[Contribution from the Dow Chemical Co., Eastern Research Laboratory]

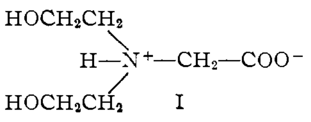
The Preparation and Chelating Properties of N,N-Bis-(2-hydroxypropyl)-glycine

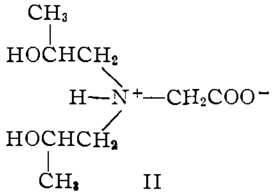
By Albert E. Frost, Stanley Chaberek and Newell J. Bicknell

Received November 29, 1956

N,N-Bis-(2-hydroxypropyl)-glycine has been synthesized and its acid dissociation constant and metal chelate stability constants with a number of metals determined. Present data indicate that this agent behaves as a tetradentate agent with all metals except copper. Comparison with the corresponding constants of N,N-bis-(2-hydroxyethyl)-glycine indicates a comparable affinity for hydrogen ion and divalent metal ions. However, the behavior with trivalent iron differs considerably from that of N,N-bis-(2-hydroxyethyl)-glycine.

Introduction.—A recent report on the chelating tendencies of the hydroxyethyl substituted glycine derivative N,N-bis-(2-hydroxyethyl)-glycine[1] (I) indicates (1) the association of hydroxyl groups with the metal ions and (2) the appreciable affinity of this derivative for transition metal ions. It, therefore, became of interest to investigate the chelating tendencies of the structurally similar N,N-bis-(2-hydroxypropyl)-glycine (DPG) (II), its homolog.


I


II

Experimental

Preparation.—N,N-Bis-(2-hydroxypropyl)-glycine was synthesized by the reaction of N,N-bis-(2-hydroxypropyl)-amine with potassium cyanide and formaldehyde in the molar ratios of 1:1.06:1.05 according to the procedure outlined by Bersworth.[2] The free acid was isolated from the straw-colored aqueous solution of the monopotassium salt by means of the hydrogen form of Dowex-50 on a column process. Elution of the column with distilled water followed by decolorization of the eluate with activated charcoal and concentration to small volume gave a gummy tan solid. Purification was accomplished by dissolution of this solid in a minimum volume of water and precipitation by the addition of a large volume (20 times) of acetone. Two such treatments produced a fine white powder melting at 129–131° (uncor.).

Anal.[3] Calcd. for $C_8H_{17}NO_4$: N, 7.3. Found: N, 7.0.

Method and Apparatus.—The experimental method employed in the study of the acid dissociation and metal chelate stability constants of N,N-bis-(2-hydroxypropyl)-glycine is essentially the same as that described by Chaberek and Martell.[4] The deviations from this procedure were the calibration of the glass electrode against a series of standard buffer solutions and the fact that all runs were made at a temperature of 29.6°. The amino acid concentration used in the several runs ranged from 3.5 to 3.8×10^{-3} *M*.

Calculations.—The calculations were carried out in the same manner as described in the above reference.[3] The metal chelate stability constants were calculated by both the algebraic and modified Bjerrum methods. Appreciable overlapping of the successive constants log K_1 and log K_2 made it necessary to correct log K values by successive approximations according to the procedure described by Carlson, McReynolds and Verhoek.[5] In the case of copper, the calculation of K_2 from the 1:1 and 2:1 titration data required a modification of the method cited above.[3] The copper–ligand interaction was sufficiently strong to lower the *p*H of the first buffer region to values considerably lower than four. A portion of the unbound ligand would, under these conditions, be converted to the positively charged species through association of a hydrogen ion with the dipolar ion (HA represents N,N-bis-(2-hydroxypropyl)-glycine)

$$HA + H^+ \longrightarrow H_2A^+ \qquad (1)$$

Formation of the positively charged species would decrease appreciably the concentration of (A^-) in this *p*H range. In order to account for the formation of H_2A^+, therefore, it was assumed that this positive ion had the same acid strength as glycine,[6] and the value of the dissociation constant for reaction 2 was taken as 4.5×10^{-3}.

$$H_2A^+ \overset{k^1}{\rightleftharpoons} HA + H^+;\ k^1 = (HA)(H^+)/(H_2A^+) \qquad (2)$$

Discussion of Results

1:1 Titration Curves.—The free acid curve of Fig. 1 has one inflection point at "*a*" value of 1 corresponding to formation of the monoalkali metal salt. The curve is typical of a weak monobasic

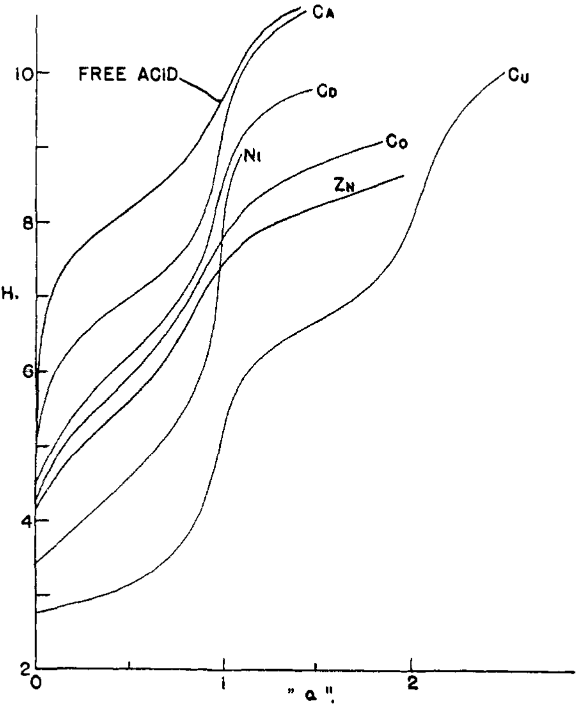


Fig. 1.—Titration of N,N-bis-(2-hydroxypropyl)-glycine (DPG): molar ratio of ligand to metal ion = 1:1; *a* = moles of base added per mole of acid.

---

[1] S. Chaberek, Jr., R. C. Courtney and A. E. Martell, This Journal, **75**, 2185 (1953).

[2] F. C. Bersworth, U. S. Patent 2,407,645, Sept. 17, 1946.

[3] Analysis by Carol K. Fitz, 115 Lexington Avenue, Needham Heights 94, Mass.

[4] S. Chaberek, Jr., and A. E. Martell, This Journal, **74**, 5052 (1952).

[5] G. A. Carlson, J. P. McReynolds and F. H. Verhoek, *ibid.*, **67**, 1334 (1945).

[6] H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1950, p. 580.

acid and exhibits a buffer region about *p*H 8.5. The calculated value of the acid dissociation constant is $10^{-8.13}$. In this respect it is similar to the homologous N,N-bis-(2-hydroxyethyl)-glycine. The greater acidity of the ammonium proton over that for glycine ($10^{-9.78}$) is probably due to hydrogen bond formation between the hydroxyl groups and the basic nitrogen atom which facilitates dissociation of the ammonium hydrogen ions as is postulated for N,N-bis-(2-hydroxyethyl)-glycine.[1]

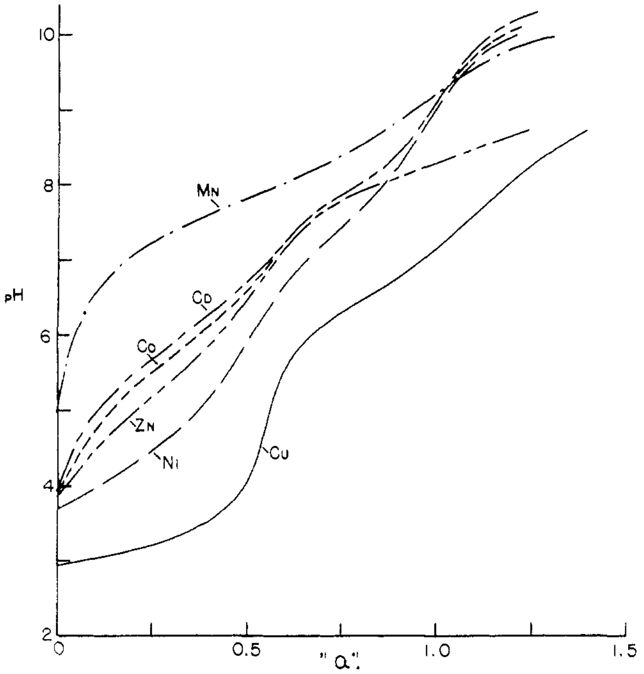


Fig. 2.—Titration of N,N-bis-(2-hydroxypropyl)-glycine (DPG): molar ratio of ligand to metal ion = 2:1; *a* = moles of base added per mole of amino acid.

The titration curves of DPG with a molar ratio of ligand to bivalent metal ion of one (Fig. 1) indicate that normal 1:1 chelates form with displacement of the single ammonium proton. The reaction

$$M^{+2} + HA + OH^- \longrightarrow MA^+ + H_2O \quad (3)$$

describes 1:1 chelate formation for all these bivalent metals. The OH^- represents the base added during the titration.

The Cu(II) chelate titration curve of Fig. 1 indicates the chelate to be of sufficient stability to form in strongly acid solution at which *p*H range the undissociated form of the DPG predominates.

The additional buffer region and inflection point of the Cu(II) titration curve at an "*a*" value of 2 indicates dissociation of a proton from a hydroxypropyl group or from a coördinated water molecule. If $HA(OH)_2$ represents the amino acid, the Cu(II) titration may be described by the reactions

First inflection point

$$HA(OH)_2 + Cu^{+2} \rightleftharpoons CuA(OH)_2^+ + H^+ \quad (4)$$

Second inflection point

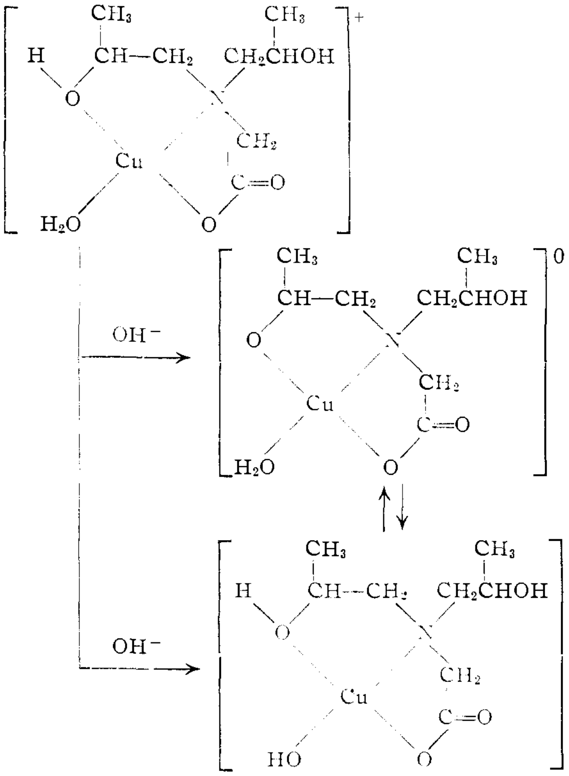
$$CuA(OH)_2(H_2O)^+ + OH^- \rightleftharpoons CuAO(OH)(H_2O) + H_2O \quad (5)$$

or

$$CuA(OH)_2(H_2O)^+ + OH^- \rightleftharpoons CuA(OH)_2(OH) + H_2O \quad (6)$$

The two possible hydrolysis products bear a tautomeric relationship to each other, and it is likely that an equilibrium exists between these structures.

That proton dissociation as indicated above and not higher complex formation occurs at the second inflection point is evident from the fact that disproportionation to a higher chelate would result in precipitation of an equivalent amount of cupric hydroxide according to the reaction



Possible hydrolysis products of the 1:1 copper chelate of DPG

$$2CuA(OH)^+_2 + 2OH^- \rightleftharpoons Cu(A)(OH)_2)_2 + Cu(OH)_2\downarrow \quad (7)$$

No precipitation was observed in this titration.

2:1 Titration Curves.—Titration curves for solutions containing ligand/metal ratios of two are shown in Fig. 2. All curves, with the exception of Mn(II)–DPG, have an inflection at an "*a*" value of 0.5 corresponding to the formation of the 1:1 metal chelate

$$M^{+2} + 2HA + OH^- \longrightarrow MA^+ + HA + H_2O \quad (8)$$

The excess DPG is present in essentially the dipolar acid species in the *p*H range of the inflections. Subsequent consumption of a second half mole of hydroxide per mole of amino acid and the presence of a second inflection at $a = 1$ for all systems except Zn(II) results from further interaction of excess ligand and the 1:1 metal chelate according to eq. 9

$$MA^+ + HA + OH^- \longrightarrow MA_2 + H_2O \quad (9)$$

In the case of the Mn(II) system, the absence of an inflection at $a = 0.5$ indicates a strong overlapping tendency involving the MA^+ and MA_2 species.

The Fe(III)–DPG System.—Titrations of Fe-

(III)–DPG mixtures with ligand/Fe(III) ratios of 1 and 2 are plotted in Fig. 3.

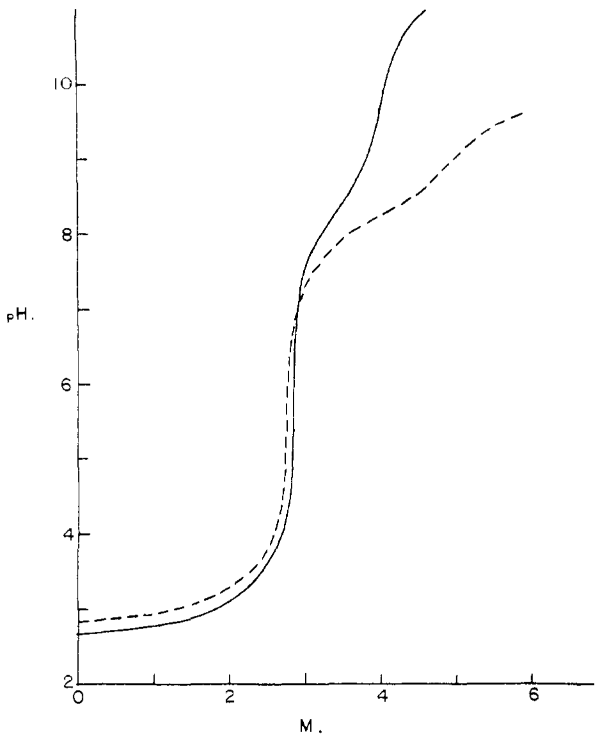


Fig. 3.—Titration of N,N-bis-(2-hydroxypropyl)-glycine in the presence of Fe(III) ions; —, Fe(III)/acid = 1:1; ----, Fe(III)/acid = 1:2; *m* = moles of base added per mole of metal ion.

The abscissa "*m*" of Fig. 3 denotes the number of moles of base added per mole of metal ion. The first inflection of both curves occurs at "*m*" ≈ 3, and a second weaker break is observed at "*m*" values of 4 and 5 for the 1:1 and 2:1 systems, respectively. Although the shapes and equivalence points for the Fe(III)–DPG system are strikingly similar to properties of the Fe(III)–bis-(2-hydroxyethyl)-glycine system for comparable ligand/metal ratios, the nature of the interactions are entirely different for these systems. Both 2:1 and 1:1 Fe(III)–DPG systems are characterized by the formation of ferric hydroxide at *p*H values of 2.75–3.0. Subsequent addition of standard base results in an extremely slow attainment of equilibrium and the precipitation of further amounts of the metal hydroxide. Consequently, the titration curves of Fig. 3 represent the stepwise formation of the ferric hydroxide and neutralization of DPG according to the reactions

1:1 titration curve

$$\mathrm{Fe}^{+3} + 3\mathrm{OH}^- \longrightarrow \mathrm{Fe(OH)_3}\downarrow \quad \frac{3(\mathrm{OH}^-)}{\mathrm{Fe}} \qquad (10)$$

$$\mathrm{HA} + \mathrm{OH}^- \longrightarrow \mathrm{A}^- + \mathrm{H_2O} \quad \frac{1(\mathrm{OH}^-)}{\mathrm{Fe}} \qquad (11)$$

$\therefore$ inflections at $m = 3$ and $m = 4$

2:1 titration curve

$$\mathrm{Fe}^{+3} + 3\mathrm{OH}^- \longrightarrow \mathrm{Fe(OH)_3} \quad \frac{3(\mathrm{OH}^-)}{\mathrm{Fe}} \qquad (12)$$

$$2\mathrm{HA} + 2\mathrm{OH}^- \longrightarrow 2\mathrm{A}^- + 2\mathrm{H_2O} \quad \frac{2(\mathrm{OH}^-)}{\mathrm{Fe}} \qquad (13)$$

$\therefore$ inflections at $m = 3$ and $m = 5$

In spite of the behavior of this chelating agent in the acid and neutral *p*H range, it has been shown qualitatively that DPG chelates Fe(III) in alkaline solutions. Present data suggest, therefore, the formation of a ferric chelate which is considerably weaker than the corresponding Fe(III)–bis(2-hydroxyethyl)-glycinate. Experimental observations are consistent with the anticipated behavior of a weak ferric chelate which is extensively dissociated in acid solution.

Metal Chelate Formation Constants.—The first and second consecutive formation constants for the metal–DPG chelates are listed in Table I along with the corresponding values of the N,N-bis-(2-hydroxyethyl)-glycinate chelates (2-HxG).[1] The comparable affinities of both ligands for these metal ions are clearly evident from the corresponding log *K* data.

TABLE I

EQUILIBRIUM CONSTANTS

$T = 29.6°$, $\mu = 0.1$, $\gamma(\mathrm{H}^+) = 0.78$

	DPG			2-HxG	
	log K_1				
Metal	1:1	2:1	log K_2	log K_1	log K_2
H^+	8.13(pk_2)			8.08(pk_1)	
Cu(II)	8.0	..	4.90	8.15	5.20
Ni(II)	6.33	6.44	3.82	6.37	4.40
Co(II)	5.16	5.48	3.35	5.25	3.52
Zn(II)	5.20	5.56	3.42	5.38	3.26
Cd(II)	4.72	5.06	3.18	4.81	3.37
Mn(II)	..	3.02	2.44	3.27	2.33
Ca(II)	..	2.65[a]	..	..	..

[a] Calculated algebraically from titration data of a solution containing a ligand/metal ratio of 10.

The comparable chelating tendencies of DPG and 2-HxG are further illustrated by comparing metal formation constants with the second ionization potential (Fig. 4) of the metal ion. Compari-

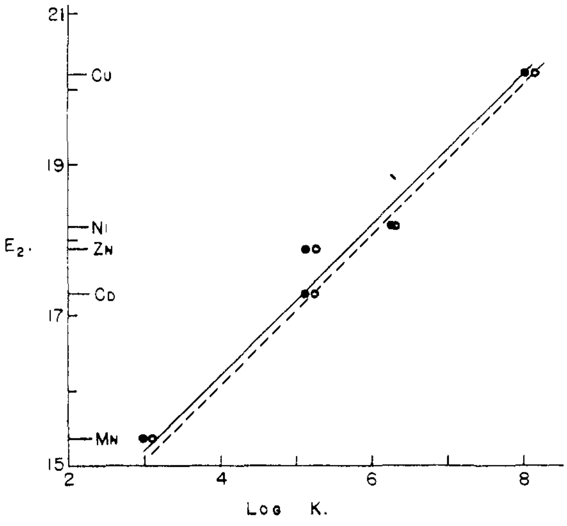


Fig. 4.—Correlation of metal chelate stability constant with second ionization potential; ●, K_{mke} for N,N-bis-(2-hydroxypropyl)-glycine; ○, K_{mke} for N,N-bis-(2-hydroxyethyl)-glycine.

son of DPG and 2-HxG of Table I indicates little or no difference in the chelating tendencies of 2-hydroxypropyl relative to 2-hydroxyethyl groups.

That N,N-bis-(2-hydroxypropyl)-glycine and the corresponding N,N-bis-(2-hydroxyethyl) derivative exhibit comparable chelating affinities for the divalent metal ions is clearly evident from the results of this investigation. This behavior is certainly predictable on the basis of the close structural similarities and the comparable basicities of these two compounds. The differences between DPG and 2-HxG with respect to the chelation of Fe(III) is, however, unexpected. A comparison of molecular models of both ligands shows no apparent steric effect with relation to the orientation of the electron donor groups around the Fe(III) ion. It is further unlikely that the substitution of a methyl group for a methylene hydrogen would alter sufficiently the basicity of the ethanolic proton to account for the difference in the Fe(III) chelating properties. Present data are insufficient to account for this difference in affinity. It is felt, however, that the difference in behavior is due to some steric factor not immediately apparent from a comparison of molecular models.

FRAMINGHAM, MASSACHUSETTS

[CONTRIBUTION FROM THE EMERYVILLE RESEARCH CENTER, SHELL DEVELOPMENT CO.]

Detection of $HO_2\cdot$ Radical in Metal Ion Catalyzed Decomposition of Hydrogen Peroxide

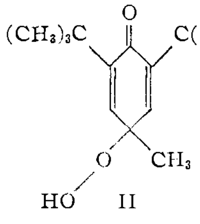
BY GALVIN M. COPPINGER

RECEIVED JANUARY 23, 1957

The appearance of $HO_2\cdot$ radical in the decomposition of hydrogen peroxide catalyzed by copper, iron or cobalt ions is detected by means of 2,6-di-*t*-butyl-4-methylphenol. A crystalline product is isolated with the structure 2,6-di-*t*-butyl-4-methyl-4-hydroperoxy-2,5-cyclohexadienone.

The radical $HO_2\cdot$ has been postulated as an intermediate in the decomposition of hydrogen peroxide in solution in the presence of a variety of metal ions.[1] Evidence for the existence of this radical is limited to inference drawn from final products of the decomposition and from the catalytic activity of the metal ion.

It has been possible to confirm the existence of the $HO_2\cdot$ radical in hydrogen peroxide decomposition by reaction of the radical with an antioxidant, utilizing a technique which has demonstrated the existence of other reactive radical intermediates.[2,3] When 2,6-di-*t*-butyl-4-methylphenol (I) is included in the system *t*-butyl alcohol, hydrogen peroxide, metal ion [Co^{++}, Fe^{++}, Fe^{+++}, Cu^{+}, Cu^{++}], a compound may be isolated whose structure is

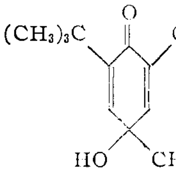


II

This compound is clearly the product of an intermediate in the metal ion catalyzed hydrogen peroxide decomposition. There is no reaction between the metal ions and the phenol in the absence of hydrogen peroxide and none between hydrogen peroxide and the phenol in the absence of metal ion under the same conditions. Oxygen has no direct effect on the reaction.

The isolation of II is accomplished by use of a large excess of hydrogen peroxide and interruption of the reaction before hydrogen peroxide is exhausted. The structure of the compound has been assigned on the basis of ultimate analysis, infrared spectrum and chemical reactivity. The infrared spectrum is the most distinctive characteristic of the cyclohexadienone structure, displaying a striking doublet at $6\ \mu$.[4] Compound II also exhibits OH stretching bands with hydrogen bonding.

Compound II is reduced with Pt and H_2 to III. This compound (III) is also obtained from the air oxidation of 2,6-di-*t*-butyl-4-methylphenol in the presence of alkali.[5] The structure of III is assigned on the basis of analysis and infrared spectrum, OH stretching and doublet at $6\ \mu$ associated with the cyclohexadienone configuration. It is transformed into 3,5-di-*t*-butyl-4-hydroxybenzyl acetate in acetic acid in the presence of a trace of strong acid.[6]



III

The hydroperoxide II is subject to metal ion catalyzed decomposition. The system II, Co^{++} and (I) in *t*-butyl alcohol, permits the isolation of three compounds: III, 1,2-bis-3,5-di-*t*-butyl-4-hydroxyphenylethane (IV) and 3,3',5,5'-tetra-*t*-butyl-stilbene-4,4'-quinone (V). There is some

---

[1] Metal ion catalysis of H_2O_2 decomposition is reviewed by J. H. Baxendale, "Advances in Catalysis," Vol. IV, Academic Press, Inc., New York, N. Y., 1952, p. 31; J. Weiss, p. 343.

[2] T. W. Campbell and G. M. Coppinger, THIS JOURNAL, **74**, 1469 (1952).

[3] A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 3211 (1953).

[4] In addition to a limited number of examples available elsewhere, (E. Müller, K. Ley and W. Schmidhuber, *Ber.*, **89**, 1738 (1956), see also reference 3) the author has examined the spectra of 15 compounds with the 2,5-cyclohexadienone structure with various substituents in the 2-, 4- and 6-positions. The very strong doublet about 6μ is always present and variation in wave length has not exceeded 0.03μ.

[5] F. C. Davis and G. M. Coppinger, unpublished.

[6] G. M. Coppinger and T. W. Campbell, THIS JOURNAL, **75**, 734 (1953).