Mr. O. W. Norton for assistance in taking the n.m.r. spectra; we thank Mr. J. Nemeth and the staff of our microanalytical laboratory for the microanalyses. We are indebted to Mr. James Ellern for the initial preparation and partial separation of the cobalt compounds described here.

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New Multidentate Ligands. I. Coordinating Tendencies of Polyamines Containing α-Pyridyl Groups with Divalent Metal Ions[1,2]

BY R. G. LACOSTE AND A. E. MARTELL[3]

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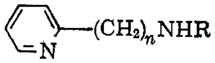
The synthesis of several polyamines containing α-pyridyl groups is described. The compounds prepared are 2-aminomethylpyridine (AMP), N-hydroxyethyl(2-aminomethyl)pyridine (HEAMP), ethylenebis-α,α′-(2-aminomethyl)pyridine (EDAMP), 2-(2-aminoethyl)pyridine (AEP), and N-aminoethyl-2-(2-aminoethyl)pyridine (EAEP). The acid dissociation constants and the stability constants of the Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) chelates are reported. The results are compared with the chelating tendencies of analogous aliphatic polyamines.

The synthesis of polyamines containing pyridyl groups was undertaken as part of a general program of investigation of the relationship between chelating tendencies and the structure of the ligand. Although the stabilities of metal chelates of dipyridyl, ethylenediamine, and analogous aliphatic polyamines have been known for some time, the properties of chelating agents containing a combination of basic aliphatic and heterocyclic nitrogen atoms had not been reported at the time of completion of this work,[1] and very few compounds containing these groups correctly arranged for the formation of metal chelate rings have been synthesized. Since pyridine-2-aldehyde, which has recently become available, offers a convenient route for the synthesis of compounds of type I, it was decided to undertake a study of polyamines containing 2-aminoalkylpyridine groups. Of the possible compounds containing favorable arrangements of nitrogen atoms, 2-aminoethylpyridine[4,5] and 2-β-aminoethylpyridine[6] had been described in the literature. Subsequent to the completion of this work, Goldberg and Fernelius[7] reported the equilibrium constants and heats of reaction of metal ions with two of the ligands (AMP and AEP) described below.



I

Experimental

Ethylenebis-α,α′-(2-aminomethyl)pyridine (EDAMP).—An alcoholic solution containing 36 g. (0.15 mole) of bis(2-pyridinal)-ethylenediimine, prepared as described by Busch and Bailar,[8] and 1 g. of 10% Pd–C catalyst was reduced for 3 hr. in a Parr hydrogenation apparatus at 50 p.s.i. pressure and at room temperature. The catalyst was filtered off and the solvent was removed under vacuum at water-bath temperature. The viscous liquid which remained was distilled under 24 mm. of pressure in the range 130–135°. The yield of distilled product, a pale yellow oil, was 25 g., or 72% of the theoretical amount. It forms a crystalline tetrahydrochloride which melts at 208–208.5°.

Anal. Calcd. for $C_{14}H_{18}N_4 \cdot 4HCl$: C, 43.52; H, 5.69; N, 14.50; mol. wt., 388. Found: C, 42.36; H, 6.05; N, 14.8; equiv. wt., 402.

2-Aminomethylpyridine (2-Picolylamine) (AMP).—Although now an article of commerce, 2-aminomethylpyridine was prepared by reduction of the corresponding Schiff's base as described for EDAMP. The product was isolated as the dihydrochloride.

Anal. Calcd. for $C_6H_8N_2 \cdot 2HCl$: C, 40.00; H, 5.6; N, 15.6; mol. wt., 180. Found: C, 39.99; H, 6.8; N, 15.8; equiv. wt., 187.

N-Hydroxyethyl(2-aminomethyl)pyridine (HEAMP).—A mixture of 0.30 mole (18.3 g.) of monoethanolamine, dissolved in 150 ml. of absolute ethanol, and 32.1 g. (0.30 mole) of 2-pyridinecarboxaldehyde was heated on a steam bath for 15 min. To the cooled reaction mixture was added 1.0 g. of 10% Pd–C catalyst, and it was then reduced at room temperature and an initial pressure of 50 p.s.i. After 3 hr. the reduction was complete, and the catalyst and solvent were removed in the usual way. The residue, a viscous oil, was distilled under 18 mm. of pressure and the material which distilled over at 164–165° (with partial decomposition) was collected as the desired product. The yield of N-hydroxyethyl(2-aminomethyl)pyridine was 32 g., which represents 72% of the theoretical amount. The product is a viscous, pale yellow oil which forms a crystalline dihydrochloride having a melting point of 123–124°.

Anal. Calcd. for $C_8H_{12}ON_2 \cdot 2HCl$: C, 42.86; H, 6.25; N, 12.50; mol. wt., 225. Found: C, 42.84; H, 6.72; N, 12.70; equiv. wt., 240.

N-Aminoethyl-2-(2-aminoethyl)pyridine (EAEP).—The addi-

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[1] Abstracted from a dissertation submitted by R. G. Lacoste to the faculty of Clark University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1957.

[2] The authors express their appreciation to the Dow Chemical Company for a research grant in support of this work.

[3] Department of Chemistry, Illinois Institute of Technology, Chicago 16, Ill.

[4] R. Graf, *J. Prakt. Chem.*, **140**, 39 (1934).

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[6] F. K. Kirchner, J. R. McCormick, C. J. Cavallito, and L. C. Miller, *J. Org. Chem.*, **14**, 388 (1949).

[7] D. E. Goldberg and W. C. Fernelius, *J. Phys. Chem.*, **63**, 1246 (1959).

[8] D. H. Busch and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **78**, 1137 (1956).

tion of 12 g. (0.2 mole) of glacial acetic acid to a cooled reaction mixture containing 52.6 g. (0.5 mole) of 2-vinylpyridine and 12 g. (0.2 mole) of ethylenediamine (33% aqueous solution) resulted in an exothermic reaction and the formation of a two-phase system. The reaction mixture became homogeneous after being heated on a steam bath for 2 hr. with continuous stirring. The unreacted materials were then distilled off under reduced pressure at steam-bath temperature. The residue, a viscous pale yellow oil, was collected at 145–147° under 15 mm. of pressure. The product was not the desired compound, ethylenebis-α,α′-2-(2-aminoethyl)pyridine, but N-aminoethyl-2-(2-aminoethyl)pyridine. The 23 g. yield of this material represented 70% of the theoretical amount.

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.45; H, 9.04; N, 25.30; mol. wt., 165. Found: C, 65.74; H, 9.09; N, 24.17; equiv. wt., 167.

2-(2-Aminoethyl)pyridine (AEP).—2-(2-Aminoethyl)pyridine was prepared by the reaction of 2-vinylpyridine with phthalimide in accordance with the procedure described by Kirchner, *et al.*[6]

Potentiometric Measurements of Dissociation and Stability Constants.—All measurements were made with a Beckman Model GS pH meter fitted with extension glass and calomel electrodes. The experimental solution contained sufficient KNO_3 to bring the ionic strength to 0.1 *M;* the temperature was maintained at 25°, and a CO_2-free stream of nitrogen was passed through the cell. Standard CO_2-free KOH solution was employed. Ligand solutions were made up from the recrystallized hydrochlorides.

In instances where the chelate stability constants were too large to be measured by a straightforward displacement of hydrogen ion from the ligand by the metal ion, potentiometric measurements were carried out in the presence of a second competing ligand, β,β′,β″-triaminotriethylamine (tren). Equimolar amounts of the ligand being studied, tren, and the metal salt were measured together under the conditions described above, considerable time being allowed in the determination of each point to ensure that equilibrium had been reached. In some cases it was necessary to wait a number of hours for each determination of hydrogen ion concentration. The approximate titration curve thus obtained was used as a basis for determining the conditions used in the precise measurements of each individual point in the buffer regions of interest.

Calculations.—The simple acid dissociation constants of AMP, HEAMP, AEP, and EAEP were carried out by standard algebraic methods. The first two acid dissociation constants of EDAMP, which were found to overlap considerably, were calculated by the graphical method of Schwarzenbach and Ackermann.[9]

The stability constants, K_{ML} and K_{ML_2}, of the metal chelates containing 1 and 2 moles of ligand per gram-ion of metal, respectively, were calculated algebraically as described previously.[10]

Determination of Stability Constants by the Use of a Competing Ligand.—The stability constants for the Cu(II) and Ni(II) chelates of EDAMP were found to be too high to calculate by the standard potentiometric titration method. It was necessary to use a competing ligand, β,β′,β″-triaminotriethylamine trihydrochloride (tren). The titration of equimolar amounts of the tetrahydrochloride of EDAMP, a divalent metal ion M(II), and tren resulted in a second buffer region in the pH range 8.5 to 9.5. The reaction which takes place in the second buffer region is illustrated below.

$$ML^{+2} + H_3B^{+3} \rightleftharpoons MB^{+2} + L + 3H^+ \qquad (1)$$

$$K^1 = \frac{[MB^{+2}][L][H^+]^3}{[ML^{+2}][H_3B^{+3}]} \qquad (2)$$

The equilibrium constant K^1 was determined by the method of Schwarzenbach and Freitag.[11]

Results and Discussion

Potentiometric Measurements.—The potentiometric titration data for solutions containing 1 mole of 2-aminomethylpyridine (AMP) per gram-ion of metal indicate an initial reaction, which is similar for all of the divalent metals, to give the normal metal chelate compound in accordance with the reaction

$$M + HL^+ \longrightarrow ML + H^+$$

where L represents the neutral diamine, the most basic form of the ligand. In the case of Cu(II) there is a second step which, in the absence of precipitation, can only be interpreted as a hydrolysis reaction in which a hydroxyl ion acts as a ligand.

$$ML + OH^- \longrightarrow M(OH)L$$

The equilibrium constants calculated from the potentiometric data are listed in Table I, along with corresponding values for ethylenediamine, en, an analogous ligand.

TABLE I

EQUILIBRIUM CONSTANTS FOR THE COMBINATION OF AMP, HEAMP, AND en WITH VARIOUS CATIONS

Positive ion	log equilibrium constants				
	en	AMP	en–AMP	HEAMP	AMP-HEAMP
H^+ pK_1	7.23	2.14		3.15	
H^+ pK_2	9.87	8.57		7.94	
Cu(II)	10.6	9.5	1.1	9.2	0.3
Ni(II)	7.5	7.1	0.4	7.1	0.0
Co(II)	5.9	5.3	0.6	5.3	0.0
Zn(II)	5.9	5.2	0.7	5.2	0.0
Cd(II)	5.5	4.5	1.0	4.4	0.1

It is noteworthy that the chelates of ethylenediamine are in all cases much more stable than those of aminomethylpyridine, as would be expected from the difference in basicity of the two ligands. It is surprising, however, that the wide difference in hydrogen ion affinities is not reflected in a corresponding difference in affinity for metal ions. The relative values of pK_1 and pK_2 are such that the slightly greater affinity of en for the metal ions shown is more than offset in the pH range 7.5–9.5. Below pH 7 the competition between hydrogen and metal ions is such that the relative concentrations of metal chelates of AMP to those of en are of the order of 10^5 in the presence of equivalent concentrations of ligand.

The titration data for N-hydroxyethyl(2-aminomethyl)pyridine (HEAMP) are very similar to those of AMP. Although the hydroxyethyl derivative is slightly less basic than the parent aminomethylpyridine, the metal chelate stabilities are nearly identical.

Potentiometric titrations of N,N′-ethylenebis(2-aminomethyl)pyridine in the presence and in the absence of equivalent amounts of various metal ions are indicated in Fig. 1. The ligand curve has three well-defined inflections at 2, 3, and 4 moles of base per mole of the tetramine. The acid dissociation con-

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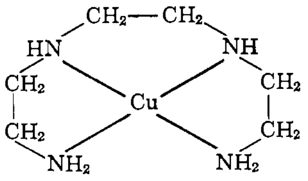
[9] G. Schwarzenbach and H. Ackermann, *Helv. Chim. Acta*, **31**, 1029 (1948).

[10] R. L. Gustafson and A. E. Martell, *Arch. Biochem. Biophys.*, **68**, 485 (1957).

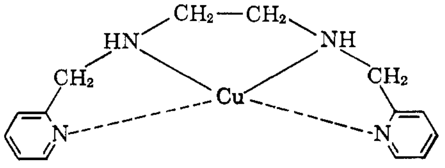
[11] G. Schwarzenbach and E. Freitag, *Helv. Chim. Acta*, **34**, 1503 (1951).

stants, compared in Table II with those of the aliphatic analog, triethylenetetramine (trien), indicate the much greater acidity of the tetrapositive ion containing pyridyl groups. The basicity of these groups toward metal ions is relatively greater than would be expected by comparison with the analogous aliphatic tetramine, trien. The very large differences in the affinities of these ligands for hydrogen ions are not generally reflected in the relative affinities for various metal ions, most of which form chelate compounds with these two ligands of about equal stabilities. Of the metal ions investigated, Cu(II) alone shows greater affinity for the more basic aliphatic tetramine. In this case the relatively lesser affinity for EDAMP is probably due to steric factors related to shorter distances between the basic nitrogen atoms in the aromatic analog, and to differences in coordinate bond angle which would introduce strain and some distortion in the EDAMP chelate, as is indicated schematically in formulas II and III. The existence of these steric factors has been demonstrated by the use of molecular models.



II

Cu(II)-trien chelate



III

Cu(II)-EDAMP chelate

TABLE II

EQUILIBRIUM CONSTANTS FOR THE COMBINATION OF EDAMP AND trien WITH VARIOUS CATIONS

Cation	log K		
	EDAMP	trien	trien–EDAMP
H⁺ pK_1	1.62	3.32	
pK_2	1.81	6.67	
pK_3	5.45	9.20	
pK_4	8.23	9.92	
Cu(II)	16.3	20.5	+4.2
Ni(II)	12.7	14.1	+1.4
Co(II)	12.8	11.0	−1.8
Zn(II)	11.5	12.1	+0.6
Cd(II)	9.9	10.0	+0.1
Mn(II)	5.9	4.9	−1.0

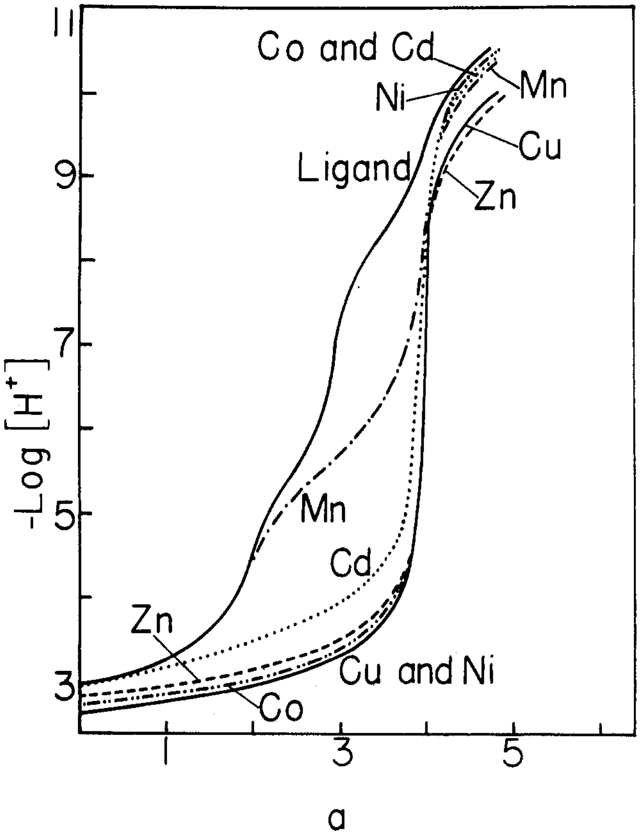


Fig. 1.—Potentiometric titration of 0.001 M N,N′-ethylenebis(2-aminomethyl)pyridine as the free ligand and in the presence of equimolar concentrations of Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) ions; $t = 25°$, $\mu = 0.100\ M$ (KNO_3).

The potentiometric data on the interaction of AEP with various metal ions are compared in Table III on the basis of relative stability constants with the analogous ligand, 1,3-diaminopropane (DAP). Both ligands have two basic nitrogen atoms separated by a three-carbon chain. As is true of the other ligands described above, the greater basicity of the aliphatic polyamine corresponds to a higher affinity for metal ions. On the other hand, this increase in stability is insufficient to counterbalance the greater competition with hydrogen ions, so that the aromatic compound binds metal ions more strongly at pH values near the neutral and acid ranges.

The titration curves of EAEP indicate the formation of rather stable complexes of Cu(II) and of Ni(II). The stability constants of various metal chelates of this ligand are compared with those of the analogous aliphatic polyamine, diethylenetriamine (dien), in Table IV. The lower stabilities of the aromatic chelates seem to be the result of the lower basicity of the aromatic ligand and the fact that it contains an additional carbon atom between the pyridyl nitrogen and the adjacent aliphatic nitrogen atom, thus forming the less stable and larger (six-membered) chelate ring.

TABLE III

ASSOCIATION CONSTANTS OF AEP AND DAP WITH VARIOUS CATIONS

Cation	log formation constants (K_1)		
	DAP	AEP	DAP–AEP
H⁺ pK_1	8.98	3.92	
pK_2	10.72	9.59	
Cu(II)	9.8	7.3	2.5
	7.2[a]	5.6[a]	1.6[a]
Ni(II)	. . .	5.2	

[a] Log K_2.

From the above discussion it appears that, for the

TABLE IV
EQUILIBRIUM CONSTANTS FOR THE COMBINATION OF EAEP AND dien WITH SIX METAL IONS

Cation	—log K— dien	EAEP	dien-EAEP
H^+ pK_1	4.34	3.50	
pK_2	9.13	6.59	
pK_3	9.94	9.51	
Cu(II)	15.9	13.4	2.5
Ni(II)	10.7	9.4	1.3
Co(II)	8.1	7.0	1.1
Zn(II)	8.9	6.7	2.2
Cd(II)	8.4	6.2	2.2

aromatic polyamines in general, the relatively low basicity of the heterocyclic nitrogen atoms generally results in a decrease of metal chelate stability compared to that of the analogous aliphatic polyamines. A few interesting exceptions to this generalization are cited in the above discussion. Although comparisons with completely heterocyclic polyamines are not possible because of a paucity of stability data for metal chelates of these substances, it seems that the compounds prepared in the present investigation have chelating tendencies intermediate between the completely aliphatic and completely aromatic polyamines. Although their chelating tendencies are somewhat lower, the α-pyridyl-substituted polyamines are more effective than are the aliphatic polyamines in binding metal ions in neutral and in acidic solutions because the aromatic compounds have much lower affinities toward hydrogen ions.

CONTRIBUTION FROM CHEMISTRY HALL,
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Phosphorus Complexes of Group III Acids. IV. B^{11}, F^{19}, H^1, and P^{31} Nuclear Magnetic Resonance Studies of Boron Complexes of Polycyclic Phosphites[1]

BY J. G. VERKADE, R. W. KING, AND C. W. HEITSCH

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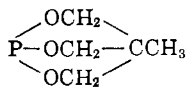
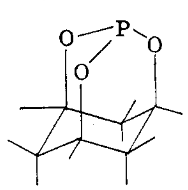
The B^{11}, F^{19}, H^1, and P^{31} nuclear magnetic resonance spectra of adducts of the polycyclic phosphites $C_5H_9O_3P$ and $C_6H_9O_3P$ with BH_3, $B(CH_3)_3$, and BF_3 have been obtained and compared with the spectra of the corresponding phosphates. The spectra of a carbon analog of $C_6H_9O_3P$, the polycyclic orthoformate of *cis*-cyclohexane-1,3,5-triol, BH_3 and $B(CH_3)_3$ adducts of trimethyl phosphite, and the BH_3 adduct of $(CH_3)_3P$ were also examined. Assignment of proton resonances in the adamantane-like compounds was effected by spin decoupling methods. Correlations of proton chemical shifts with Lewis acidity of the boron moiety were obtained for the protons of the polycyclic bases. Possible contributions to chemical shifts in these polycyclic molecules are discussed.

Recently a number of 1:1 adducts of the two polycyclic phosphites 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane, $C_5H_9O_3P$, and 1-phospha-2,8,9-trioxaadamantane, $C_6H_9O_3P$, with several boron Lewis acids have been synthesized and characterized.[2,3] The rigidity of the polycyclic structures of $C_5H_9O_3P$ and $C_6H_9O_3P$ tends to minimize rehybridization of the atomic orbitals in the molecules upon coordination to various acceptor systems. The possibility that minimal conformational changes from one adduct to another in the base moiety would perhaps lend some simplifying aspects to n.m.r. spectral interpretation as well as to speculations on the relative acid strengths of the borane groups, boron trimethyl, and boron trifluoride led us to study the n.m.r. spectra of the B^{11}, F^{19}, H^1, and P^{31} nuclei in these adducts.



$P(OCH_2)_3CCH_3$

$C_5H_9O_3P$



$C_6H_9O_3P$

The acid strengths of the boron moieties of the adducts of the phosphite bases are $BH_3 > B(CH_3)_3 \cong BF_3$. The BH_3 adducts of $C_5H_9O_3P$ and $C_6H_9O_3P$ are undissociable high-melting solids whereas the $B(CH_3)_3$ adducts are easily dissociable solids.[2,3] Due to the reaction of BF_3 with phosphites to produce cleavage products in the presence of moderate BF_3 pressures, dissociation studies of these systems could not be carried out. However, the ease with which BF_3 could be pumped away from the solid polycyclic phosphite complexes indicates an acid strength comparable to that of boron trimethyl. Substantiation for the order of acid strengths given is obtained from a consideration of thermodynamic data obtained for BH_3, $B(CH_3)_3$, and BF_3 adducts of $(CH_3)_3P$. The $B(CH_3)_3$ and BF_3 moieties of the $(CH_3)_3P$ adducts are of about the same acid strength as is shown by the relative heats of dissociation (ΔH) of the adducts, which are 16.47 and 18.9 kcal./mole, respectively.[4] That the

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[1] Presented in part at the 4th Omnibus Conference on Experimental Aspects of Nuclear Magnetic Resonance Spectroscopy, Mellon Institute, Pittsburgh, Pa., March, 1963.

[2] C. W. Heitsch and J. G. Verkade, *Inorg. Chem.*, **1**, 392 (1962).

[3] J. G. Verkade and C. W. Heitsch, *ibid.*, **2**, 512 (1963).

[4] F. G. A. Stone, *Chem. Rev.*, **58**, 101 (1958).