Activation of Epoxides as Electrophiles by Transition Metal Ions in Dilute Aqueous Solution

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Abstract: The hydration of 2-pyridyloxirane (2-PO, **1**) to the corresponding diol, **3**, is strongly catalyzed by Cu(II) in dilute aqueous solution. The reaction is first order in both copper and epoxide. Bidentate (but not monodentate) pyridine ligands inhibit the reaction approximately 50% when present at concentrations close to the epoxide concentration. Kinetic analyses of these reactions allowed determination of the Cu(II)-complexation constants for **1**, **3**, 1-(2-pyridyl)ethanol (**2**), 2-methoxymethylpyridine (**4**), and 2-vinylpyridine (**5**). A plot of ligand pK_a vs. log K_1^E for Cu(II) complexation indicated that ligands **1** and **4** are definitely *bidentate* in nature. All of the kinetic data could be fitted to the rate law $v = k'K_1^E[Cu][E] + k''K^* \cdot [Cu][E][L]$, and it was found that for various L, $0.75k' < k'' < k'$. In 50 mol % aqueous alcohol slightly more ether than diol was formed from **1** and Cu(II). Although k' was ca. 10^4 times the uncatalyzed hydration rate, the solvent isotope effects (k_{D_2O}/k_{H_2O}), both with and without Cu(II) catalysis (0.91 and 0.85, respectively), are similar to others reported for the spontaneous hydration of simple epoxides. Together with the previously reported regiospecificity (i.e., C_β–O bond cleavage) of the Cu(II)-catalyzed reaction of **1** with water (~96%) or other nucleophiles (~100%), these results support a mechanism in which a Cu(II) *chelate* of **1** undergoes external attack by water or other nucleophiles present in the solution. The analogy of this form of epoxide activation to that brought about by intramolecular hydrogen bonding is discussed in relation to the toxic biological effects of epoxides.

Catalysis of the hydrolysis of amino acid esters by transition metal ions was first reported by Kroll in 1952.[1] Since then a number of research groups have investigated the effects of metal ions on hydrolysis and group-transfer reactions of a wide variety of derivatives of sulfuric, phosphoric, and carboxylic acids.[2] Several years ago we reported[3] that the hydration of 2-pyridyloxirane (2-PO, **1**) was strongly catalyzed by transition metal ions in dilute aqueous solution, and that this reaction mimics the rate acceleration and regiospecificity of the enzyme epoxide hydrase.[4] Although epoxide hydrase was subsequently purified and shown not to be a metalloenzyme,[5] the metal-catalyzed reaction of 2-PO with water and other nucleophiles has considerable relevance for both chemistry and biology.

Epoxides are well known for their deleterious biological effects, which are ascribed to their nonenzymatic reaction as electrophiles with nucleophilic groups on vital macromolecules, particularly proteins and nucleic acids.[6] Epoxides which are activated, e.g., through intramolecular hydrogen bonding, have increased reactivity toward nucleophiles, and may have considerably increased biological activity as well. For example, diol epoxides of benzo[a]pyrene are extremely potent mutagens, and are 150–500 times more reactive toward *p*-nitrothiophenoxide than related epoxides which lack hydrogen-bonded interactions with neighboring hydroxyl groups.[7] Similar chemical reactivity has been observed in related (nonmutagenic) diol epoxides derived from naphthalene,[8] in the antileukemic diterpene epoxide triptolide,[9] and in a series of epoxy sterols.[10]

For 2-pyridyloxirane, an analogous form of activation could be achieved through *chelation* of a metal ion by the substrate, as shown in **1a**. In effect, such coordination would make the

oxygen atom a very much better leaving group for nucleophilic displacement. However, metal-catalyzed hydration of 2-PO could in principle occur by other mechanisms, as indicated in **1b** or **1c**, for example. In fact, precedent has already been established for intramolecular attack of a coordinated hydroxide (cf. **1b**) on N-coordinated amino acid derivatives at substitutionally inert Co(III) centers,[11] and on carboxylic esters and anhydrides in labile Co(II), Ni(II), and Zn(II) complexes.[12,13] In this paper we report the details of our study of the Cu(II)-catalyzed hydration of 2-PO, and present four separate lines of evidence which support the mechanism depicted in **1a**.[4] We also note the potential biological implications of this type of epoxide activation for epoxide drugs and drug metabolites which are potential chelating agents.

Experimental Section

Materials. 2-Vinylpyridine (**5**) was obtained from Aldrich and distilled (bp 79–82 °C at 29 Torr) before use. Epoxide **1** and diol **3** were synthesized as described previously,[4] and were purified by distillation (45–49 °C at 0.05 Torr) or sublimation (80 °C at 0.1 Torr), respectively. Borohydride reduction of 2-acetylpyridine in 95% EtOH, followed by distillation (92 °C at 28 Torr), gave 2-(1-hydroxyethyl)-pyridine (**2**). Borohydride reduction of 2-picolinaldehyde in 95% EtOH, followed by methylation (NaH/CH₃I in tetrahydrofuran, 25 °C) and distillation (bp 65–68 °C at 28 Torr), gave pure 2-methoxymethylpyridine (**4**). All synthetic compounds gave satisfactory CHN analyses and NMR spectra; their purity was also confirmed by numerous liquid chromatography systems used in the course of the kinetic studies.

For the titrations 1 M NaOH was standardized potentiometrically against primary standard potassium hydrogen phthalate. Cupric nitrate solutions (0.1 M) were prepared from the hydrate and standardized with 0.1 M Na₂S₂O₃ solution which had previously been standardized against electrolytic copper as described by Vogel.[14] Nitric acid solutions (2 M) were prepared by dilution of the concentrated reagent which had been boiled until it was free of coloration; they were titrated against standardized NaOH prepared above.

Titrations. All acid–base titrations were carried out using an Orion Model 112 digital pH meter which was equipped with Corning glass and saturated calomel electrodes, and calibrated with pH 4.00 and 7.00 standard buffers. Ligand pK_as were determined in duplicate from the pH at their half-neutralization point when titrating an acidic solution with base. Titrimetric Cu(II)-complexation constants for ligands **2**–**5** were determined from a plot of $\bar{n}$ vs. $-\log$ [L] as described by Freiser, Charles, and Johnston.[15] For each ligand, determinations were made at two different Cu:L ratios.
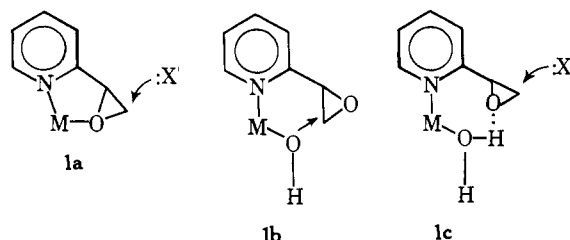
X = H₂O, MeOH, EtOH,
     Cl⁻, Br⁻, AcO⁻

Table I. Titrimetrically Determined pK_as and Cu(II)-Complexation Constants for Pyridine Ligands[a]

Ligand	pK_a	Log K_1^L	Log K_2^L	Ref
1	3.84			c
2	4.98	3.64	2.56	c
3	4.64	3.75	2.66	c
4	4.53	2.93	1.78	c
5	5.05[b]	1.72[b]		c
2-Picoline	6.21[d]	1.69[d]		e
2,5-Lutidine	6.63[d]	1.78[d]		e
2-Phenylpyridine	4.77[f]	1.30[f]		g

[a] Determined at 25 °C and μ = 0.1 (NaNO$_3$) unless otherwise noted. [b] μ = 0.23. [c] This work. [d] μ = 0.61 (KNO$_3$). [e] Reference 16. [f] μ = 0.1 (NaClO$_4$). [g] Reference 24.

Kinetics. Reactions were run at 25 °C in 25-mL volumes of 0.1 M acetate buffer, pH 4.30, at the concentrations of substrate and ligands listed in Table II. Reactions were initiated after temperature equilibration had occurred by adding a 0.10-mL aliquot of Cu(NO$_3$)$_2$ solution to bring T_{Cu} to 0.10 mM. Reactions were monitored by HPLC as described previously,[3,4] except that a Whatman Partisil-ODS column was used. The conditions listed below gave very good resolution of the ligand species, and it was possible to quantitate each by using their peak heights and appropriate calibration curves. Better precision was obtained when ligands other than **1** and **3** were also present because they could serve as an internal standard.

Ligands present	Mobile phase	Flow, mL/min
1 + 2 + 3	pH 3 formate (0.1 M)/MeOH (85:15)	2.5
1 + 3 + 5 (or **4**)	pH 4.3 acetate (0.1 M)/MeOH (75:25)	2.5 (or 2.0)

Plots of ln [E]$_0$/[E]$_t$ vs. t were linear (slope = k_a) for at least 30–40 min (eight to ten HPLC injections, two to five turnovers of Cu^{2+} catalyst), and initial rates, v, were calculated by multiplying k_a by [E]$_0$.

Results

Determination of Ligand pK_as and Cu(II)-Complexation Constants. The pK_as of 2-PO and the related ligands **2–5** were determined by direct titration and are listed in Table I. Stepwise constants K_1^L and K_2^L for copper complexation by these ligands (see Scheme I) were determined using the Calvin-Bjerrum method[15] and are also listed in Table I. The corresponding values for 2-PO (K_1^E, K_2^E) could not be determined this way because its hydration was very rapid under the titration conditions. Instead K_1^E was determined kinetically, as described below, and K_2^E was estimated to be 0.08K_1^E based on comparisons of K_1^L and K_2^L for pyridine derivatives taken from Table I and elsewhere.[16]

Kinetic Analysis of the Cu(II)/2-PO Reaction System. We have previously shown that the catalyzed hydration of 2-PO is first order in Cu(II), and that the rate of the uncatalyzed reaction is extremely slow and may therefore be neglected.[3]

Scheme I

$$E = 2\text{-PO} = \mathbf{1}$$
$$L = \mathbf{2} - \mathbf{5}$$
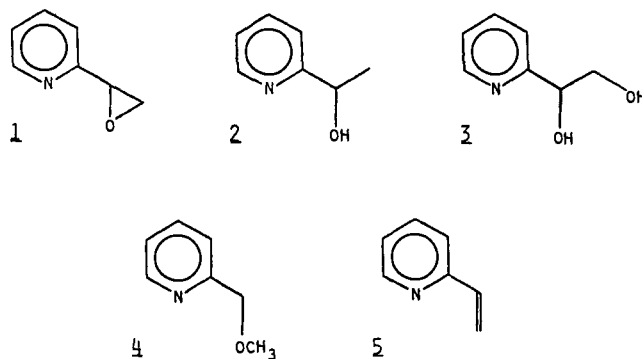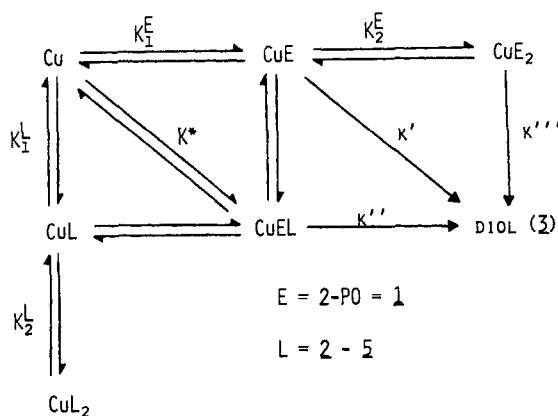
In this study the total copper, T_{Cu}, was held constant at 0.1 mM, and the total epoxide concentration, T_E, was varied from 1.0 to 18.0 mM ([E] = 0.74–13.3 mM after correcting for the fraction protonated). A plot of this data in the form 1/v vs. 1/[E] gave a straight line (five points, r = 0.9862). Assuming that the diol product arises from reaction of a copper–epoxide complex (i.e., CuE) one may write the rate law given in eq 1. Substituting for [Cu] obtained from eq 2, the copper mass-balance equation, gives eq 3. Since the experimentally derived plot of 1/v vs. 1/[E] was strictly linear, its slope and intercept were used with the first two terms of eq 3, respectively, to determine the values of k' and K_1^E listed in the first line of Table II.

$$v = k'[\text{CuE}] = k'K_1^E[\text{Cu}][\text{E}] \tag{1}$$

$$T_{Cu} = [\text{Cu}]\{1 + K_1^E[\text{E}] + K_1^E K_2^E[\text{E}]^2\} \tag{2}$$

$$\frac{1}{v} = \frac{1}{k'K_1^E[\text{E}]T_{Cu}} + \frac{1}{k'T_{Cu}} + \frac{K_2^E[\text{E}]}{k'T_{Cu}} \tag{3}$$

By estimating K_2^E to be 0.08K_1^E, or 11 M^{-1}, one can calculate that [CuE$_2$] is at all times only 1% of [CuE]. Furthermore, ignoring the third term of eq 3 leads to an error of only 0.07%

Table II. Kinetically Determined Rate- and Cu(II)-Complexation Constants for Pyridine Ligands[a]

Ligand	Concn range, mM T_L	Concn range, mM [L]	I_{50}, mM[b]	n (r)[c]	k', s^{-1}	Log K_1^L
1	1.00–18.0	0.737–13.3		5 (0.9862)	0.0222	2.14[d]
2	0.46–14.4	0.076–2.5	0.3	13 (0.9986)	0.0226	3.58
3	0.52–5.22	0.164–1.64	0.6	7 (0.9747)	0.0249	3.25
4	4.63–24.1	1.71–8.93	5.4	7 (0.9637)	0.0239	2.31
5	6.47–60.6	0.97–9.15	46.4[e]	8 (0.5711)[f]	0.0221	1.38

[a] Determined at 25 °C in 0.1 M acetate buffer (pH 4.30), μ = 0.03, T_E = 1 mM, and T_{Cu} = 0.1 mM. [b] Value of [L] giving 50% inhibition of hydration rate. [c] Number of points and regression coefficient of plot of v^{-1} vs. [L]. [d] Corresponds to K_1^E. [e] Extrapolated value. [f] An actual plot of the data definitely describes a straight line; the apparently poor regression coefficient results from scatter (±5%) due to measurement of small levels of inhibition (20% at 9.15 mM [L]).

when $T_E = 1.0$ mM and $T_{Cu} = 0.1$ mM, the standard conditions used for all the other kinetic studies. Finally, a plot of log $(v/[Cu])$ vs. log $[E]$ gave a straight line having a slope of 1.13 $(r = 0.9889)$, thus indicating that the hydration is first order in epoxide as well as copper. The function $v/[Cu]$ rather than v is used here because the reaction is first order in copper, and $[Cu]$ decreases as T_E, and concomitantly $[E]$, are increased.

Effects of Added Ligands. The addition of various mono- and bidentate pyridine ligands to the standard kinetic system invariably decreased the rate of 2-PO hydration. With ligands **2–5**, plots of $1/v$ vs. $[L]$ gave straight lines whose slopes and intercepts were used to determine the rate constants (k') and complexation constants (K_1^L) listed in lines **2–5** of Table II. The equations used for these analyses were derived from an assumed rate law, eq 4, which recognizes the possibility of diol arising from the mixed-ligand complex CuEL as well as from CuE. Total ligand, T_L, and total copper, T_{Cu}, are given by the mass-balance equations 5 and 6, respectively.

$$v = k'K_1^E[Cu][E] + k''K^*[Cu][E][L] \qquad (4)$$

$$T_L = [L] + [LH^+] + [CuL] + 2[CuL_2] + [CuEL] \quad (5)$$

$$T_{Cu} = [Cu]\{1 + K_1^E[E] + K_1^E K_2^E[E]^2 + K_1^L[L]$$
$$+ K_1^L K_2^L[L]^2 + K^*[E][L]\} \quad (6)$$

$$T_L = [L]\left\{1 + \frac{[H^+]}{K_a^L}\right\} \qquad (7)$$

Generally for calculation of $[L]$, $[CuL] + 2[CuL_2] + [CuEL]$ $\ll [L] + [LH^+]$, in which case eq 5 simplifies to eq 7. However, for low concentrations of total ligands **2** or **3**, the last three terms of eq 5 had to be retained, and both $[L]$ and $[Cu]$ were estimated by a reiterative process.[17] Substituting eq 6 for $[Cu]$ in eq 4 then leads to eq 8.

$$\frac{1}{v} =$$

$$\frac{1 + K_1^E[E] + K_1^E K_2^E[E]^2 + K_1^L[L] + K_1^L K_2^L[L]^2 + K^*[E][L]}{k'K_1^E[E]T_{Cu} + k''K^*[E][L]T_{Cu}}$$

$$(8)$$

Since our experimental plots of $1/v$ vs. $[L]$ were strictly linear, it was assumed that the second-order terms in eq 8 were small, as was observed in the epoxide-only case described above. Thus eq 8 could be simplified to eq 9, which ultimately was used with the slopes and intercepts of the $1/v$ vs. $[L]$ plots to determine the rate constants and complexation constants listed in lines **2–5** of Table II.

$$\frac{1}{v} = \frac{1}{k'K_1^E[E]T_{Cu}} + \frac{1}{k'T_{Cu}} + \frac{K_1^L[L]}{k'K_1^E[E]T_{Cu}} \qquad (9)$$

Effects of D$_2$O and Alcohols. In unbuffered solutions 2-PO hydrolyzed slightly faster in H$_2$O than in D$_2$O $(k_{D_2O}/k_{H_2O} = 0.85)$. Addition of catalytic amounts of Cu(II) to these solutions greatly increased the hydration rate, but changed the solvent isotope effect only slightly (Table III). In absolute methanol or ethanol containing catalytic amounts of Cu(II), 2-PO reacts rapidly to give exclusively 2'-methoxy- or 2'-ethoxy-1'-(2-pyridyl)ethanol, respectively. In 50 mol % water/alcohol solutions, both the ether product and diol **3** are formed; in ethanol the ether:diol ratio was 1.1 while in methanol it was 2.5.

Discussion

In mechanistic studies of metal ion catalyzed hydrolysis reactions one of the main points of interest is to determine the relative roles of two basic mechanisms. One mechanism involves external nucleophilic attack on a coordinated (and

therefore presumably polarized or "activated") substrate, while the other involves an intramolecular or intracomplex (and therefore presumably entropically advantaged) reaction of substrate and nucleophile. Since these processes are kinetically equivalent, indirect methods must be used to determine their relative importance. Some of the indirect methods that have been employed include (1) analysis of activation enthalpies and entropies,[13,18,19] (2) alteration of substrate to impose steric constraints against the intramolecular reach of a coordinated nucleophile to the reaction center, or against coordination of the reactive functional group to a metal ion bound to other strong coordination sites within the substrate,[12,13] (3) analysis of the relative reactivity of a series of nucleophiles vis-à-vis their relative metal binding affinity,[13,20] (4) linear free energy relationships and other comparisons between the rate constants for reaction of the coordinated ligand and the equilibrium constant for binding of the reactant to a metal or metal–coligand center,[18,19,21] (5) solvent deuterium isotope effects,[22] (6) analysis of the inhibitory effects of competing ligands,[21] and (7) use of nucleophiles attached to a chelating agent.[13,21,23] While none of these approaches independently affords sufficient information to differentiate the inter- vs. intramolecular pathways with confidence, a convincing case can be made when several of these criteria all support the same conclusion.

The ligands used in this study were chosen with several reasons in mind. First, like **1**, ligands **2–4** are *potentially N,O-bidentate* ligands. Diol **3** is also the reaction product, and its inhibitory effect on the hydration of **1** was noted previously.[3] Alcohol **2** is a bidentate model for **3**, and was found to be more easily separable from **3** on LC than 2-pyridylcarbinol. It was hoped that ether **4** would be a model for the metal complexation behavior of **1**, which could not be investigated directly because it was too reactive. Finally, 2-vinylpyridine (**5**), a *monodentate* 2-substituted pyridine with a low pK_A, was also chosen as a potential model for the complexation behavior of **1**.

Because ether oxygens are not known as particularly strong donor groups for transition metals in aqueous solution, it was of interest with respect to **1a** to know whether the oxygen atom in ligands such as 2-PO or 2-methoxymethylpyridine (**4**) enhanced their binding compared to strictly monodentate 2-substituted pyridines. While the complexation constants K_1^L and K_2^L for **4** could be evaluated by titrimetric as well as kinetic methods, only a kinetic estimate could be made for K_1^E. The kinetically determined complexation constants consistently came out smaller than those determined titrimetrically. A small part of this difference may be due to differences in ionic strength, etc., in the two experiments, but most of the difference is probably inherent in the two approaches to the quantity being estimated. Thus, while the titrimetric K's come from plots of the *calculated average* number of ligands bound ($\bar{n}$) vs. the negative logarithm of the free ligand concentration, the kinetic K's are derived by observing a parameter (i.e., reaction rate) which is *stoichiometrically* related to the concentration of the complexed species present.

Within a series of ligands possessing the same basic donor group(s), it is often possible to relate the binding constants for a particular metal to the pK_a of the ligand using a linear free energy relationship such as[24]

$$\log K_1^L = a(\text{p}K_a) + b \qquad (10)$$

Since by definition monodentate and bidentate ligands do not possess comparable donor groups, eq 10 affords a means of determining whether 2-PO and **4** are significantly bidentate in nature, and thus whether structure **1a** is a realistic possibility. From a plot of the pK_a and K_1^L data in Tables I and II it can readily be seen that the oxygen atoms in 2-PO and **4** enhance their metal binding by an order of magnitude over

what would be expected for a strictly monodentate 2-substituted pyridine *of comparable pK_a*. Although the ether oxygens in 1 and 4 do not contribute as much to metal binding as do the hydroxyl groups in ligands 2 and 3, 1a is undoubtedly the preferred form of the Cu(II) complex of 2-PO in solution (cf. CuE in Scheme I).

While 1a may be the predominant form of CuE in solution, it does not necessarily follow that 1a is also the reactive form of CuE. However, if it were, one would expect that bidentate but not monodentate ligands would inhibit the catalyzed reaction about 50% at concentrations comparable to the substrate concentration. Under the standard conditions of the kinetic assays, the concentration of *free* 2-PO is 0.737 mM. Table II shows that the I_{50} values (interpolated from $1/v$ vs. [L] plots) for the free forms of the bidentate ligands 2–4 range from 0.3 to 5.3 mM, whereas the monodentate ligand 5 has an extrapolated I_{50} value of ca. 46 mM.

The metal-independent hydration of 2-PO is extremely slow compared to the Cu(II)-catalyzed hydration.[3] Thus for practical purposes, the reactions outlined in Scheme I include all the reasonable possibilities, assuming that Cu(II) is 4-coordinate, and that 2-PO is a bidentate *reactant*. As mentioned above, in the absence of added ligands eq 1 and 3 fit the observed rate data very well, and allow one to estimate k' and K_1^E. The same is true for eq 1 and 9 when weak ligands (i.e., 4 and 5) or low concentrations of strong ligands (i.e., $\leq 3 \times I_{50}$ for 2 or 3) are added to the basic reaction system. However, at higher concentrations of ligands 2 and 3 it is necessary to take into account diol formation by reaction of CuEL as well as that arising from CuE; hence eq 8 must be used. This equation can be fitted quite well to *all* the observed data by making two additional assumptions. The first assumption is that $K^* \approx K_1^E K_2^L \approx K_1^L K_2^E$; the second is that k' and k'' are of comparable magnitude.[25] In fact extremely good fits of the data are obtained if $k'' = 0.9k'$ for the complex [Cu(2-PO)(2)], and $k'' = 0.75k'$ for the complex [Cu(2-PO)(3)].

The approximation of K^* taken above depends on the absence of any special ligand–ligand effects mediated through the metal in a mixed complex such as CuEL, compared to those present in the 1:2 complexes CuE$_2$ or CuL$_2$. Symbiotic mixed ligand effects are most pronounced when one ligand is a soft π acceptor such as bipyridyl and the other ligand is a hard σ donor such as oxalate.[2,26] Conversely, when both ligands are of the same chemical type, one observes the usual declining order of stepwise complexation constants $K_1 > K_2 > \ldots > K_n$. Since the ligands of concern here (1–3) are relatively similar, each containing a pyridine donor and a neutral oxygen donor which participate to form a 5-membered chelate ring, special mixed-ligand effects are unlikely to be important. Thus, the first approximation is not unreasonable. With respect to the second approximation one might expect the presence of a bound ligand to a metal center to influence the *reactivity* of a second ligand, just as it influences its binding. In fact this has been observed in linear free energy relationships between the rate of methyl glycinate hydrolysis catalyzed by various Cu(II)[19] and Ni(II)[18] complexes, and the binding strength of coligands in the complex; the stronger the binding of the coligand the weaker the observed catalysis. From this one might at first expect that k'' and k''' should be considerably less than k'. However, the relationships mentioned above were established in a range of log K from 10 to 16, which is enormously greater than K_1^L for any of the ligands in this study. It is difficult to imagine extrapolating such relationships over a jump of 7 or 8 log units, much less over the even greater jump from catalysis by such strong complexes to catalysis by the free metal ion for which the value of log K is undefined. The ligands used in our study are not particularly strong complexing agents, and since any reduction in the Lewis acidity of CuL caused by the σ-donor effects of L will tend to be offset by the π-acceptor

Table III. Solvent Deuterium Isotope Effects on Epoxide Hydrations

Epoxide	Conditions	k_{obsd}, s^{-1}	k_{D_2O}/k_{H_2O}	Ref
2-PO	H$_2$O	$(3.94 \pm 0.12) \times 10^{-7}$	0.85	a
2-PO	D$_2$O	$(3.36 \pm 0.12) \times 10^{-7}$		a
2-PO	pH 5.10^b	$(1.24 \pm 0.3) \times 10^{-5}$	0.91	a
2-PO	pD 5.10^{b,c}	$(11.3 \pm 0.3) \times 10^{-5}$		a
C$_2$H$_4$O	H$_3$O$^+$		2.20	d
C$_2$H$_4$O	HO$^-$		1.14	d
C$_3$H$_6$O	HO$^-$		1.04	d
C$_3$H$_6$O	pH 6.4		0.08	d
i-C$_4$H$_8$O	pH 7.4		0.09	d

^{a} This work. ^{b} 0.1 M phosphate buffer, 0.01 M epoxide, 10^{-4} M Cu(II). ^{c} pD = pH meter reading + 0.4. ^{d} J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 6008 (1956).

property of the pyridine ring in L, it is not really surprising, particularly in terms of mechanism 1a, that diol formation from CuE and CuEL should occur at roughly the same rates.

If the major pathway leading to diol formation involved mechanism 1a, one would expect water and other nucleophiles to react in proportion to their relative nucleophilicities, irrespective of their affinity for Cu(II) in solution. This line of reasoning was used by Breslow and co-workers to argue for an external attack mechanism in the Ni(II)-catalyzd hydrolysis of *o*-phenanthroline-2-carbonitrile (eq 11); in 50 mol %

(11)
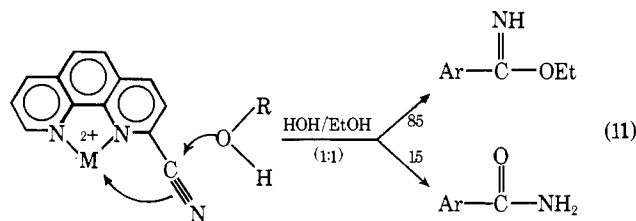
aqueous ethanol they observed an 85:15 ratio of imino ester to amide. Similarly, the observation that the Cu(II)-catalyzed hydration of 2-PO in 50 mol % aqueous methanol and ethanol led, respectively, to 2.5 and 1.1 times as much ether product as diol may be taken in support of mechanism 1a. The difference in the abilities of the nitrile and 2-PO to discriminate between alcohols and water as nucleophiles probably lies in the relative reactivities of the two coordinated substrates, i.e., the greater the reactivity of a species the less it discriminates among competing reactants. Studies of the effects of D$_2$O on the hydration of 2-PO and other epoxides also support 1a as the predominant mechanism for Cu(II) catalysis. As shown by the data in Table III, the solvent isotope effects observed for 2-PO hydration, *both with and without Cu(II) catalysis*, are similar to those for other spontaneous hydrations, but unlike those observed for acid or base hydration of epoxides. These observations effectively rule out mechanism 1c. Although they appear to fit mechanism 1a more readily than 1b, it is not clear that a metal-coordinated hydroxide would necessarily display the same isotope effect as "free" hydroxide when reacting with an epoxide in solution. A further argument against mechanism 1b, however, is that it should lead to extensive if not exclusive C_α-O bond cleavage via a chelated five-membered transition state.[27] In contrast ^{18}O-tracer studies indicate that $\geq 96\%$ of the hydration involves C_β-O bond cleavage as predicted by mechanism 1a.[4] Finally, the formation of 1b should be pH dependent, increasing with pH. The pH–rate profile[3] for the reaction shows a maximum around pH 5.1, an inflection point at pH 3.7 (the pK_a of 1), and another inflection point around pH 6.0, at which the rate is *decreasing* rather than increasing with pH.

We have presented four separate lines of evidence pointing to chelation as a mechanism for greatly increasing the susceptibility of an epoxide to attack by nucleophiles. Currently there is a great deal of interest in the reaction of epoxides with important *cellular* nucleophiles as the probable basis of the toxic effects of epoxides. Since it has been shown that intramolecular hydrogen bonding activates diol epoxides and related compounds, some of which are potent toxins, 150–500-fold toward nuelcophiles, the question arises as to whether metal chelation in vivo by structurally suited epoxides could bring about similar increases in the toxicity of these compounds. Data with which to answer this question are not at present available. However, it is not unreasonable to suspect that this mechanism could be involved in mediating the hepatotoxic and porphyrinogenic effects of metabolites derived from allyl barbiturates and the related toxin allylisopropylacetamide.[28-32]

References and Notes

(1) H. Kroll, *J. Am. Chem. Soc.*, **74**, 2036 (1952).
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