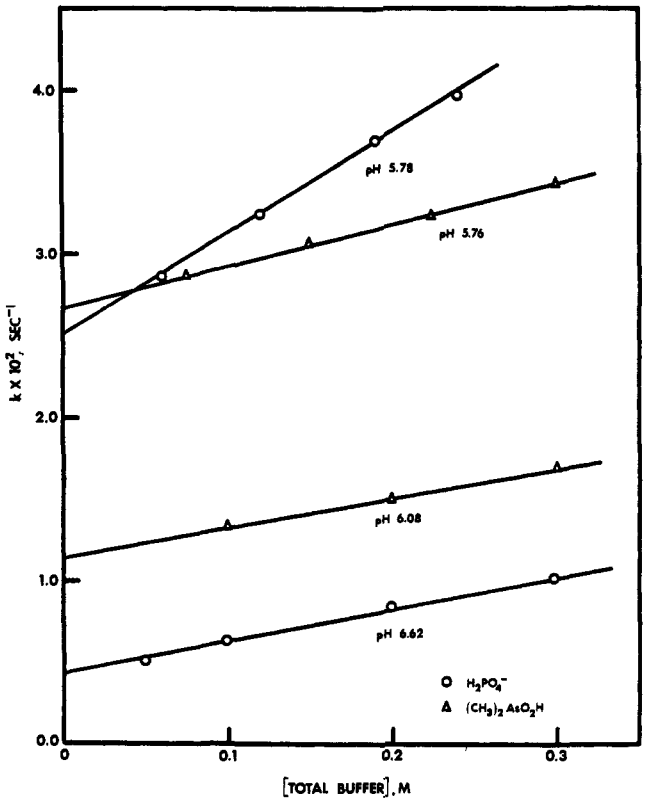


Figure 1. Plot of k_{obsd} for hydrolysis of cyclohexadiene oxide (**1**) at 25° *vs.* total concentration of phosphate and cacodylic acid buffers (HA + A^-); μ = 1.0 (KCl for phosphate and NaCl for cacodylic acid).

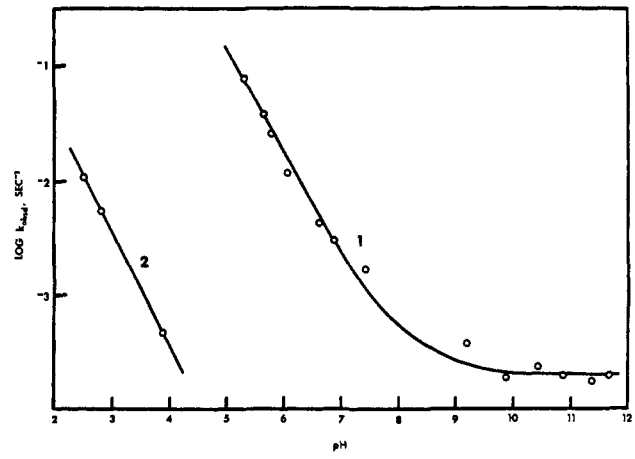
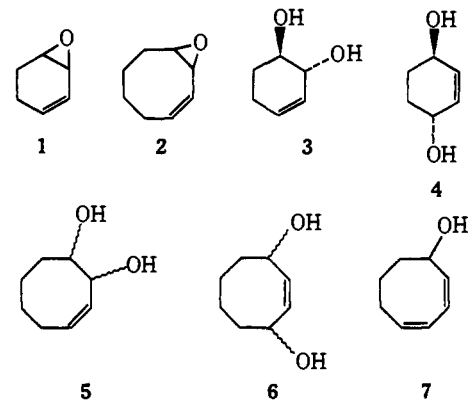


Figure 2. Plot of log k_{obsd} for hydrolysis of **1** and **2** at 25° *vs.* pH; μ = 1.0 (KCl) for **1** and 0.1 (NaCl) for **2**. All data points between pH 3 and 11 were obtained from buffer solutions, extrapolated to zero buffer concentration.



diates in the metabolism of aromatic hydrocarbons,[1] and accordingly may also be responsible for the carcinogenic effects of certain aromatic hydrocarbons.[2] The mechanisms whereby epoxides are converted to diols or other rearranged materials therefore take on added importance.

Previous investigations have revealed that epoxide hydrolysis can be catalyzed by both acid and base[3] and in some cases occurs *via* an additional pH-independent process.[1f-h] General acid catalysis in simple epoxide hydrolysis has not been previously observed.[4]

In this communication it is reported that the hydrolysis of 1,3-cyclohexadiene oxide (**1**) exhibits buffer catalysis[5a] with dihydrogen phosphate ion ($H_2PO_4^-$) and cacodylic acid (Figure 1). Other general acids, *i.e.*, cyanomethylamine hydrochloride at pH 5.65 and tris(hydroxymethyl)aminomethane hydrochloride at pH 7.5–8.5, were not catalytic. Buffer catalysis by dihydrogen phosphate, acetic acid, or malonic acid buffers was not detected in the hydrolysis of cyclooctadiene oxide (**2**).[6]

The pH–rate profiles for the hydrolysis of **1** and **2** are shown in Figure 2. The hydrolysis of **1** shows acid catalysis at low pH, a rate plateau at pH 9–12, and hydroxide catalysis at pH >12. The total rate expression is given by eq 1, and values of the respective rate constants are listed in Table I.

$$k_{obsd} = k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{HA}[HA] \quad (1)$$

In the acid-catalyzed region,[7] **1** hydrolyzed to a mixture containing 55% 3-cyclohexene-*trans*-1,2-diol (**3**)

(1) (a) D. Jerina, J. Daly, B. Witkop, P. Zaltaman-Nirenberg, and S. Udenfriend, *Arch. Biochem. Biophys.*, **128**, 176 (1969); (b) D. M. Jerina, J. W. Daly, and B. Witkop, *Biochemistry*, **9**, 147 (1970); (c) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6523, 6525 (1968); (d) D. R. Boyd, D. M. Jerina, and J. W. Daly, *J. Org. Chem.*, **35**, 3170 (1970); (e) E. Boyland and P. Sims, *Biochem. J.*, **95**, 788 (1965); (f) G. J. Kasperek and T. C. Bruice, *J. Amer. Chem. Soc.*, **94**, 198 (1972); (g) G. J. Kasperek and T. C. Bruice, *Chem. Commun.*, 784 (1972); (h) G. J. Kasperek, T. C. Bruice, H. Yagi, N. Kaubisch, and D. M. Jerina, *J. Amer. Chem. Soc.*, **94**, 7876 (1972).

(2) P. L. Grover and P. Sims, *Biochem. Pharmacol.*, **19**, 2251 (1970); P. L. Grover, J. A. Forrester, and P. Sims, *ibid.*, **20**, 1297 (1971); P. L. Grover, P. Sims, E. Huberman, H. Marguardt, T. Kuroki, and C. Heidelberger, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1098 (1971); B. N. Ames, P. Sims, and P. L. Grover, *Science*, **176**, 47 (1972).

(3) L. L. Ingraham and S. Winstein, *J. Amer. Chem. Soc.*, **74**, 1160 (1952); F. A. Long and J. G. Pritchard, *ibid.*, **78**, 2663 (1956); J. G. Pritchard and F. A. Long, *ibid.*, **78**, 2667 (1956); J. G. Pritchard and F. A. Long, *ibid.*, **78**, 6008 (1956); C. G. Swain and R. Thornton, *ibid.*, **83**, 3890 (1961); H. J. Lichtenstein and G. H. Twigg, *Trans. Faraday Soc.*, **44**, 905 (1948); A. Rosowsky in "Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter 1.

(4) Phosphate buffer has been reported to catalyze the hydrolysis of an epoxy ether: A. L. Mori and L. Schaleger, *J. Amer. Chem. Soc.*, **94**, 5039 (1972).

(5) (a) Specific salt effects[5b] appear not to be responsible for these results in view of the fact that catalysis by dihydrogen phosphate buffer at pH 6.5 is more pronounced in solutions with ionic strength held constant at 2.0, where the concentration of buffer is small relative to added electrolyte, than in solutions with ionic strength held constant at 1.0. The observed rate of **1** at pH 5.75 in cacodylic acid buffer with sodium chloride as added electrolyte (μ = 1.0) was identical with the rate of **1** in the same buffer with sodium perchlorate as added buffer, (b) P. Salomaa, A. Kankaanperä, and M. Lahti, *J. Amer. Chem. Soc.*, **93**, 2084 (1971).

(6) The formation of dienol **7** was monitored spectrophotometrically.

(7) Significant salt effects were observed in the acid-catalyzed region for **1** and **2**. At pH 5.8–6.1 k_{H^+} of hydrolysis for **1** in 1.0 *M* KCl solution was 1.6 times larger than in 0.1 *M* KCl solution.

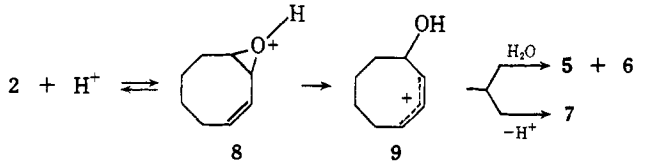
Table I. Values of k_0, k_{H^+}, k_{OH^-}, and k_{HA} for Aqueous Hydrolysis of **1** and **2** at 25°[a]

	1	**2**
$k_0 \times 10^4$, sec^{-1}	2.2 ± 0.3[b,d]	
k_{H^+}, M^{-1} sec^{-1}	$1.64 \pm 0.04 \times 10^4$[b,e]	3.55 ± 0.06[h]
$10^3 k_{OH^-}$, M^{-1} sec^{-1}	1.48 ± 0.03[b]	
$10^2 k_{H_2PO_4^-}$, M^{-1} sec^{-1}	7.4 ± 0.5[b,f]	
$10^2 k_{(CH_3)_2AsO_2H}$, M^{-1} sec^{-1}	3.4 ± 0.2[c,g]	

[a] The reactions were monitored spectrophotometrically in the thermostated cell compartment (±0.15°) of a Gilford 2400 spectrophotometer. The reaction of **1** was followed by decrease of absorbance at 220–227 nm, and reaction of **2** was followed by increase of absorbance at 230 nm due to formation of **7**. [b] $\mu = 1.0$, maintained with KCl. [c] $\mu = 1.0$, maintained with NaCl. [d] Average of ten runs at pH 10–12. [e] Average of five runs at pH 5.65 in cyanomethylamine buffer. [f] pH 5.79. [g] Identical slopes were obtained at pH 5.75 and 6.08 from plots of k_{obsd} *vs.* [HA]. [h] $\mu = 0.1$ (NaCl).

and 44% 2-cyclohexene-*trans*-1,4-diol (**4**).[8,9a] The related epoxide **2** yielded approximately equal amounts of 1,2- and 1,4-diols **5** and **6**[9b] and conjugated dienol **7**.[9a] The products from hydrolysis of **1** and **2** can be rationalized by loss of a proton from or collapse of solvent with intermediate allyl cations (*i.e.*, Scheme I).

Scheme I



Inverse kinetic solvent isotope effects (k_{D_2O}/k_{H_2O}) of 2.3 and 2.1 were observed for the hydronium ion catalyzed hydrolyses of **1** and **2**, respectively.

Catalysis by dihydrogen phosphate ion ($H_2PO_4^-$) and cacodylic acid ($(CH_3)_2AsO_2H$) in the hydrolysis of **1** requires a mechanism in which general acid is involved in the rate-determining step. The kinetic isotope effect ($k_{H_2PO_4^-}/k_{D_2PO_4^-}$) was found to be 2.3 and provides additional evidence for the involvement of $H_2PO_4^-$ at the transition state of the rate-determining step. The product distribution from hydrolysis of **1** in 1 *M* KH_2PO_4 solution ([HA]/[A$^-$] = 5) was the same as the product distribution in nonbuffered solution at pH 5.5, and suggests that a common intermediate (presumably an allyl cation) is formed from catalysis by both hydronium ion and dihydrogen phosphate ion. The ability of phosphate and cacodylate buffers to catalyze the hydrolysis of **1**, while amine acids do not provide detectable catalysis, most likely results from the bifunctional nature of dihydrogen phosphate ion and cacodylic acid. One possibility is that C–O bond breaking is concurrent with proton transfer from the general acid,[10] and the phosphate ion is able to provide electrostatic stabilization[11] of the partially formed allylic cation at the transition state.

In the pH-independent range (pH 9–12),[8] the product mixture contained 98% of the *trans*-1,2-diol **3**, and only 1–2% of *trans*-1,4-diol **4**.[12] Formation of predominately trans 1,2-product **3** from **1** in the pH-independent range suggests considerable nucleophilic involvement of water at the transition state. The solvent isotope effect (k_{H_2O}/k_{D_2O}) of 1.26 at pH (pD) 11.7–11.8 is also consistent with a nucleophilic attack of water on the epoxide.

The lack of buffer catalysis or a significant pH-independent term in the hydrolysis of **2** is probably related to the fact that **2** is much less reactive than **1** to acid-catalyzed hydrolysis.[10] If the ratio ($k_{H^+}/k_{H_2PO_4^-}$) for the hydrolysis of **2** is approximately equal to that same ratio (*ca.* 2×10^5) for the hydrolysis of **1**, then the value of $k_{H_2PO_4^-}$ for **2** would be *ca.* 2×10^{-5} M^{-1} sec^{-1}, and could not be detected experimentally by the spectroscopic method used in this study. Other highly reactive epoxides might also be expected to show buffer catalysis, and this possibility is being further explored.

Acknowledgment. This work was supported in part by the Research Corporation. Discussions with Drs. V. P. Vitullo and R. M. Pollack are appreciated.

(8) Product analyses were carried out throughout the pH range by injecting an ethanol solution of **1** in a nonbuffered solution maintained at constant pH for *ca.* 10 half-lives with a Radiometer pH-Stat. After the pH of the reaction solution was changed to *ca.* 7–9, it was analyzed directly by glpc on a 1/8-in., 5% hyprose column.

(9) (a) Products **3**, **4**, and **7** were hydrogenated to known saturated compounds. (b) Structures **5** and **6** were assigned on the basis of nmr spectra. Stereochemistry was not determined.

(10) It has been suggested that release of ground-state strain leads to general acid catalyses in acetal hydrolysis: T. F. Fife, *Accounts Chem. Res.*, 5, 264 (1972).

(11) B. M. Dunn and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 5725 (1971); V. P. Vitullo and N. R. Grossman, *J. Org. Chem.*, **38**, 179 (1973).

(12) 3-Cyclohexene-*cis*-1,2-diol, prepared from the reaction of osmium tetroxide with 1,3-cyclohexadiene, possessed a glpc retention time different from **3** and **4** and was shown to be stable throughout the pH range studied.

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Metal Complex Promoted Decomposition of the Carbene Precursor Chlorodifluoroacetate

Sir:

As part of an investigation into the synthesis of new carbene complexes and carbenoid systems, we have undertaken a study of the reactions of nucleophilic metal complexes with known carbene precursors. Reactions of this type have been reported before,[1-3] such as by Mango and Dvoretzsky on the catalytic decomposition of diazomethane by $IrCl(CO)(PPh_3)_2$,[1] but few well characterized organo transition metal products have been obtained. Our studies have focussed on the use of trihaloacetate ions and in particular chlorodifluoroacetate as the carbene precursors. These studies have led to the establishment of a novel reaction sequence whose principal features include (1) two distinctly different metal-promoted pathways for the decomposition of CF_2ClCOO^-, (2) the formation of difluoromethyl complexes, and (3) evidence for the intermediacy of a metallocarbanion. In addition, the de-

(1) F. D. Mango and I. Dvoretzky, *J. Amer. Chem. Soc.*, **88**, 1654 (1966).

(2) P. Hong, N. Nishii, K. Sonogashira, and N. Hagihara, *J. Chem. Soc., Chem. Commun.*, 993 (1972).

(3) Reactions of carbenes and carbene precursors with metal hydride complexes have also been reported as in T. S. Piper and G. Wilkinson, *J. Inorg. Nucl. Chem.*, 3, 104 (1956); and K. S. Chen, J. Kleinberg and J. A. Landgrebe, *J. Chem. Soc., Chem. Commun.*, 295 (1972).