pared from the monoetherates by adding the more polar solvent and distilling out the ether under vacuum. The complete removal of ether from the THF solutions required evaporation to dryness twice, followed by dilution with enough THF to bring the sample to the required concentration.

Samples for electronic spectra were transferred to evacuated cells by means of breakseal tubes. Spectra were run at approximately 10^{-2} and 10^{-3} M using a 1.0-mm cell equipped with a removable 0.9-mm spacer. The spectra were recorded on a Cary 14 spectrophotometer.

The nmr samples were filtered through a sintered glass filter into an nmr tube attached to the vacuum apparatus and sealed under vacuum. Spectra were recorded on a Varian HA 100 spectrometer in frequency sweep mode using solvent peaks for a lock. Frequency measurements were made using a frequency counter and the chemical shifts were referenced to TMS by adding the chemical shift of the lock peak. In THF and HMPA the methylene protons could not be observed because of overlap with the solvent peaks. In the case of THF this was remedied by the use of THF-d_8 as a solvent. TMS was used for a lock in these samples.

Temperatures were measured using the Varian-supplied methanol and ethylene glycol samples. Frequency measurements of the methanol peaks in the -5 to $+10°$ range were not reproducible because the peaks are very broad. Interpolation was therefore necessary. In the vicinity of 40°, temperature measurements with the two samples agreed to $\pm 1°$.

Chemical Shifts of Naphthalene in THF and HMPA. The 100-MHz spectra of 0.20 M solutions of naphthalene in CCl_4, THF, and HMPA were obtained. The patterns were all very similar, but reasonably large shifts in the α and β proton patterns were apparent. Using the value of Cooper and Manatt[51] for the chemical shift between the α and β protons (35.7 Hz) and the midpoint between their patterns in the CCl_4 spectrum (7.56 ppm), the chemical shifts are calculated to be 7.74 and 7.38 ppm, respectively, for the 0.2 M solution.[52] In THF the α and β patterns were 0.06 and 0.04 ppm downfield from the corresponding patterns in CCl_4. The α and β chemical shifts in THF are then approximately 7.80 and 7.42 ppm, respectively. In HMPA the patterns were shifted downfield 0.22 and 0.12 ppm, making the approximate chemical shifts 7.96 and 7.50 ppm.

(51) M. A. Cooper and S. L. Manatt, *J. Amer. Chem. Soc.*, **91**, 6325 (1969).

(52) The naphthalene chemical shifts were observed to be quite concentration dependent.

Dependence of Mechanism on pH for Deuterium–Hydrogen Exchange in 1-Methyltetrazole-5-*d*. Transition Metal Ion Catalysis of a Deprotonation Process

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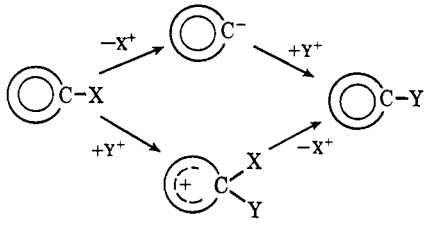
Abstract: The pH–rate profile of protium for deuterium exchange of 1-methyltetrazole-5-*d* in aqueous solution at 67.6° has been determined and used as a control experiment in a demonstration that σ complexation of a heteroaromatic substrate with a transition metal cation (Cu^{2+} and Zn^{2+} used) can have a major rate-enhancing effect on processes in which substrate ring substituents are eliminated to produce formal sp^2 carbanion intermediates. The control experiment is itself of interest, since in addition to a flattened exchange rate minimum at pH 4, a rate maximum is found at $-H_0$ 1-1.5, well below the experimental H_0 (*ca.* -2.4) for half-protonation of 1-methyltetrazole.

Electrophilic substitution at annular positions in heteroaromatic compounds *via* carbanionic intermediates (mechanism 1) has been amply and rigorously documented[1] and in many systems rivals in importance the much better known pathway 2 involving initial addition of the electrophilic reagent at the carbon atom being substituted. Moreover, the synthetic transformations which may readily be accomplished by each route are usually complementary because positional specificities and reaction condition requirements are ordinarily quite different.



(1)

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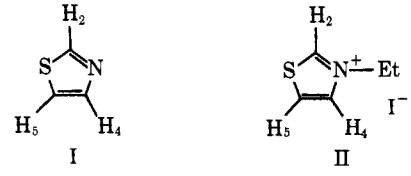
(1) Though this area has never been generally reviewed, references are too numerous to reproduce here. Some of this work and leading references to most of the remainder can be found in the papers cited in ref 2–10.

The present investigation has two origins: first, a desire to devise practical methods to increase the facility of electrophilic substitution by the ionization pathway 1 and thus increase its utility; and second, a suspicion that catalytic mechanisms are available by which biological systems could make greater use of this process than would be expected from predicted reactivities. The analysis which led to the specific experiments reported here is outlined below.

In OD^-–D_2O at 31°, thiazole (I) readily undergoes H–D exchange of H_2 and H_5 (relative rate 1:0.9) by a simple ionization pathway, rate = k_2[thiazole][OD^-].[2] N-Alkylation (→II) produces a vast selective increase

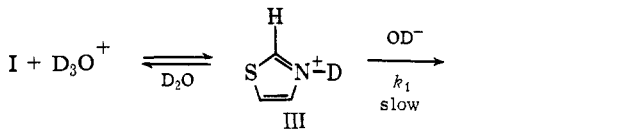


(2) R. V. Kendall, Dissertation, The Pennsylvania State University, 1970; R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966).

in the ease of proton loss,[3] and the kinetic C–H acidity difference between I and II is one of many simple comparisons available[1] demonstrating the powerful effect of increasing the electrophilicity of the heteroaromatic ring on the facility of removal of its annular protons, even though the sp^2 carbanions generated are orthogonal to the π system and thus not subject to resonance stabilization of the classical enolate type. In H–D exchange by eq 1 of I, II, and related substrates, hydroxide catalysis overwhelms reactions with other bases (buffer anions and water).[4]

The practical irreversibility of I → II and related reactions limits their use as part of an overall method for the more facile substitution *via* eq 1 of I and other neutral heteroaromatic substrates. However, the spectacular ionization rate enhancement effected by this route increases the attractiveness of other more reversible schemes for increasing the electrophilicity of the ring by withdrawing electron density through sp^2 lone pairs on N or other ring heteroatoms.

One such pathway (eq 3) is already known and has

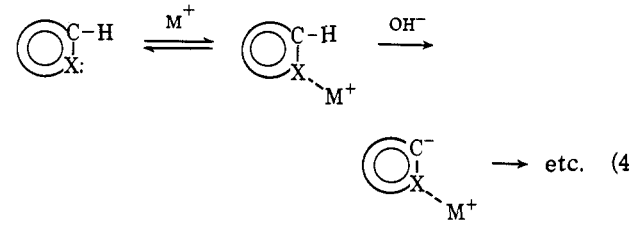


$$\text{rate} = \frac{k_1 K_w(\text{I} + \text{III})}{K_{BH^+} + [D_3O^+]}$$

$$K_{BH^+} = \frac{[\text{I}][D_3O^+]}{[\text{III}]}$$

even been studied using thiazole (I) as the substrate.[5] This reaction, which is also mentioned here because it may be a complication in the present study, follows the rate equation depicted; exchange rate is constant at high basicity (when $K_{BH^+} \gg [D_3O^+]$) but decreases in acid media as a function of the concentration of I (inflection in the pH–rate profile at K_{BH^+}). Though pathway 3 sometimes provides a convenient method for increasing the facility of electrophilic substitution reactions of class 1 (for example, the decarboxylation of thiazole-2-carboxylic[6] and other acids[7]), its practical application is limited by the invariant rate ceiling (for any particular system) imposed by kinetic eq 3 and by other factors.[5]

Another possible catalytic mechanism (eq 4) to expedite eq 1 substitution, the use of transition metal



cations (M^+) to withdraw electron density from the heteroaromatic ring by complexation with sp^2 electron pairs, is examined here.

The metal ions, Cu^{2+} and Zn^{2+}, were selected as the potential catalysts. 1-Methyltetrazole was picked as the test compound because 1-substituted tetrazoles are very stable toward both acid- and base-induced decomposition and are also among the most readily C–H ionized heteroaromatic rings.[2,8,9] This last is important because of the necessity of performing the kinetics in slightly acidic media[10] to avoid problems caused by precipitation of the transition metal hydroxides. Route 1 H–D exchange kinetic studies for 1-methyl-,[9] 1-ethyl-,[2,8] and 1-*p*-X-phenyltetrazoles[8] are available; the (nonuseful) antiinflammatory activities of the aryl compounds parallel their C–H_5 ionization rates.[8]

1-Substituted tetrazoles as well as the pharmacologically important 1,5-dialkyl analogs (Cardiazole, etc.) are very weak bases. Potentiometric or conductometric pK_B values for the latter could not be determined in water, though carboxylic acids have been successfully used as solvents for this purpose.[11] Desirable consequences of this low basicity include the expectation that any complications due to substitution *via* eq 3 can be easily factored out because of the invariance of exchange rate with $[OH^-]$ in the pH region of interest.

The essential nonbasicity of 1- and 1,5-substituted tetrazoles is paralleled by their poor complexing ability with metal cations. Complexation in water has not been reported, though the generation of complexes in less polar solvents has been described and some stability constant measurements have been published.[12] Though this factor would minimize the anticipated catalytic effect, the offsetting advantage of being able to disregard equilibria involving more than one tetrazole per M^+ in the data analysis was considered more important. A second deficiency of 1-methyltetrazole as a test substrate is the availability for coordination with M^+ of three different sp^2 electron pairs, especially since bonding at N_4 should have a much greater catalytic effect than complexation at N_2 or N_3; the relative C–H_5 ionization rates of 1-ethyltetrazole, 1,3-diethyltetrazolium cation, and 1,4-diethyltetrazolium cation are 1, $\sim 10^5$, and $\sim 10^{11}$.[2,8,9,13a] However, the crystal struc-

(3) By $10^{+10.6}$ for H_2 and by $\sim 10^{+6}$ for H_5: R. A. Olofson and J. M Landesberg, *ibid.*, **88**, 4263 (1966). Ionization of C–H_2 in another thiazolium cation, vitamin B_1, is the first step in the mechanism of its catalytic biological activity: R. Breslow, *ibid.*, **79**, 1762 (1957).

(4) For excellent data on thiazolium and related cations see: P. Haake, L. P. Bausher, and W. B. Miller, *ibid.*, **91**, 1113 (1969); D. S. Kemp and J. T. O'Brien, *ibid.*, **92**, 2554 (1970). For less systematic data on other five-membered ring cations and bases see ref 2 and 3.

(5) For data on thiazole and references to other examples see: R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, **26**, 685 (1970).

(6) H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 924 (1948).

(7) For data, review, and discussion see: P. Haake and J. Mantecón, *J. Amer. Chem. Soc.*, **86**, 5230 (1964); K. W. Ratts, R. K. Howe, and W. G. Phillips, *ibid.*, **91**, 6115 (1969); H. Quast and E. Schmitt, *Justus Liebigs Ann. Chem.*, **732**, 42 (1970).

(8) A. C. Rochat and R. A. Olofson, *Tetrahedron Lett.*, 3377 (1969).

(9) H. Kohn, Dissertation, The Pennsylvania State University, 1971.

(10) (a) J. A. Zoltewicz and L. S. Helmick, *J. Amer. Chem. Soc.*, **92**, 7547 (1970), and references 8–13 therein; (b) D. G. B. Boocock, R. Darcy, and E. F. Ullman, *ibid.*, **90**, 5945 (1968); (c) P. Beak and J. Bonham, *ibid.*, **87**, 3365 (1965); P. Beak and E. McL. Monroe, *J. Org. Chem.*, **34**, 589 (1969); P. Beak and R. N. Watson, *Tetrahedron*, 27, 4323 (1971).

(11) R. H. Erlich and A. I. Popov, *J. Phys. Chem.*, **74**, 338 (1970); A. I. Popov and R. D. Holm, *J. Amer. Chem. Soc.*, **81**, 3250 (1959).

(12) G. L. Gilbert and C. H. Brubaker *Inorg. Chem.*, **2**, 1216 (1963); H. B. Jonassen and R. A. Henry, Abstracts of the 10th International Conference on Coordination Chemistry, Tokyo, Sept 1967, p 367; A. I. Popov, *Coord. Chem. Rev.*, **4**, 463 (1969).

(13) (a) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, **86**, 1865 (1964); (b) N. C. Baenziger and R. J. Schultz, *Inorg. Chem.*, **10**, 661 (1971).

ture of dichlorobis(1-methyltetrazole)zinc(II) has been determined and here bonding is between zinc and the sp^2 lone pair at N_4.[13b] The presence of at least some $N_4\cdots M^+$ bonded material among the equilibrium species in solution would thus be expected.

Experimental Section

Materials. 1-Methyltetrazole was made by the acid-catalyzed reaction of methyl isocyanide with hydrazoic acid in ether:[14] mp 37.5–39° (lit.[15] mp 36–37°, 38–39°); nmr (ppm of 10% solution in $CDCl_3$ *vs.* internal TMS) 8.88 (s, 1 H), 4.24 (s, 3 H) [2% solution: 8.67, 4.19]. 1-Methyltetrazole-5-*d* (96% D by nmr using internal weight standard) was obtained by exchange of the undeuterated compound in Na_2CO_3–D_2O (>99.8% D), isolated by continuous extraction into ether, and purified by three successive vacuum sublimations (bath at 55° at 0.7 Torr); mp 37.5–39°.

All solutions for kinetics studies were prepared using doubly distilled deionized water and Baker Analyzed Reagent Grade concentrated HNO_3 and salts.

Kinetics. Except for the two high Cu^{2+} concentration experiments, the ionic strength (μ) of all solutions above pH 1 was adjusted to 0.15 with KNO_3. Solutions with time-constant pH values usually could be obtained just by adding the appropriate amount of HNO_3, but for studies in the pH range 5.4 and above, the use of KH_2PO_4–K_2HPO_4 buffers (0.005 *M* total phosphate) was required to maintain constant pH. Though experimental rates at 0.05 *M* buffer concentration were always higher, the difference was within the experimental error and extrapolation to zero buffer strength was neither valid nor necessary (at most, k_{obsd} would decrease 1%).

A weighed quantity of the tetrazole was added to a stirred (immediate dissolution) known volume of temperature-equilibrated exchange medium in a 1-l. stoppered flask immersed in a constant temperature bath maintained at 67.6 ± 0.2°. Aliquots (100-ml) of this aqueous solution were withdrawn at appropriate time intervals and rapidly added to 150 ml of cold (0°) CH_2Cl_2 into which the partly exchanged methyltetrazole was extracted. Two additional 150-ml portions of CH_2Cl_2 were used to complete the extraction. The combined extracts were dried (Na_2SO_4) and then evaporated to dryness at reduced pressure to provide the sample for nmr analysis. Though extraction from the 5 and 10 *M* HNO_3 solutions was less efficient and the final residue contained traces of acid, the isolation method above could also be used here without complications.

The pH values of aliquots of all reaction solutions above pH 0 were measured at both the beginning and conclusion of each rate experiment at 67.6° with a Radiometer pH Meter 26 equipped with a GK2021CH high-temperature electrode. Except for Zn^{2+} results 32 and 33 where the variation was almost 0.2 pH unit (average used), the maximum change was 0.05 unit and generally 0.01–0.02. The experimental pH of a 1.00 *M* HNO_3 solution containing 0.025 *M* methyltetrazole was +0.03 at 67.6° (H_0 for 1.00 *M* HNO_3 at 20° is −0.3[16]).

The amount of protium incorporation in each isolated sample above (*ca.* 20% solution in $CDCl_3$) was determined on a Varian A-60A spectrometer by comparing the ratio of H area at the reacting position with the area for the nonexchanging *N*-methyl. The average of five integrations in each direction was used in the calculation for each point. Generally, seven points (plus time 0) spread out over at least 2 half-lives were obtained. Standard data plots yielded nicely linear slopes through this period from which pseudo-first-order rate constants were calculated. The error in k_{obsd} is estimated at <10% except for the fastest reactions ($t_{1/2} < 20$ min). In the calculations of $[OH^-]$ from measured pH, 1.43×10^{-13} was used for K_w at 67.6°.[17] An ir spectrum was taken of the final sample from each rate experiment as a further check on product structure and purity.

Attempts to prepare 0.025 *M* $Zn(NO_3)_2$ and $Cu(NO_3)_2$ solutions of pH above 5.4 and 4.4 (at 67.6°), respectively, were unsuccessful because of partial precipitation of the metal hydroxides.

Determination of pK_{BH^+} of 1-Methyltetrazole. The crude nmr procedure of Taft and Deno as applied by Levy was followed.[18] The chemical shift of the C–H_5 resonance of 1-methyltetrazole (0.25 *M*) *vs.* an internal standard ($Me_4N^+Cl^-$, 0.05 *M*) in aqueous solutions of varying HNO_3 concentration at 37.5° was determined and plotted as an ordinary titration curve. The H_0 for the HNO_3 concentration at which this weak base was half-protonated is −2.4.[16,19] Analysis of the titration curve at several points from 20 to 80% protonation indicated that the standard H_0 function was followed quite well; thus, −2.4 is probably a reasonable value for the pK_{BH^+} of 1-methyltetrazole.[20]

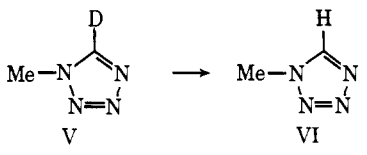
Since the ratio of nmr intensities of methyl to C–H_5 did not change in increasingly acidic solution (both peaks shifted downfield [*ca.* 60–65 Hz for C–H_5]), protonation does not occur at the tetrazole ring carbon.

Hydrolysis of Cu^{2+} under Experimental Conditions. The titration curve of a solution of 0.025 *M* $Cu(NO_3)_2$ in 0.075 *N* HNO_3 at 67.6° was determined by using 0.075 *N* KOH as the base and enough KNO_3 to maintain μ at 0.15. (The same curve was obtained when the experiment was repeated with 0.025 *M* 1-methyltetrazole present, indicating that the substrate had no effect on the equilibria under study.) This curve was compared with that obtained in the absence of $Cu(NO_3)_2$ and an approximate combined first hydrolysis constant of $10^{-7.1}$–$10^{-7.4}$ *M* was calculated from these data by the procedure of Chaberek, Courtney, and Martell.[21] The value obtained by these authors in an experiment done using 0.01 *M* $CuCl_2$, 0.1 *M* HCl, 0.1 *M* KOH, and μ of 0.1 at 30° was $10^{-6.8}$ *M*. In both sets of experiments precipitation of cupric hydroxide began at *ca.* 4.6 and the constant pH in the buffering region was 4.7.

Spectrophotometric Investigation of 1-Methyltetrazole–Cu^{2+} Complexes. No complex formation was detected in solution containing both $Cu(NO_3)_2$ and 1-methyltetrazole at low concentration. At high concentrations of either component, the region of the spectrum below 350 nm could not be used because of interference from the tail of the tetrazole absorption and the NO_3^- maximum at 300 nm. The 400–950-nm region (Cary Model 14 spectrophotometer) was therefore selected for this study, which was performed by use of aqueous solutions containing 0.025 *M* $Cu(NO_3)_2$, 0.02 *M* HNO_3, and 0.075 *M* KNO_3 (μ = 0.15) and varying tetrazole concentrations. The addition of more HNO_3 had no effect on the spectra. The λ_{max} of $Cu(NO_3)_2$ occurred at 830 nm (broad, flat). As tetrazole was added the absorption shifted to shorter λ and a new maximum at 750–760 nm was observed. From data in 0.2, 0.4, 0.8, 1.0, and 2.0 *M* tetrazole, a K_{CuT} of *ca.* 2 was calculated for the following assumed 1:1 equilibrium: $(tetrazole)Cu^{2+}(H_2O)_{n-1} \rightleftharpoons Cu^{2+}(H_2O)_n$ + tetrazole. Probable changes in activity coefficients were ignored in the computation. The measurements at higher heterocycle concentrations were further complicated by dispersion effects due to the presence of traces of unidentified colloidal material. At 5 *M* tetrazole this became a major problem and new maxima at 710 and 640–650 nm were also observed. Though it could be shown that the 640–650-nm peak involved the less favored process, the dispersion problem eliminated the possibility of determining *K* values or identifying the equilibria involved (spectrum unaffected by adding HNO_3). The overlap of the 710 and 750–760 peaks also increased the error in K_{CuT} because the equilibrium constants involved were not sufficiently distinct.

Results and Interpretation

The experimental data for exchange of 1-methyltetrazole-5-*d* (V) at 67.6° in aqueous solutions of



V VI

(14) D. M. Zimmerman and R. A. Olofson, *Tetrahedron Lett.*, 5081 (1969).

(15) E. Oliveri-Mandala, *Atti Accad. Naz. Lincei*, **19** (I), 228 (1910); O. Gryszkiewicz-Trochimowski, *C. R. Acad. Sci.*, **246**, 2627 (1958).

(16) H_0 and a_{H_2O} values for HNO_3 solutions were taken from J. G. Dawber and P. A. H. Wyatt, *J. Chem. Soc.*, 3589 (1960).

(17) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 645.

(18) R. W. Taft and P. L. Levins, *Anal. Chem.*, **34**, 436 (1962); N. C. Deno and M. J. Wisotsky, *J. Amer. Chem. Soc.*, **85**, 1735 (1963); G. C. Levy, J. D. Cargioli, and W. Racela, *ibid.*, **92**, 6238 (1970).

(19) The temperature dependence of H_0 is usually small: M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(20) For discussion, review, and references see: N. C. Deno and P. C. Scholl, *J. Amer. Chem. Soc.*, **93**, 2702 (1971).

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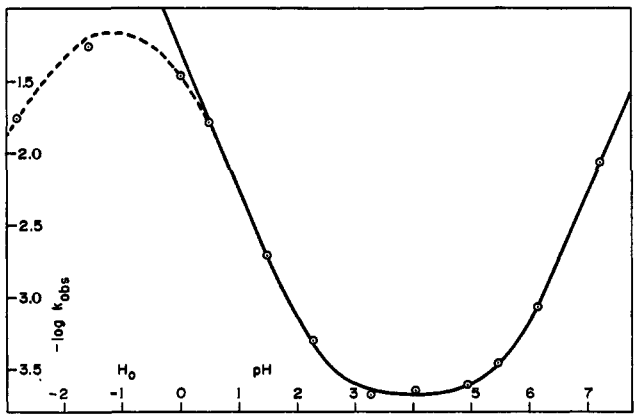


Figure 1. $C_5D \rightarrow C_5H$ exchange rates at 67.6° of 1-methyltetrazole-*5-d* (0.025 *M*) in aqueous solutions of varying acidity.

Table I. 1-Methyltetrazole-5-*d* Exchange in H_2O at 67.6°[a]

No.	pH	$t_{1/2}$, min	k_{obsd}, min^{-1}	log k_{obsd}
1	−2.80[b]	40	1.72×10^{-2}	−1.76
2	−1.57[c]	13	5.48×10^{-2}	−1.26
2A	*d*	29	2.39×10^{-2}	−1.62
3	0.03[e]	20	3.42×10^{-2}	−1.47
4	0.50	43	1.61×10^{-2}	−1.79
5	1.49	356	1.95×10^{-3}	−2.71
6	2.28	1420	4.89×10^{-4}	−3.31
7	3.28	3300	2.10×10^{-4}	−3.68
8	4.06	3120	2.22×10^{-4}	−3.65
8A[a]	4.19	3250	2.13×10^{-4}	−3.68
9	4.95	2830	2.45×10^{-4}	−3.61
10	5.47[f]	1990	3.49×10^{-4}	−3.46
11	6.16[f]	806	8.60×10^{-4}	−3.07
12	7.23[f]	82	8.47×10^{-3}	−2.07

[a] Substrate concentration at 0.025 *M* except for run 8A (0.05 *M*). [b] H_0 value for 10.0 *M* HNO_3 at 20°. [c] H_0 value for 5.0 *M* HNO_3 at 20°. [d] Solution 5.0 *M* in HNO_3 as in run 2, but also 5.0 *M* in LiCl. [e] Measured pH of 1.00 *M* HNO_3 (see Experimental Section). [f] KH_2PO_4–K_2HPO_4 buffer (0.005 *M*) required to keep pH constant (see Experimental Section); for runs 5–12, μ adjusted to 0.15 with KNO_3.

varying acidity are given in Table I (rate = k_{obsd}[substrate], see 8A) and k_{obsd} is plotted against pH (H_0) in Figure 1. The pH–rate profile in this control experiment is more complicated than originally anticipated, but above pH 0.5 it can be fitted to the three-term rate equation (5) in which k_a, k_n, and k_b are all empirical

$$k_{obsd} = k_n + k_b[OH^-] + k_a[H_3O^+] \qquad (5)$$

constants: $k_n = 2.0 \times 10^{-4}$ min^{-1}, $k_b = 3.4 \times 10^{+3}$ M^{-1} min^{-1}, $k_a = 5.2 \times 10^{-2}$ M^{-1} min^{-1}. At higher acidity the exchange rate reaches a maximum and even decreases in strong acid. A brief mechanistic analysis follows.

At higher pH the $k_b[OH^-]$ term and the simple ionization mechanism 1′ prevails ($rate_{D \rightarrow H} = k_b[V][OH^-]$).

$$V + OH^- \xrightarrow{k_b} \text{Me-N}\overset{\bar{}}{\text{C}}\text{=N-N=N} \longrightarrow VI \qquad (1')$$

VII

Below pH 2 the acidity–rate profile for tetrazole exchange is empirically the same as that found for the extensively investigated acid-catalyzed hydrolysis of simple amides and esters.[22] One of the two available exchange pathways (6), preequilibrium N-protonation followed by $C-H_5$ ionization, can be depicted in a form kinetically equivalent to the $A_{Ac}2$ mechanism generally

$$V + H_3O^+ \overset{1/K_{BH^+}}{\rightleftharpoons} \text{Me-N(D)-N=N-N(H)}^+ \qquad (6)$$

VIII[23]

$$VIII + (H_2O)_x \xrightarrow{k} \left[\text{Me-N}\overset{\bar{}}{\text{C}}\text{=N-N=N(H)}^+\right] \longrightarrow \text{products}$$

IX

accepted for the hydrolysis reaction. In amide and ester hydrolysis the rate decrease in strong acid is generally attributed to a reduction in the activity of water,[24] though a decrease in the activity coefficient of the substrate has also been implicated.[25] When 5 *M* LiCl was included in the reaction medium for the 5 *M* HNO_3 run 2, k_{obsd} was smaller by a factor of 2.3 (run 2A).[26] Alternately, similar arguments would allow the ordinary electrophilic aromatic substitution mechanism[27] modified by the N-protonation equilibrium (mechanism 6, first step) to account satisfactorily for the acidity–rate profile in acid. This step must be included as an important complicating factor, since from nmr evidence (see Experimental Section) it is necessary that VIII be the only protonated species present in significant concentration, even in strong acid.

In the pH region 3–5, the acidity independent term, k_n, is predominant. The schemes which fit this result are: (1) an eq 3 type route (*vide supra*) in which the key intermediates are the N-protonated cation VIII and the ylide IX; (2) an ionization mechanism in which VII is generated by attack of V with water (and any other nucleophiles besides OH^- present in solution) as base; and (3) a pathway equivalent to the electrophilic substitution mechanism but with H_2O as the acid and OH^- as the base. In the 1-methyltetrazole system these schemes are not kinetically differentiated because the simplified rate equation for pH 3–5 is in all cases rate = k_n[V].

The experimental data for exchange of V in the presence of Cu^{2+} and Zn^{2+} are given in Table II. In Figure 2 the catalytic effect of the presence of 0.025 *M* Cu^{2+} or Zn^{2+} (V = 0.025 *M*) is depicted as a function of pH. The decreased catalytic activity of Zn^{2+} *vs.* Cu^{2+} is in agreement with the empirical fact that complexes be-

(22) K. Yates, *Accounts Chem. Res.*, 4, 136 (1971); C. O'Connor, *Quart. Rev., Chem. Soc.*, 24, 553 (1970); C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter 15.

(23) This structure is meant to depict the presence of one or more $^+$N–H isomers. Though these species would have different formation and reaction constants, all the associated reactions can be considered in a single combined equation.

(24) In amide and ester hydrolysis, rate decreases proportional to $[a_{H_2O}]^x$ with $x = 2$ or 3 are common.[22] As a result the rate maximum often occurs at lower acidity than the H_0 at half-protonation of the substrate.

(25) C. A. Bunton and T. Hadwick, *J. Chem. Soc.*, 943 (1961).

(26) As an added base, the normal effect of Cl^- would be to increase the mechanism 6 exchange rate; in pure CF_3CO_2D at 78°, 1 *M* 1,4-diethyltetrazolium Cl^- ionizes at $C-H_5$ 23 times faster than the BF_4^- salt.

(27) Protonation at C_5 with H_3O^+ followed by D^+ loss with water as base.

Table II. M^{2+}-Catalyzed Exchange in H_2O at 67.6°[a]

No.	pH	M^{2+} concn, M	$t_{1/2}$, min	k_{obsd}, min^{-1}	log k_{obsd}
13	0.46	0.025 Cu	39	1.78×10^{-2}	−1.75
14	1.43	0.025 Cu	293	2.36×10^{-3}	−2.63
15	2.04	0.025 Cu	792	8.75×10^{-4}	−3.06
16	2.08	0.025 Cu	828	8.37×10^{-4}	−3.08
17	2.86	0.025 Cu	1300	5.32×10^{-4}	−3.28
18	3.24	0.200 Cu	275	2.52×10^{-3}	−2.60
19	3.29	0.050 Cu	697	9.94×10^{-4}	−3.00
20	3.33	0.025 Cu	1010	6.83×10^{-4}	−3.17
21	3.27	0.0125 Cu	1700	4.08×10^{-4}	−3.39
22	3.27	0.00625 Cu	2560	2.70×10^{-4}	−3.57
23	3.81	0.025 Cu	591	1.17×10^{-3}	−2.93
24	4.05	0.025 Cu	356	1.95×10^{-3}	−2.71
25	4.33	0.025 Cu	203	3.42×10^{-3}	−2.47
26	2.54	1.000 Cu	184	3.76×10^{-3}	−2.42
27	1.43	0.025 Zn	297	2.34×10^{-3}	−2.63
28	2.03	0.025 Zn	825	8.40×10^{-4}	−3.08
29	3.20	0.025 Zn	1970	3.51×10^{-4}	−3.45
30	3.82	0.025 Zn	2130	3.26×10^{-4}	−3.49
31	4.49	0.050 Zn	1200	5.79×10^{-4}	−3.24
32	4.43	0.025 Zn	1820	3.81×10^{-4}	−3.42
33	4.45	0.0125 Zn	2390	2.90×10^{-4}	−3.54
34	5.35	0.025 Zn	756	9.17×10^{-4}	−3.04

[a] 1-Methyltetrazole concentration is 0.025 M in all experiments. All runs except 13, 18, and 26 adjusted to $\mu = 0.15$ with KNO_3.

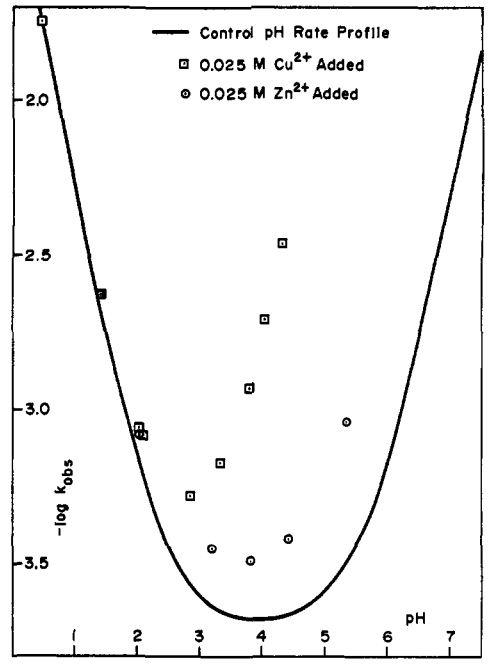


Figure 2. Effect of M^{2+} on 1-methyltetrazole-5-*d* exchange.

tween Zn^{2+} and simple ligands are almost always less favored than the related Cu^{2+} complexes. The rate constants $k_{Cu^{2+}}$ and $k_{Zn^{2+}}$ for each kinetics experiment were calculated by using eq 7 and the best empirical

$$k_{Cu^{2+}} \text{ or } k_{Zn^{2+}} = k_{obsd} - k_a[H_3O^+] - k_n - k_b[OH^-] \quad (7)$$

values of k_a, k_b, and k_n given in eq 5. The results are presented in Tables III and IV for those runs in which

Table III. Effect of M^{2+} Concentration on $k_{M^{2+}}$ at Constant pH

No.	M^{2+} concn, M	$k_{M^{2+}}$, $min^{-1} \times 10^4$ [a]	$k_{M^{2+}}/[M^{2+}]$, $M^{-1}\ min^{-1} \times 10^3$
	Cu^{2+} Series at pH 3.27[b]		
18	0.200	24.4 ± 2.0	12 ± 1
19	0.0500	7.4 ± 0.8	15 ± 2
20	0.0250	4.2 ± 0.6	17 ± 2
21	0.0125	1.8 ± 0.4	14 ± 3
22	0.00625	0.4 ± 0.4	
	Zn^{2+} Series at pH 4.45[b]		
31	0.0500	3.5 ± 0.5	7 ± 1
32	0.0250	1.7 ± 0.5[a]	7 ± 2
33	0.0125	0.7 ± 0.4[a]	6 ± 3

[a] Error in k_{obsd} and $k_{control}$ both estimated to be 7% except for runs 32 and 33 where 10% error in k_{obsd} was assumed (the latter may be too small; see Experimental Section). Errors added in calculation. [b] Correction of $k_{M^{2+}}$ for the minor variation in experimental pH was accomplished using the $k_{1m} + k_{2m}[OH^-]$ dependence given in Table IV. Maximum corrections are −9% for run 20 and +6% for run 18. 1-Methyltetrazole concentration was 0.025 M in all runs.

the error in $k_{Cu^{2+}}$ or $k_{Zn^{2+}}$ is small enough so that the data are quantitatively significant.

The effect on the exchange rates of varying Cu^{2+} and Zn^{2+} concentrations at constant $[H_3O^+]$ is outlined in Table III. The essentially first-order M^{2+} dependence of both reactions is in accord with the inability of earlier workers to obtain measurable concentrations of M^+ complexes of 1-substituted tetrazoles in dilute aqueous solution (see above).

Table IV. Effect of OH^- Concentration on $k_{M^{2+}}$ at $[M^{2+}] = 0.025\ M$[a]

No.	OH^- concn, $M \times 10^{10}$	$k_{M^{2+}}$, $min^{-1} \times 10^4$ [b]	$k_{M^{2+}}/[OH^-]$, $M^{-1}\ min^{-1}$	$k_{1m} + k_{2m}[OH^-]$, $min^{-1} \times 10^4$
		Cu^{2+} Series		
17	1.03	2.6 ± 0.6	25×10^5	2.5
20	3.05	4.6 ± 0.6	15×10^5	4.6
23	9.2	9.6 ± 1.0	10×10^5	10.7
24	16.0	17.4 ± 1.5	11×10^5	17.5
25	30.5	32.1 ± 2.5	11×10^5	32.0
26[c]	0.50	34 ± 3	*c*	*c*
		Zn^{2+} Series (Qualitative Utility Only)		
29	2.3	1.2 ± 0.4	52×10^4	1.0
30	9.4	1.1 ± 0.4	12×10^4	1.2
32	38.0	1.7 ± 0.5[b]	4×10^4	1.6
34	320.0	6.1 ± 0.9	2×10^4	6.1

[a] At stoichiometric 1-methyltetrazole concentration of 0.025 M. [b] See footnote *a*, Table III, for error. [c] Experiment at 1.00 M Cu^{2+} concentration.

From Table IV it is evident that the M^{2+} reaction is not simply first order in hydroxide ion. However, for the Cu^{2+} experiments a good correlation is obtained with $[OH^-]^1$ over a factor of 30 in hydroxide concentration after a small but real pH independent term is included (eq 8). The result is qualitatively mirrored in

$$k_{M^{2+}} = k_{1m} + k_{2m}[OH^-] \quad (8)$$

the Zn^{2+} experiments where the error is much larger because of the diminished catalytic effect. At stoichiometric Cu^{2+} and substrate concentrations of 0.025 M, $k_{1c} = 1.5 \times 10^{-4}\ min^{-1}$ and $k_{2c} = 1.0 \times 10^6\ M^{-1}\ min^{-1}$. The fit of eq 8 to the data with the use of these constants is given in the final column of Table IV. The related Zn^{2+} values are $k_{1z} = 1.0 \times 10^{-4}\ min^{-1}$ and $k_{2z} = 1.6 \times 10^4\ M^{-1}\ min^{-1}$.

Since k_{1c} and k_{1z} are both somewhat smaller than k_n ($= 2.0 \times 10^{-4}\ min^{-1}$), the pH-independent rate constant in the absence of metal ion, they may be considered perturbations of this latter term and just indicate

that the difference between $Cu(NO_3)_2$ or $Zn(NO_3)_2$ and KNO_3 is not completely eliminated, just by keeping μ constant. No unusual assumptions are required to account for this "salt effect" in terms of the mechanisms previously postulated to account for k_n. It is, however, also possible that k_{1c} and k_{1z} measure the M^{2+} catalyzed reaction in which water has replaced $[OH^-]$ as the base.

The rate data for the Cu^{2+} (or Zn^{2+}) catalyzed reaction are in agreement with the predicted pathway 9 for

$$Cu^{2+}(H_2O)_n + V \underset{}{\overset{1/K_{CuT}}{\rightleftharpoons}} \underset{X}{(V)Cu^{2+}(H_2O)_{n-1}} \quad (9)$$

$$X + :B \xrightarrow{k} (VII)Cu^{2+}(H_2O)_{n-1} \longrightarrow \longrightarrow VI$$

this exchange. If both OH^- and water can act as the attacking base (B) to remove the proton at C_5 from the intermediate 1-methyltetrazole–Cu^{2+} complex (X), then, assuming that the first step of mechanism 9 is a rapid preequilibrium and that other processes are not important, the rate is: Cu^{2+} rate $= (k_1 + k_2[OH^-])[X]$.

If the stoichiometric substrate concentration is $[S] = [V] + [X]$ and the stoichiometric cupric ion concentration is $[Cu^s] = [Cu^{2+}] + [X]$, then it is easily shown that

$$Cu^{2+} \text{ rate} = \frac{(k_1 + k_2[OH^-])[S][Cu^s]}{(K_{CuT} + [S] + [Cu^s])} \quad (10)$$

provided that [X] is $\ll [Cu^{2+}]$ and [V] (otherwise an $[X]^2$ term cannot be ignored in the derivation). Attempts to determine the constant, K_{CuT}, spectrophotometrically (see Experimental Section) yielded a value of *ca.* 2 *M*. Because of the assumptions and errors involved in the measurements and calculations, the true K_{CuT} could be much larger but not significantly smaller. Since K_{CuT} is large *vs.* ($[S] + [Cu^s]$), the denominator in eq 10 is nearly constant, affording the observed, essentially first-order dependence on $[Cu^s]$ and the observed relationship of rate to pH.

Unfortunately the small decrease in $k_{Cu^{2+}}/[Cu^s]$ with increasing $[Cu^s]$ (Table III) cannot be used to give an estimate of K_{CuT}. The rigorous rate equation (in which $[X]^2$ is not ignored) required for this purpose[28] will only provide values with acceptable errors from data containing much greater curvature.[28] Other factors can also be responsible for the minor variation of $k_{Cu^{2+}}/[Cu^s]$ found: the ionic strength of the solution is higher in experiment 18; the dependence of the salt effect part of k_{1c} on $[Cu^{2+}]$ is unknown; and the hydrolysis, olation, and counterion complexation equilibria involving Cu^{2+} which have been identified in the past[29] may be significant. However, calculations based on literature data[21,29] partially confirmed under the present conditions (see Experimental Section) indicate that the concentrations of the ions, $CuOH^+$, Cu_2OH^{3+}, Cu_2O^{2+}, $(NO_3^-)Cu^{2+}(H_2O)_{n-1}$, etc., present in a 0.025 *M* Cu^s solution are small even at the limiting pH (4.6), where hydrated cupric oxide begins to precipitate.

Some intramolecular analogs of the preferred mechanism 4 for the metal ion catalyzed exchange of V are not excluded by the kinetics. In one variation (eq 11)

$$\underset{X}{(V)Cu^{2+}(H_2O)_{n-1}} + OH^- \rightleftharpoons \underset{XI}{(V)CuOH^+(H_2O)_{n-2}} + H_2O \quad (11)$$

$$XI \longrightarrow (VII)Cu^{2+}(H_2O)_{n-2}(HDO) \longrightarrow \text{products}$$

the complex X is attacked by base to produce the $CuOH^+$ complex XI which continues to product by ligand OH abstraction of substrate deuterium. The intermediate XI might also be formed by reaction of V with $CuOH^+$. It is believed, however, that any intramolecular advantage of eq 11 and related processes is more than compensated by their objectionable features: (1) the decreased activating effect on substrate CH acidity of Cu^{2+} which has been partially neutralized by the OH ligand; (2) the similarly reduced intrinsic reactivity of ligand *vs.* medium OH^-; and (3) the expectation that the equilibrium V + $CuOH^+ \rightleftharpoons$ XI should be more unfavorable than the equilibrium V + $Cu^{2+} \rightleftharpoons$ X.

Discussion

As a demonstration of the significance and potential value of transition metal ion catalysis of electrophilic substitution by mechanism 1, the preceding study is highly encouraging. The observed rate enhancement of ring proton exchange of 1-methyltetrazole at constant pH 4.33 (experiment 25) caused by the presence of only 0.025 *M* Cu^{2+} is a factor of 15. When other mechanisms are factored out and the simple hydroxide-induced ionization processes are compared, this translates to a catalytic effect of 0.025 *M* Cu^{2+} of 300 (k_{2c}/k_b). The expected rate accelerations for other heteroaromatic substrates where the complexation constants are generally much more favorable[30] are better estimated from the predicted rate of the 1-methyltetrazole reaction if both the substrate and the metal ion were present completely as the 1:1 complex.[31] If the spectrophotometric K_{CuT} of 2 *M* is real, the magnitude of the rate increase is 25,000. Otherwise it is larger (*vide supra*). Substrate structure changes which favor complex formation also operate to strengthen the metal–substrate bond. Generally this is accomplished by draining more electron density from the heterocycle, a direct consequence of which is a possibly very large further rate enhancement. Finally, since the complex X may consist partially or even primarily of tetrazole bonded at one of the β-nitrogen atoms (species much less activated than material complexed α to the ionization site), the reactivity at certain positions in other substrates could be still higher. Thus, the predicted Cu^{2+} catalytic effect of $10^{4.5}$ for ionization at α positions in simple heteroaromatic bases should represent a minimum value. It is likely that the actual catalysis

(28) S. J. Benkovic and L. K. Dunikoski, *J. Amer. Chem. Soc.*, **93**, 1526 (1971).

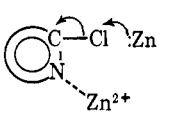
(29) K. J. Pedersen, *Kgl. Dan. Vidensk. Selsk. Mat.-Fys. Medd.*, **20**, No. 7, (1943); F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York N. Y., 1967, pp 31–33; J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," Hasse, Copenhagen, 1941, p 75; W. Feitknecht and P. Schindler, *Pure Appl. Chem.*, **6**, 130 (1963); R. Kruh, *J. Amer. Chem. Soc.*, **76**, 4865 (1954); H. McConnell and N. Davidson, *ibid.*, 72, 3164 (1950). For the equilibrium, $ClCu^+(H_2O)_{n-1} \rightleftharpoons Cu^{2+}(H_2O)_n + Cl^-$, K values of 0.8–4 *M* have been reported.

(30) For the equilibrium (pyridine)$Cu^{2+}(H_2O)_{n-1} \rightleftharpoons Cu^{2+}(H_2O)_n$ + pyridine at 25°, $K_{CuP} = 2.5 \times 10^{-3}$. The higher order complexation of Cu^{2+} with Py is also favored: D. Leussing and R. C. Hansen, *J. Amer. Chem. Soc.*, **79**, 4270 (1957).

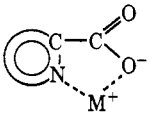
(31) In this limiting case the rate constant is unaffected by concentration or excess of either component. Note, however, that complexes with more than one substrate molecule per metal ion should also be active intermediates.

is greater and conceivably even several orders of magnitude greater.

Metal ion catalysis of eq 1 electrophilic substitution may already be known. For example, the annoying and sometimes interminable induction period often observed in the zinc-induced reductive dehalogenation of aza aromatics in alcohol (and rationalized by the classical etching a clean surface explanation) could indicate that the process illustrated by XII is operative. If XII is important, the induction period should be eliminated and the reaction accelerated just by adding some soluble cupric salt. When chelation is geometrically allowed as in some decarboxylations and deacylations (*i.e.*,

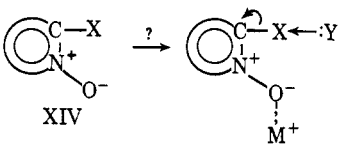


XII

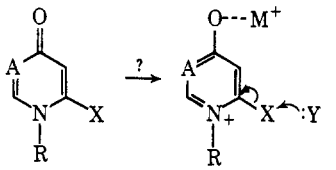


XIII

XIII), the reaction rate may be depressed by the addition of M^{2+}.[7] Catalysis by M^{2+} of pathway 1 substitution reactions should not be limited to heterocyclic bases as substrates. Other prime candidates for such catalysis where simple eq 1 or eq 3 processes are already known are *N*-oxides[10a] XIV, the related nitronyl nitroxides,[10b] and species such as XV[10c] and its five-membered ring mesoionic analogs.



XIV



XV

Though the high dilution experiments in aqueous media above were useful for mechanistic studies, a different reaction environment is recommended in synthetic work, where the primary purpose is to experimentally realize as much as possible of the maximum catalytic effect predicted from the rate extrapolations above. Generally one will begin with an enormous advantage, since the metal ion complexation constants of most classes of heteroaromatic compounds (imidazoles, pyridines, purines, isothiazoles, oxazoles, etc.) are several orders of magnitude more favorable than that found in the Cu^{2+}–tetrazole system above. When increased complexation is desired, this can be accomplished by raising the concentration of the reactants and in other ways. For example, complex formation is usually more favored in less polar solvents ($Cu(NO_3)_2 \cdot 3H_2O$ is very soluble, 100 g/100 ml at 13°, in ethanol, $Co(ClO_4)_2$ dissolves in acetone, and $Cu(ClO_4)_2$ is even soluble in ether). The use in such media of anhydrous salt to eliminate the competing ligand, water, and for similar reasons of NO_3^-, BF_4^-, or ClO_4^- salts of the catalyst cation should also be beneficial. For some processes a heterogeneous system can have important advantages.

The preceding demonstration that transition metal ion catalysis of route 1 substitution can add several orders of magnitude to reaction rate greatly increases the attractiveness of biochemical mechanisms (with M^+ requirements) involving the generation as reaction intermediates of sp^2 carbanions at certain predictable ring sites in purines, pyrimidines, imidazoles (possibly), and other heteroaromatic and related compounds indigenous to the living cell as part of the biosynthesis, the further transformations, or the catalytic activity of such substances. Metal ion induced pathway 1 substitution at an electrophilic site (*e.g.*, a disulfide group) of an enzyme or other biological substrate must also be considered as a possible chemical mechanism for the pharmaceutical activity of known heteroaromatic drugs containing ring positions with actual or potential (*e.g.*, by oxidation) eq 1 type reactivity. One potentially useful corollary of the concepts above is the following: heterocyclic compounds, which are calculated to undergo facile M^+ accelerated ring C–H ionization in biological media, are expected to be exceptionally good candidates for general pharmaceutical screening.

Finally, in a reversal of focus, it is worthwhile to note that in the study reported here the existence of a specific ligand–transition metal cation complex has been conclusively demonstrated in a medium where physical evidence for its presence is at best ambiguous. Though binding constant estimates and information on structural detail (for example, which tetrazole nitrogen is attached to the Cu^{2+}) are most conspicuous for their absence, the completion of other model studies promises improvement in both these areas.

Acknowledgments. We are indebted to Professor N. C. Deno for valuable advice on p*K* determinations of weak bases and on the usefulness and limitations of acidity functions. We also gratefully acknowledge the U. S. Public Health Service for a grant (GM 13980) in partial support of this research and the NSF and NIH for predoctoral fellowships for H. K.