However, a number of tentative conclusions can be reached. The slopes and half-wave potentials of electron-transfer controlled polarographic waves are markedly affected by electrolyte concentration and constitution in a manner which suggests strongly that the double-layer structure at the electrode surface is an important factor in these reactions. Interpretations of data which do not take this influence into account are strongly suspect.

Acknowledgments.—The authors are indebted to Professor R. A. Marcus for stimulating discussions and the opportunity to view his manuscript prior to publication. The authors wish to thank Professor D. C. Grahame for providing a Russian translation. This work was supported in part by the Atomic Energy Commission under Contract AT(30-1)-905.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

A Potentiometric Study of 2-Substituted Benzimidazole Ligands[1]

BY T. J. LANE, C.S.C. AND JOHN M. DALY[2]

RECEIVED OCTOBER 29, 1958

The dissociation constants for several 2-substituted benzimidazole ligands have been determined in 50% v./v. dioxane-water. The stability constants of the ligands with various metals are reported. Thermodynamic result for 2-benzimidazoleacetic acid and for 2-benzimidazolepropionic acid agrees with crystal field treatment by George.[16]

As part of a program investigating effect of donor groups, ring size and steric effects on stabilities of chelate compounds several 2-substituted benzimidazole ligands have been prepared and their metal complexes have been investigated by potentiometric methods. The compounds studied in this work are shown in Fig. 1.

Experimental

Preparation of Reagents.—2-Benzimidazolecarboxylic acid,[3] 2-methylhydroxybenzimidazole,[3] 2-benzimidazoleacetic acid[3] and 2-benzimidazolepropionic acid[4] were prepared from known methods in the literature.

The standardization procedure for sodium hydroxide and perchloric acid is the same as that described by Freiser, Charles and Johnston.[5] Carbide and Carbon Co. technical 1,4-dioxane was purified according to method of Vogel[6] (final m.p. 11.65°). Stock solutions of approximately 0.01 *M* metal ion were prepared from reagent grade perchlorates (G. F. Smith Co.) and standardized by either electrodeposition (Cu(II), Co(II), Pb(II)), precipitation with dimethylglyoxime (Ni(II)) or precipitation as the 8-hydroxyquinolate (Mn(II) and Zn(II)).[7]

Apparatus and Procedure.—The titration apparatus consisted of a silvered water jacketed Pyrex vessel fitted with a leucite top through which holes were bored to accommodate microburets, thermometer, inlet and outlet tubes for Lamp nitrogen and the external glass-saturated calomel electrode pair. The system was thermostatically controlled to maintain the desired temperatures. Rapid mixing was effected by a magnetic stirrer. A Beckman Model G *p*H meter was standardized with Beckman buffer solutions (*p*H 4, 7, 10). The titration procedure is essentially the same as that described by Calvin and Wilson.[8]

The pK_{NH^+}, pK_{COOH} and pK_{OH} values were calculated by assuming that the *pK* of the protonated nitrogen is equal to the *p*H at the mid-point of the neutralization curve of the ligand and that the same is true of pK_{OH} and pK_{COOH} values. Stability constants of the chelates were calculated from equations developed by Freiser.[5] $\Delta H°$ values were determined from plots of $\ln K_n$ *vs.* $1/T$ for 2-benzimidazoleacetic acid and 2-benzimidazolepropionic acid.

Results and Discussion

As seen in Table I, the most basic ligand, as expected, is 2-hydroxymethylbenzimidazole. A gradual increase in basicity among the acids occurs with increasing distance between the basic nitrogen and the carboxylate group. This effect, also noted in amino acids,[9] is expected when an inductive group is further from the reaction center. The rather low basicity of 2-benzimidazolecarboxylic acid is explained by conjugation between the carboxylate group and the pyridine nitrogen.

TABLE I

ACID DISSOCIATION CONSTANTS IN 50% DIOXANE AT 25°

	pK_{NH^+}	pK_{COOH}
2-Hydroxymethylbenzimidazole	4.90	12.70[a]
2-Benzimidazolecarboxylic acid	3.04	6.48
2-Benzimidazoleacetic acid	4.14	7.20
2-Benzimidazolepropionic acid	4.72	6.52

[a] pK_{OH} in case of 2-hydroxymethylbenzimidazole.

The pK_{COOH} value of benzimidazoleacetic acid compared to that of benzimidazolecarboxylic acid shows the expected decrease in acid strength because of the shielding effect of the methyl group between the carboxylate group and the nitrogen of the ring. The surprising increase in the acidity of benzimidazolepropionic acid may be explained by its ability to form an intramolecular lactam.[10] In such a structure, ionization could take place easier and the acid dissociation constants as listed in Table I are the expected values.

Stability Constants.—Data for the determination of stability constants for all the ligands with all the metals could not be obtained because formation of the system occurred at low *p*H value or at *p*H value above the hydrolysis *p*H of metal ion used. As

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[1] Presented in part before the Division of Physical and Inorganic Chemistry, 133rd National Meeting of the American Chemical Society held in San Francisco, California, April, 1958.

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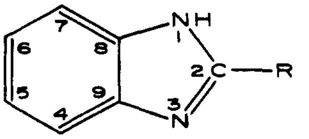

R= –CH$_2$OH   R'= –COOH

R''= –CH$_2$·COOH   R'''= –CH$_2$·CH$_2$·COOH

Fig. 1.—2-Substituted benzimidazoles.

seen in Table II, the most stable chelates of the ligands which form five-membered rings are those of 2-hydroxymethylbenzimidazole. This stability is favored by the higher basicity of this ligand and its more favorable ring size. Correlation of ligand basicity with stability has been pointed out by Verhoek,[11] Calvin[8] and Fernelius.[12] Recently, Rossotti[13] reviewed this relation. The order of stability of the complexes of the various ligands with respect to K_{av} is in fairly good agreement with the so-called natural order,[14] namely, Mn < Fe < Co < Ni < Cu > Zn.

TABLE II

STABILITY CONSTANTS IN 50% V./V. DIOXANE–WATER

	Cu (II)	Ni(II)	Co(II)	Pb (II)	Fe (II)	Zn (II)	Mn (II)
	A. 2-Hydroxymethylbenzimidazole at 25°						
Log K_1	10.98	(13.20)	(10.95)	..	10.90	..	7.98
Log K_2	7.80	5.50	...	..	6.40	..	6.32
	B. 2-Benzimidazolecarboxylic acid at 25°						
Log K_1	...	...	...	..	6.95	..	5.54
Log K_2	...	...	...	..	4.93	..	4.24
	C. 2-Benzimidazoleacetic acid						
Log K_1 3°	...	...	5.25	6.00	...	7.90	5.75
Log K_2	6.94	6.77	5.10	5.13	...	7.36	4.57
Log K_1 25°	7.85	6.98	5.09	2.76	...	7.59	5.40
Log K_2	6.72	6.50	4.37	2.45	...	6.95	3.95
Log K_1 40°	7.11	5.36	4.72	..	...	4.68	5.26
Log K_2	6.61	5.01	4.00	..	...	4.40	3.70
	D. 2-Benzimidazolepropionic acid						
Log K_1 3°	5.99	5.20	5.84	..	...	5.90	4.00
Log K_2	5.85	3.37	3.40	..	...	5.13	3.26
Log K_1 25°	5.25	4.11	3.79	..	...	4.65	3.61
Log K_2	4.15	3.27	3.37	..	...	3.95	3.21
Log K_1 40°	5.10	3.64	3.63	..	...	4.14	3.58
Log K_2	3.50	3.17	3.27	..	...	3.73	3.19

Thermodynamic Values.—Heats of chelate formation for 2-benzimidazoleacetic acid and 2-benzimidazolepropionic acid are presented in Table III.

TABLE III

HEATS OF CHELATE FORMATION, ΔH_n^0, IN 50% V./V. DIOXANE–WATER FOR 2-BENZIMIDAZOLEACETIC ACID AND 2-BENZIMIDAZOLEPROPIONIC ACID

	2-Benzimidazoleacetic acid		2-Benzimidazolepropionic acid	
	$-\Delta H_1^0$ (kcal./mole)	$-\Delta H_2^0$ (kcal./mole)	$-\Delta H_1^0$ (kcal./mole)	$-\Delta H_2^0$ (kcal./mole)
Cu(II)	11.7	8.9	8.1	2.1
Ni(II	9.7	8.3	6.5	4.2
Co(II)	7.3	6.4	7.3	4.2
Pb(II)	3.0	3.2	..	..
Zn(II)	9.8	9.3	18.0	2.5
Mn(II)	4.5	8.4	4.5	4.0

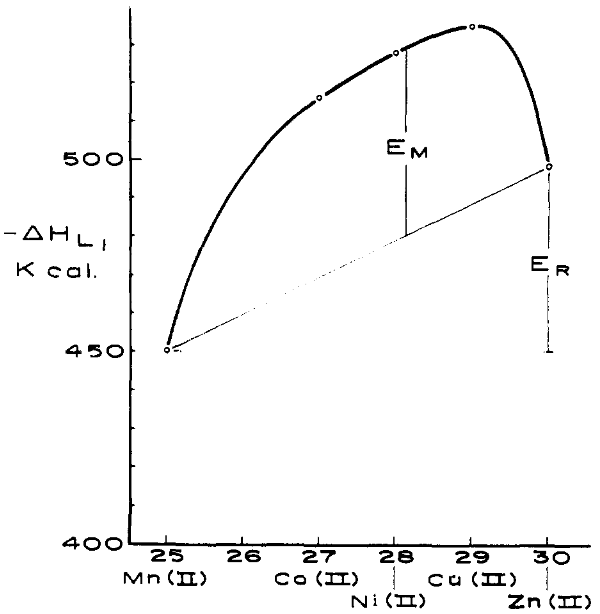

Fig. 2.—Plot of ΔH_{L_1} *vs.* atomic number of chelates of 2-benzimidazolaecetic acid.

The maximum deviation for any one determination was ±2 kcal./mole.

Extending Orgel's[15] work to quantitative aspects of the solvation data for the M^{2+} ions in 2nd and 3rd series, George[16] established how ΔH_L varies with atomic number. Quantitative data for ligands are discussed in terms of ΔH_L for the reaction

$$M_g^{2+} + nL_{aq} \rightleftarrows [ML_n]_{aq}^{2+} + \Delta H_L \qquad (1)$$

Values of enthalpy change can be determined experimentally for the following reactions

$$[M(H_2O)_x]_{aq}^{2+} + nL_{aq} \rightleftarrows [ML_n]_{aq}^{2+} + xH_2O + \Delta H_c \qquad (2)$$

$$M_g^{2+} + xH_2O \rightleftarrows [M(H_2O)_x]_{aq}^{2+} + \Delta H_s \qquad (3)$$

Inspection shows that

$$\Delta H_L = \Delta H_c + \Delta H_s \qquad (4)$$

George has computed "maximum stabilization energies" E_m for various ligands. As seen in Fig. 2, E_m is the maximum height of the smooth curve passing through the ΔH_L values for the Co(II), Ni(II) and Cu(II) ions above the straight line joining the values for Mn(II) and Zn(II) ions and E_r is the "transition series contraction energy," $\Delta H_{Zn} - \Delta H_{Mn}$. And for ligands containing one oxygen and one nitrogen donor George found $E_r/E_m = 1.28$. The ratio E_r/E_m for 2-benzimidazoleacetic acid is 1.28 (∓0.03). Data from a similar graph gave a ratio of 1.35 (∓0.03) for 2-benzimidazolepropionic acid, which forms a 7-membered ring complex and consequently cannot be compared with George's calculated data for 5- and 6-membered rings.

The entropy effects in this study were not clearly defined. An attempt to use the recently advanced correlation of Martell,[17] who plotted *Ze/R vs.* ΔS, gave a poorly defined plot.

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Acknowledgment.—The authors gratefully acknowledge financial aid from the Radiation Project of the University of Notre Dame, supported in part under U. S. Atomic Energy Commission Contract AT(11-1)-38 and from a research grant H-2218 (C) from the Department of Health, Education and Welfare, Public Health Service.

NOTRE DAME, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF INORGANIC CHEMISTRY, JOHN CURTIN SCHOOL OF MEDICAL RESEARCH, AUSTRALIAN NATIONAL UNIVERSITY]

The Preparation of 1,2-Propylenediaminetetraacetic Acid and its Resolution through the Cobalt(III) Complex

BY FRANCIS P. DWYER AND FRANCIS L. GARVAN[1]

RECEIVED DECEMBER 17, 1958

Racemic propylenediaminetetraacetic acid and the optically active forms have been prepared in good yield by the condensation of the *dl* and active bases with sodium chloroacetate at 20°. The optical isomers gave $[\alpha]_D \pm 47°$ for the monohydrate. The pure optical forms were also obtained from the Co(III) complex which had been resolved through the active *cis*-dinitrobis-(ethylenediamine)-cobalt(III) salt.

Introduction

The only references in the literature to 1,2-propylenediaminetetraacetic acid, (H_4PDTA), are to patents[2-9] in which the preparation of the acid and some of the esters and sodium salts are quoted in relation to a number of general preparative reactions for aminopolycarboxylic acids and esters. No metal complexes have been isolated.

The preparation of the racemic acid, and its resolution, have been undertaken in order to carry out ligand exchange studies with metal complexes, in which the ligand is labeled by its optical activity, and to investigate the principle of stereospecific limitation in complexes containing a single optically active organic molecule. This work will be described later.

The detailed method of preparation[10] of ethylenediaminetetraacetic acid when applied to H_4-PDTA gave only a viscous sirup which could not be induced to crystallize.[11]

The difficulty of crystallization, and the low yields of aminopolycarboxylic acids after acidification of the reaction mixture, have been ascribed to enhanced solubility due to dissolved inorganic and organic compounds and reaction by-products.[3]

It has been found that *dl*-propylenediamine condenses readily at room temperature with sodium chloroacetate in strongly alkaline solution, but low yields result when the reaction mixture is heated.[11] Slow crystallization of the amino acid ensues on acidification, but ultimately a good yield results. Unlike the racemic compound, the optical forms are quite soluble in water and do not crystallize when the reaction mixture is acidified. Great difficulty was found in separating the active acid from the extraneous sodium salts. After addition of hydrochloric acid to *p*H 3.5, the solution was evaporated to one-third volume and sodium chloride and a sodium salt of the acid precipitated by a large volume of ethanol. The latter salt was dissolved in glacial acetic acid, in which sodium chloride is insoluble and precipitated with benzene. Finally it was converted to the optically active acid itself by the use of the hydrogen form of a strong cation exchange resin. Some retention on the resin lowered the yield.[12] The exchange column was heated to prevent crystallization. Strong cation exchange resins of the sulfonic acid type adsorb Fe^{+3} very strongly, and as supplied usually contain this ion. In order to avoid contamination of the acid, the iron was removed from the column by prolonged washing with hot hydrochloric acid[13] rather than with the more efficient disodium salt of ethylenediaminetetraacetic acid.[14] After passage through the column the active acids crystallized as the monohydrates, ($[\alpha]_D \pm 47°$), from a small volume of water.

The specific rotation decreases with increasing deprotonation. The respective values of $[\alpha]_D$ in 0.5% solution in the presence of 1,2,3 and 4 equivalents of potassium hydroxide were ±39, ±37, ±30 and ±22°. The rotation rose to ±42° in the presence of 15 equivalents of alkali.

The infrared spectra of the *dl* and active acids in Nujol show differences in the 1500 to 1800 cm.$^{-1}$ region, the former having bands at 1700 cm.$^{-1}$ (strong) and 1620 cm.$^{-1}$ (weak). The 1700 cm.$^{-1}$ band is due to carboxyl groups. Evidently hydrogen bonding has decreased the frequency as double bond character is lost for the COOH group. The optically active acids (monohydrates) show bands at 1727 cm.$^{-1}$ (strong), 1630 cm.$^{-1}$ (weak) and 1570 cm.$^{-1}$(strong). The carboxyl groups show the normal frequency, revealing less effective hydrogen bonding. The band at 1570 cm.$^{-1}$ can be assigned to OH bending from the water of crystallization. The OH stretching frequency is also shown by a strong 3470 cm.$^{-1}$ band. The

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