

COMPLEX COMPOUNDS OF BIGUANIDES AND GUANYLUREAS WITH METALLIC ELEMENTS

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Received June 7, 1960

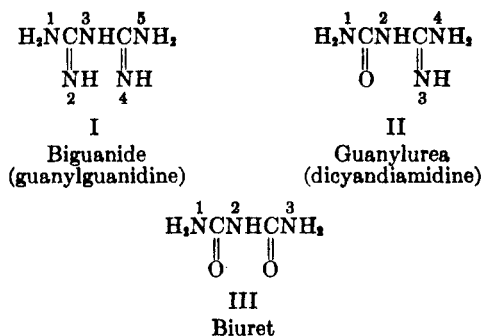
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I. INTRODUCTION

Chemically and structurally biguanide (I), guanylurea (II), and biuret (III) are closely related compounds. Both I and II may be derived from III by the substitution of both or only one of the oxygen atoms of the latter by the corresponding number of imino (=NH) groups.



The nitrogen atoms are numbered in order to indicate the position of the substituents in the various alkyl and aryl derivatives of the compounds. Dicyandiamidine is also used as an alternative name for guanylurea, but the latter name has some advantage as it indicates directly the position of a substituent in the guanyl or urea end of the molecule. Some workers write "diguanide" for biguanide. The latter term is, however, preferred as it offers no difficulty in naming, for instance, a derivative of the composition $\text{C}_2\text{H}_4(\text{C}_2\text{H}_5\text{N}_5)_2$ as ethylenedibiguanide.

An exhaustive review of biuret and related compounds, including a short account of the biuret reaction and the structure of biuret-metal complexes, has recently been published (80).

The present article attempts to offer a comprehensive review of the metal complexes of biguanide and guanylurea, inclusive of their many substituted derivatives. Some metal complexes of guanylthiourea (thiodicyandiamidine), the sulfur analog of guanylurea, have also been incorporated. These two types of chelating ligands combine with many metals of the transition series to give a large and remarkable variety of complexes. A systematic study of these in comparatively recent times has not infrequently led to interesting and illuminating conclusions on problems of valency and as to the structure and stability of coordination compounds.

For obvious reasons a short account of the preparation, properties, and structure of biguanides and guanylureas has been embodied as a necessary prelude with a view to elucidating their complex-forming character. These two classes of compounds have attracted considerable attention recently, since the discovery of the antimalarial activity of paludrine, N^1 -(*p*-chlorophenyl)- N^5 -isopropylbiguanide (30). This has led to the study of many substituted biguanides, as well as of guanylureas and biurets corresponding to

paludrine, with particular reference to their physiological and chemotherapeutic properties (25, 26, 27, 28).

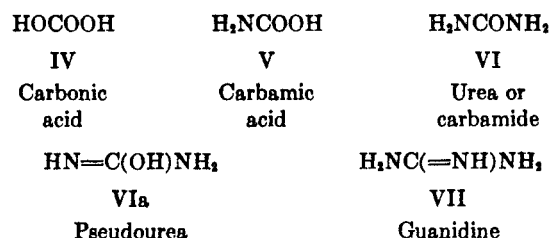
Relevant literature references have been covered up to December, 1958, but a number of later papers and communications have also been noted.

II. BIGUANIDES AND GUANYLUREAS

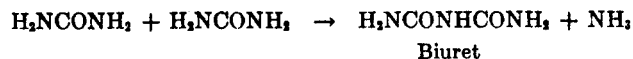
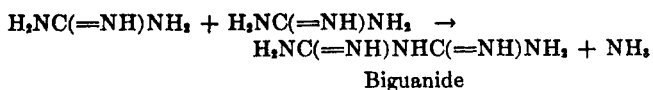
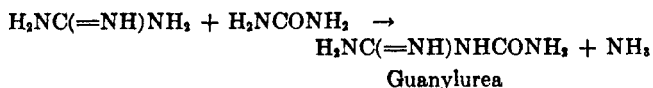
A. MUTUAL RELATION, TRANSFORMATION, AND STRUCTURE

1. Mutual relation

The close resemblance among biguanide (I), guanylurea (II), and biuret (III) may be attributed to their derivation from the same parent source, i.e., carbonic acid (IV) or its amides, carbamic acid (V) and urea (VI). Guanidine, an amidine of carbamic acid, is also included in this group.

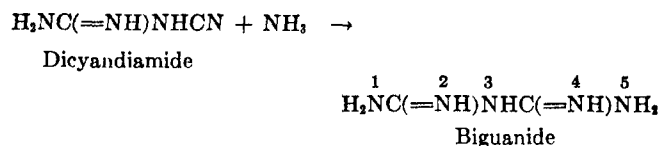
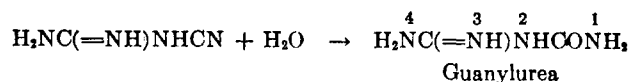


Guanylurea may thus be regarded as a guaneide of carbamic acid, just as biuret may be viewed as a ureide of the same. In a similar manner biguanide may be considered as a guaneide of pseudourea (VIa). The formation of guanylurea from a guanidine salt and urea by fusion (10), in which a molecule of guanidine combines with a molecule of urea liberating a molecule of ammonia, is quite analogous to that of biguanide from guanidine hydrochloride at 180–185°C. (6), when two molecules of guanidine condense together, losing a molecule of ammonia. This exactly resembles the formation of biuret from the thermal decomposition of urea nitrate (187).



The reverse reaction, leading to the formation of guanidine from the fusion of a mixture of biguanide and an ammonium salt, has also been described (15, 90). The name biguanide, therefore, seems appropriate by analogy with the name biuret. Another name used for biguanide, guanylguanidine, also bears the same significance. The close relationship between guanylurea and biguanide is evident from their formation

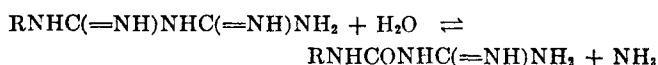
from one and the same source material, dicyandiamide, by its union with a molecule of water and one of ammonia, respectively.



2. Transformation

Some substituted biguanides suffer more or less rapid hydrolysis in acid solution. A solution of paludrine, *N*¹-(*p*-chlorophenyl)-*N*⁵-isopropylbiguanide, in moderately strong hydrochloric acid, when kept for about a year, deposited crystals of *N*¹-(*p*-chlorophenyl)-*N*⁴-isopropylguanylurea (26). But much more rapid hydrolysis occurred in the case of *N*¹-(*p*-sulfamoylphenyl)biguanide and some of its substituted derivatives (78). Almost complete conversion was observed within 12 hr. at room temperature. The presence of a sulfamoyl group in the para position of the phenyl radical in a substituted biguanide molecule appears particularly responsive to its rapid hydrolytic change. The substitution of the amine hydrogen in the sulfamoyl group by alkyl, dialkyl, or aryl radicals exerts no appreciable effect upon the rate of this change, but, on the other hand, it is more or less strongly retarded by alkyl, dialkyl, or aryl substitution at the other end (*N*⁵-position) of the biguanide molecule. This stabilizing influence of substitution at the *N*⁵-position is attributed by Kundu and Rây (78) to increased resonance, arising from conjugation in the case of aryl or some hyperconjugation in the case of alkyl groups. A quantitative study of the kinetics of transformation has been made by Kundu (77) at two different temperatures, 32° and 46°C.

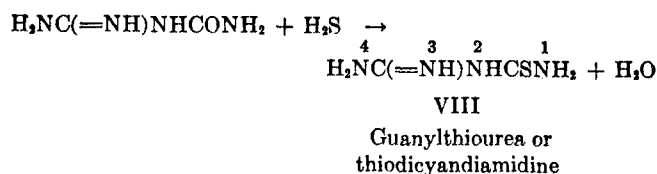
Obviously in an aqueous solution of a biguanide there tends to be an equilibrium between the biguanide molecule and the products of its hydrolysis, a guanylurea and ammonia, though the amount of the latter might be negligibly small to begin with:



In acid solution the equilibrium reaction proceeds rapidly to the right, owing to removal of ammonia as an ammonium salt. If the guanylurea salt formed by hydrolysis be sparingly soluble, the hydrolytic change proceeds almost to completion. The reverse change, the ammonolysis of guanylurea to biguanide, is also suggested by the above reaction.

Guanylurea is readily transformed into its sulfur analog, guanylthiourea (VIII), by heating any of its

salts with hydrogen sulfide water (171). The reaction may be regarded as a case of sulphydrolysis of guanyl-

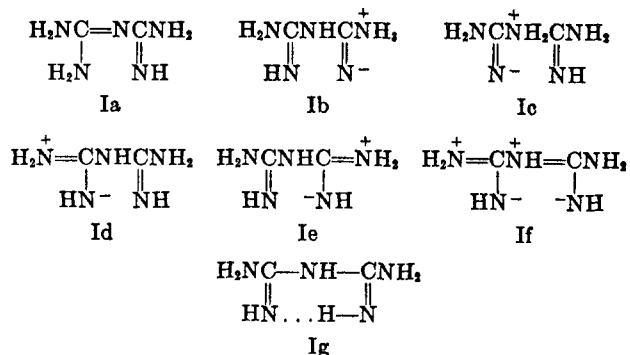


urea. The reverse change, the hydrolysis of guanylthiourea to guanylurea, is also implied. The transformation of guanylthiourea into biguanide is illustrated by the preparation of some substituted biguanides from amines and (*S*-ethyl)guanylthiourea (170, 171) as also from guanidine and substituted thiocarbamide (24).

3. Structure

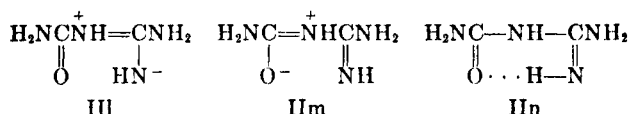
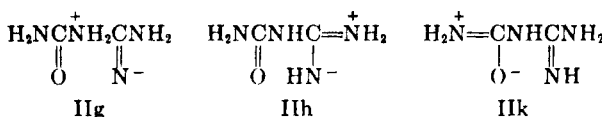
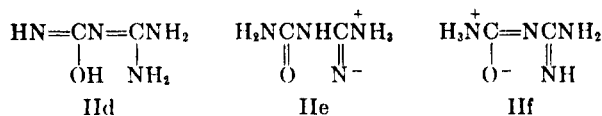
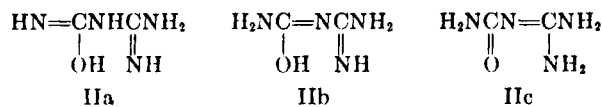
In view of the remarkable complex-forming capacity of biguanides and guanylureas a consideration of their structure is of special significance. As in the case of biuret (80), no definite and unambiguous structure can necessarily be assigned to the biguanide or guanylurea molecule. The structures of these compounds are most satisfactorily represented like that of biuret as a resonance hybrid, to which contribution is made by several tautomeric configurations including some zwitter ions.

Besides the conventional structure (I), the biguanide molecule may occur in the form of tautomers (Ia, Ib, and Ic), owing to prototropy. Each of these may again resonate among several valence-bond structures. Structure I, for instance, furnishes possibilities of seven different modifications by resonance, of which Id, Ie, and If are examples. Besides, the molecule may be further modified by hydrogen bonding, giving rise to cyclic structures like Ig. Similar cyclic structures of paludrine and other substituted biguanides are supposed to influence profoundly their physiological properties (30).



In a similar manner guanylurea can also be represented as occurring in various tautomeric forms, IIa, IIb, IIc, and IId, including the zwitter ions like IIe, IIf, and IIg. The usual conventional structure (II) of the compound may resonate with the four different

structures IIh, IIk, III, and IIm. In addition a cyclic structure of the type of II n may arise through the formation of a hydrogen bond.



The structure of guanylthiourea is closely analogous to that of guanylurea in all respects and requires, therefore, no special treatment.

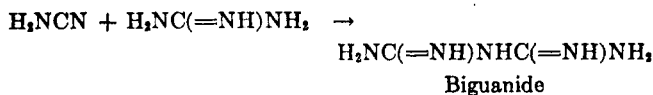
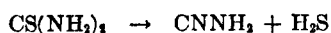
The molecules of biguanide, guanylurea, and guanylthiourea all possess active functional groups which readily lend themselves to the formation of metal complexes in a suitably activated state of the molecule, most favorable for the purpose (*cf.* Section III, B).

B. GENERAL METHODS OF PREPARATION

1. Biguanide and substituted biguanides

(a) Biguanides

In 1879 Rathke (101) first prepared biguanide by digesting a mixture of thiocarbamide and guanidine thiocyanate with phosphorus trichloride. The reaction obviously occurs through the formation of cyanamide from thiocarbamide, which then reacts with guanidine to yield biguanide. But the method gave a very poor yield. The sulfate of the base was obtained in the form



of rhombic crystals having the composition $\text{C}_2\text{H}_7\text{N}_5 \cdot \text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$. The author observed that the substance reacted with a solution of copper(II) sulfate to give rose-red crystals of a complex copper(II) base and the corresponding sulfate having the composition $\text{Cu}(\text{C}_2\text{H}_5\text{N}_5)_2 \cdot 2\text{HX}$, where $\text{X} = \text{OH}$ or $\frac{1}{2}\text{SO}_4$.

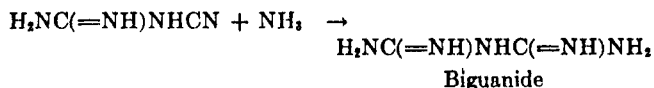
A better yield was obtained by heating dicyandiamide with ammoniacal copper(II) sulfate solution at 105–110°C. for 12 hr. in a sealed tube. A solution of the complex copper(II) biguanide sulfate in the least possible excess of dilute sulfuric acid, on evaporation

in a vacuum over sulfuric acid, gave crystals of the biguanide sulfate (71). The method was found quite satisfactory, as regards both yield and the absence of secondary products.

The preparation of biguanide hydrochloride by heating an alcoholic solution of dicyandiamide with ammonium chloride served as an improvement upon the previous method (173).

Still better results were obtained by heating an intimate mixture of ammonium chloride (8 g.) and dicyandiamide (5 g.) at 195°C. for 5–10 min. (6). Substitution of ammonium iodide for ammonium chloride further increased the yield from 21 to 45 per cent (89). An intimate mixture of finely powdered dicyandiamide and ammonium chloride was heated to 173°C. for 5 min. The cooled product of the reaction was extracted with water and filtered from any insoluble residue. From the filtrate copper(II) biguanide sulfate was precipitated by the addition of ammoniacal copper(II) sulfate solution. The copper compound was dissolved in the least excess of dilute sulfuric acid, and the biguanide acid sulfate was crystallized from the solution by concentration on the water bath. The free biguanide base in the anhydrous crystalline state has also been isolated from the sulfate by reaction with barium hydroxide solution (99) or with metallic sodium in alcoholic solution (170).

The reaction leading to the formation of biguanide from dicyandiamide and ammonium chloride or iodide consists merely in the addition of a molecule of ammonia to one of dicyandiamide.



Preparation of biguanide in good yields (18–30 per cent) with the use of ammonium methane- or benzene-sulfonate in place of ammonium chloride has also been described (90).

(b) Substituted biguanides

Methylbiguanide has been prepared through its copper derivative by triturating dicyandiamide with copper(II) sulfate and digesting the mixture with a 20 per cent solution of methylamine. On keeping the deep blue liquid for several days, or preferably upon heating it in a sealed tube for a few hours at 100–110°C., the complex copper(II) biguanide sulfate separated in the form of red needles. From the complex copper salt the methylbiguanide sulfate can then be obtained as in the case of the simple biguanide. The free methylbiguanide base has also been obtained in the form of an uncrystallizable mass (154).

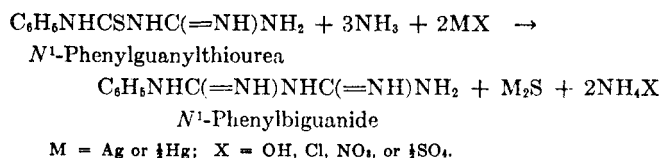
Ethylbiguanide sulfate and ethylbiguanide base in crystalline form have also been prepared in the same manner (49). Preparation of ethylbiguanide hydrochloride by heating an alcoholic solution of dicyandi-

amide with ethylamine hydrochloride has also been described (173).

Fusion of 2-aminoethanesulfonic acid (taurine) with dicyandiamide has led to the direct preparation of N^1 -(2-sulfoethyl)biguanide, $\text{HO}_3\text{SCH}_2\text{CH}_2\text{NHC}(=\text{NH})\text{NHC}(=\text{NH})\text{NH}_2$, from an aqueous solution of the melt by precipitation with alcohol (159).

N^1,N^1 -Diethylbiguanide has been prepared as its sulfate from its copper compound. A mixture of diethylamine hydrochloride and dicyandiamide was heated at 130°C . for several hours and the product extracted with chloroform. The chloroform was then evaporated and the residue dissolved in water. From the aqueous solution copper(II) N^1,N^1 -diethylbiguanide was precipitated by the addition of copper(II) sulfate and potassium hydroxide. The copper compound was dissolved in dilute sulfuric acid, and the copper was removed by precipitation with hydrogen sulfide. From the filtrate diethylbiguanide sulfate was precipitated by alcohol (51). A more direct method consists in heating together dicyandiamide, diethylamine (33 per cent solution), copper(II) sulfate, and water under pressure on the water bath with frequent shaking; copper(II) sulfate solution should be added in small portions at a time, a fresh quantity being introduced as soon as the precipitated copper hydroxide from the previous addition dissolves to give a red solution. The complex copper(II) N^1,N^1 -diethylbiguanide sulfate readily separates in red crystals (137).

Phenylbiguanide base and its salts (chloride, nitrate, and sulfate) were first prepared by Bamberger (3) by treating N^1 -phenylguanylthiourea with silver oxide, mercuric chloride, silver nitrate, and silver sulfate, respectively, in the presence of ammonia.



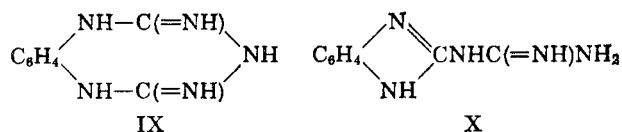
Phenylbiguanide hydrochloride (173), p -tolylbiguanide hydrochloride (57), and N^1,N^1 -diphenylbiguanide hydrochloride (51) have been prepared by heating an alcoholic solution of dicyandiamide with aniline hydrochloride, p -tolylamine hydrochloride, and diphenylamine hydrochloride, respectively. An alternative method is to fuse the two reactants together on an oil bath. p -Hydroxyphenyl-, p -anisyl-, and o - and p -phenetylbiguanide hydrochlorides have been prepared in this manner (83).

A number of N^1 -substituted biguanides have been prepared by the fusion of dicyandiamide with alkyl- or arylamine salts of methanesulfonic, benzenesulfonic, or toluenesulfonic acid. Methyl-, isopropyl-, cyclohexyl-, benzyl-, phenyl-, p -sulfamoylphenyl-, dimethyl-, diethyl-, and diphenylbiguanides, besides N^1 -methyl-

N^1 -phenylbiguanide and pentamethylenedibiguanide, have thus been obtained (90).

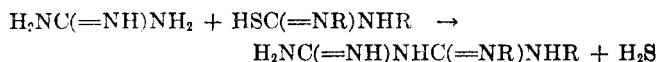
Heating dicyandiamide with hydrochlorides of aromatic amines in aqueous solution serves, however, as a general method of preparing the hydrochlorides of N^1 -arylbiguanides (23). Good yields of the hydrochlorides of phenyl-, m -nitrophenyl-, p -hydroxyphenyl-, p -phenetyl-, p -ethylcarboxylate phenyl-, N^1 -methyl- N^1 -phenyl-, and 1-naphthylbiguanides have been obtained by this method. Hydrochlorides of m -phenylenedibiguanide, diphenyldibiguanide, and 4-amino-4'-(N^1 -biguanido)biphenyl ($4\text{-H}_2\text{NC}_6\text{H}_4\text{C}_6\text{H}_4\text{C}_2\text{H}_5\text{N}_5\text{-4}$) have also been obtained in the same way (23).

The same method was employed for preparing the salts of N^1 -(p -methoxyphenyl)biguanide (171), N^1 -(4-sulfophenyl)biguanide (153), and N^1 -(2-sulfo-1-naphthyl)biguanide (132), as well as for (p -acetylaminophenyl)biguanide and p -phenylenedibiguanide (134). Preparation of o -phenylenebiguanide by this method has been described by some workers. The cyclic structures IX (37, 188) and X (39, 94, 95) have been assigned to this compound. Structure X represents the molecule as an iminazole derivative.



Biguanides substituted in positions N^1 and N^2 were first prepared by Bamberger (3) through the removal of sulfur from phenylguanylthiourea in the presence of aniline.

A number of N^1,N^2 -disubstituted arylbiguanide bases (anhydrous) and their hydrochlorides have been prepared by the action of guanidine upon disubstituted thiocarbamides in alcoholic solution in the presence of mercuric oxide (24).



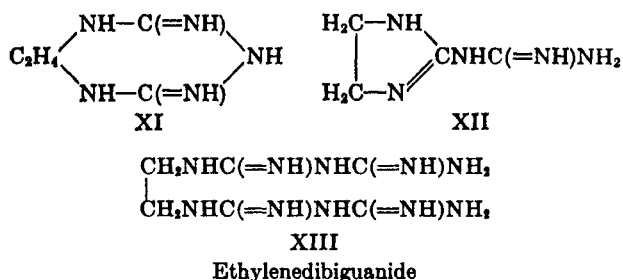
Various substituted biguanides with substituents at the N^1 - or N^2 -position of the molecule have been prepared from dicyandiamide and the corresponding aryl- or alkylamine either by heating the reactants in aqueous solution in the presence of copper(II) sulfate or by fusing the amine hydrochloride with dicyandiamide and then precipitating the copper(II) biguanide sulfate from the solution of the reaction product by treatment with ammoniacal copper(II) sulfate solution. Copper is removed from the latter by hydrogen sulfide, and the filtrate from copper(II) sulfide is evaporated under reduced pressure or else treated with alcohol or acetone. The sulfates of the substituted biguanide bases are thus obtained in well-formed crystals. In some cases crystals of the sulfate separate out directly from the solution of the copper complex

in dilute sulfuric acid. The preparation of the following substituted biguanides in the form of their sulfates by the general reaction outlined above has been reported: *N*¹-propyl-, *N*¹-isoamyl-, *N*¹,*N*¹-dimethyl-, *N*¹-hexyl-, *N*¹,*N*¹-diallyl-, *N*¹-crotyl-, and *N*¹-isoamyl-enebiguanides (171); 2-hydroxyethyl-, 3-hydroxypropyl-, 2-hydroxypropyl-, 2-methoxyethyl-, and 3-methoxypropylbiguanides (84, 162); isopropyl- and *n*-butylbiguanides (159); benzylbiguanide (108); hexamethylenedibiguanide (43); piperazinedibiguanide (125).

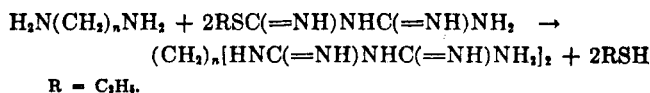
Ethylenedibiguanide has been prepared by the reaction between molecular proportions of ethylenediamine hydrochloride and dicyandiamide at 140–150°C. The aqueous solution of the cooled and solidified melt is treated with an ammoniacal solution of copper(II) sulfate, when copper(II) ethylenedibiguanide sulfate is precipitated. From a solution of the complex copper compound in dilute sulfuric acid copper is removed by hydrogen sulfide. The filtrate from copper(II) sulfide, on treatment with alcohol, gives crystals of the biguanide sulfate (37).

The yield obtained is, however, extremely poor. A much better result is obtained by heating a mixture of ethylenediamine hydrochloride (1 mole), dicyandiamide (2 moles), and anhydrous copper(II) sulfate (0.25 mole) at 140–145°C. with constant stirring to a perfectly homogeneous blue melt. The cooled mass is treated with slightly ammoniacal water. The rose-red silky residue of the copper compound is filtered off and decomposed with dilute sulfuric acid (1:1 v/v), when crystals of ethylenedibiguanide sulfate are obtained (22).

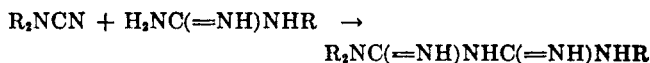
All doubts regarding the composition and constitution of ethylenedibiguanide have been finally set at rest by an analysis of the product thus prepared (22), and the previously suggested cyclic monobiguanide formulas XI (37) and XII (39) have been replaced by XIII (22).



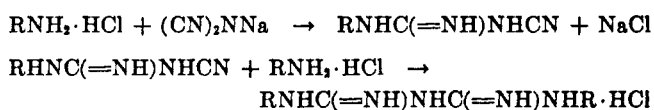
Ethylenedibiguanide, hexamethylenedibiguanide, and decamethylenedibiguanide have also been prepared as their sulfates from the corresponding amines by interaction with (*S*-ethyl)guanylylthiourea, followed by treatment with sulfuric acid (171). The reaction occurs with elimination of ethyl mercaptan.



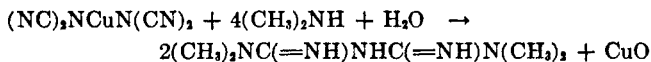
Biguanides substituted at the *N*¹- and *N*⁶-positions were prepared for the first time by the action of a dialkylcyanamide on an alkylguanidine (156).



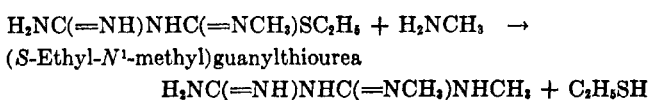
*N*¹,*N*⁶-Dimethyl- and *N*¹,*N*⁶-diallylbiguanides were prepared (170) by heating a mixture of methylamine and allylamine hydrochloride (three moles) and sodium dicyanimide at 130°C. From the solution of the cooled melt the pure biguanide was obtained through its copper compound as usual. The reaction occurs through the intermediate formation of a substituted dicyandiamide. The latter reacts with the excess of amine hydrochloride, yielding the *N*¹,*N*⁶-disubstituted biguanide. Using dimethylamine, *N*¹,*N*¹,*N*⁶,*N*⁶-tetramethylbiguanide sulfate was also synthesized by this method (170). The same product was also obtained by heating



copper dicyanimide with dimethylamine in aqueous solution in a sealed tube at 120°C. (170).

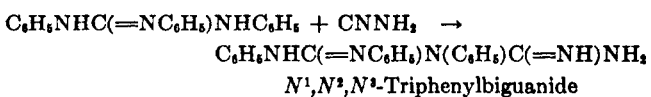


Interaction between (*S*-ethyl-*N*¹-methyl)guanylylthiourea and methylamine in aqueous solution on the water bath leads to the formation of *N*¹,*N*²-dimethylbiguanide with liberation of ethyl mercaptan.



With dimethylamine under the same conditions *N*¹,*N*¹,*N*²-trimethylbiguanide is the product formed (170).

When a benzene solution of *sym*-triphenylguanidine is mixed with an ethereal solution of cyanamide, and the mixture is evaporated over sulfuric acid in a desiccator under ordinary pressure, crystals of *N*¹,*N*²,*N*²-triphenylbiguanide separate out (170).



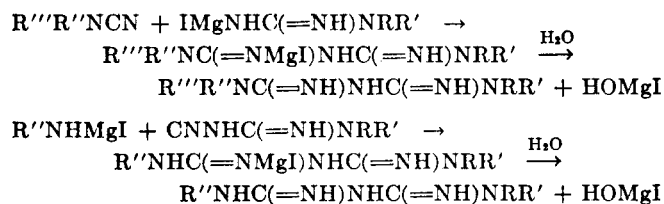
Since the discovery of the antimalarial activity of paludrine numerous substituted biguanides have been prepared and their physiological activities studied. Biguanides with alkyl or aryl substitution at the *N*¹- and *N*⁶-positions of the molecule have been synthesized by the interaction of an aryl- or alkyl dicyandiamide

either with an amine hydrochloride or with the amine in the presence of copper(II) sulfate, in boiling aqueous ethanol, dioxane, or ethoxyethanol (7, 28, 30).

A number of N^2, N^5 -dialkyl (or N^2, N^5, N^5 -trialkyl)- N^1 -arylbiguanides have also been synthesized in two different ways: (a) from mono- and dialkylamines and an N^2 -alkyl- N^1 -aryldicyandiamide and (b) from an N^1 -alkyl (or N^1, N^1 -dialkyl)- N^4 -arylguanylthiourea by desulfurization with mercuric oxide in the presence of an alkylamine (25).

A series of N^4, N^5 -dialkyl- N^1 -arylbiguanides has been similarly obtained from an N^1, N^2 -dialkyldicyandiamide and an arylamine, as well as by desulfurization of an N^1 -alkyl- N^4 -arylguanylthiourea in the presence of an alkylamine (27).

Substituted biguanides are also formed by the reaction between cyanamides and substituted guanidino-magnesium halides, as well as by that between cyanoguanidines and substituted aminomagnesium halides (18).



A biguanide derivative of an amino acid type, biguanidoacetic acid, $\text{C}_2\text{H}_6\text{N}_6\text{CH}_2\text{COOH}$, has been prepared in the form of its hydrochloride from biguanide and monochloroacetic acid in alcoholic solution. It reacts with both acids and alkalis, and forms the sodium salt, $\text{C}_4\text{H}_8\text{O}_2\text{N}_6\text{Na}$, and the hydrochloride, $\text{C}_4\text{H}_8\text{O}_2\text{N}_6 \cdot \text{HCl}$ (99). Using dimethylbiguanide the preparation of a dimethyl derivative, N^5, N^5 -dimethylbiguanide- N^1 -acetic acid, has also been reported (170).

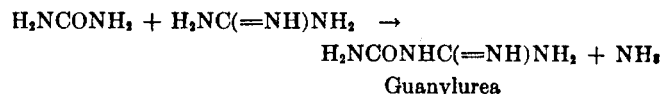
A biguanide derivative of acid amide type, oxalylbiguanide, $\text{C}_2\text{O}_2[\text{HNC(=NH)NHC(=NH)NH}]$, has been obtained by the action of ethyl oxalate on biguanide in alcoholic solution (99). It forms colorless needles and yields, when warmed with dilute hydrochloric acid, biguanidoglyoxylic acid, $\text{H}_2\text{NC(=NH)NHC(=NH)NHCOCOOH}$, m.p. 240°C . It forms a sodium salt (99). Malonylbiguanide has also been prepared in a similar manner from ethyl malonate and biguanide (99).

2. Guanylurea and substituted guanylureas

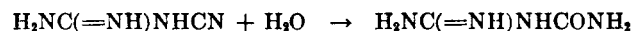
(a) Guanylurea

The formation of guanylurea from dicyandiamide by acid hydrolysis was observed as early as 1862 (68).

The preparation from urea or urethan and guanidine carbonate by fusing a mixture of the two was described several years later (5, 10). Cyanuric acid has also been used in place of urea (174).



The usual preparation of the salts of the base is, however, based on the acid hydrolysis of dicyandiamide (68, 74, 175, 183).



Commercial calcium cyanamide is generally treated with dilute sulfuric acid for the preparation of guanylurea. The cyanamide is gradually added to a solution of 33 per cent sulfuric acid. The cooled product is extracted with hot water. The filtrate is concentrated and the calcium sulfate that separates first is removed. Further concentration gives crystals of guanylurea acid sulfate, $\text{C}_2\text{H}_6\text{ON}_4 \cdot \text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$. The free base has been obtained as prismatic crystals by treating the sulfate with barium hydroxide solution (70, 175).

(b) Substituted guanylureas

Since from the nature of its composition the constitution of guanylurea is more unsymmetrical than that of biguanide, there may be many more possible isomeric modifications for a monosubstituted guanylurea than for a monosubstituted biguanide; substitution may occur here either in the guanyl or in the urea part of the molecule.

The seven methods employed for the preparation of substituted guanylureas are discussed below.

(1) *Acid hydrolysis of substituted dicyandiamides:* This method may result in the formation of N^4 -mono-substituted or N^4, N^4 -disubstituted guanylureas. The preparation of the chloride and the sulfate of phenylguanylurea from phenyldicyandiamide by heating with hydrochloric acid and sulfuric acid, respectively, serves as an illustration (30). N^1 -(*p*-Chlorophenyl)guanylurea sulfate and N^4 -(*p*-sulfamoylphenyl)guanylurea sulfate have also been prepared by this method (78).

Benzeneazodicyandiamide and its derivatives are also converted by treatment with alcoholic hydrochloric acid into arylguanylureas with elimination of nitrogen (185).

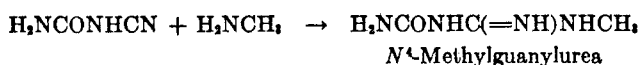
(2) *Acid hydrolysis of substituted biguanides:* Some substituted biguanides are more or less readily hydrolyzed and deaminated into the corresponding guanylureas in aqueous acid solution (26, 78). Biguanides, more or less readily susceptible to such deamination by hydrolysis leading to the formation of corresponding guanylureas, can be represented by the general formula



where $\text{R} = \text{H, Cl, or H}_2\text{NO}_2\text{S}$ (also with its hydrogen atoms partially or wholly replaced by $\text{CH}_3, \text{C}_2\text{H}_5, \text{or C}_6\text{H}_5$); $\text{R}' = \text{H, CH}_3, \text{or C}_2\text{H}_5$; and $\text{R}'' = \text{CH}_3,$

C_2H_5 , C_3H_7 , C_4H_9 , etc. Deamination occurs invariably at the carbon atom nearest to the phenyl and *p*-sulfamoylphenyl groups in particular, giving $RC_6H_4-NHCONHC(=NH)NR'R''$.

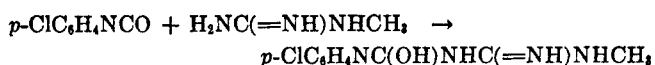
(3) *Reaction between cyanourea and amines*: N^4 -Methylguanylurea has been prepared by this method from cyanourea and methylamine by heating an alcoholic solution of the two in a sealed tube.



Dimethyl- and diphenylguanylureas have also been prepared in this manner, using dimethylamine and diphenylamine, respectively (84, 170). The preparation of N^4 -methylguanylurea by the action of ammonia on 1-cyano-3-methylurea, $CH_3NHCONHCN$, has also been described (169).

(4) *Reaction between a substituted urea or urethan and guanidine or a substituted guanidine carbonate at the melting point of the mixture*: N^1 -Phenylguanylurea, N^1 -(*p*-chlorophenyl)guanylurea, N^1 -(*p*-acetylaminophenyl)guanylurea, and N^1, N^1 -diethyl- N^4 -phenylguanylurea have been prepared by this method (79).

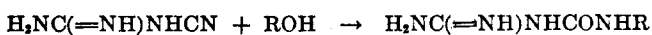
(5) *Interaction of an aryl isocyanate in acetone solution with a monoalkyl- or dialkylguanidine*: The reaction leads to the formation of N^4 -alkyl (or N^4, N^4 -dialkyl)- N^1 -arylguanylureas (26);



The only compound of the N^1 -alkyl- N^4 -arylguanylurea series prepared in a similar manner was N^4 -(*p*-chlorophenyl)- N^1 -isopropylguanylurea, which resulted from the interaction of isopropyl cyanate and *p*-chlorophenylguanidine.

(6) *Action of nitrous acid on substituted biguanides*: Arylbiguanides of the formula $XC_6H_4NHC(=NH)-NHC(=NH)NH_2$ are converted by nitrous acid into the corresponding dicyandiamide and arylguanylurea (91). Several N^4 -alkyl (or N^4, N^4 -dialkyl)- N^1 -(*p*-chlorophenyl)guanylureas have been prepared by this reaction (26). The formation of N^1 -methyl- N^1 -phenylguanylurea from N^1 -methyl- N^1 -phenylbiguanide and of piperidylguanylurea from piperidylbiguanide by the action of nitrous acid was, however, observed much earlier by Pellizzari (96).

(7) *Action of alcohol on dicyandiamide in the presence of a copper(II) salt*: This elegant and interesting method of preparing monoalkylguanylureas has been recently reported (45). The reaction is analogous to the acid hydrolysis of dicyandiamides except that the presence of a copper(II) salt in place of an acid is necessary for its occurrence.



where $R = CH_3$, C_2H_5 , $n\text{-C}_4\text{H}_9$, $iso\text{-C}_4\text{H}_9$, $iso\text{-C}_6\text{H}_{11}$, and $n\text{-C}_8\text{H}_{17}$. Evidence has also been obtained for the

formation of N^1 -(2-hydroxyethyl)-, N^1 -isopropyl-, N^1 -(2-methoxyethyl)-, and N^1 -benzylguanylureas. The term alcoholysis is probably not inappropriate for this type of reaction. The action of hydrogen ions or of copper(II) ions may be due to their capacity to enhance the reaction rate and/or to shift the equilibrium by removing the product of reaction. Copper(II) ion is more powerful than the hydrogen ion, as it can accelerate the formation of guanylurea in both aqueous and alcoholic solutions.

Among the copper salts copper(II) acetate was found to be most satisfactory. From a solution of the complex copper(II) alkylguanylurea acetate, which separates in the form of red-violet crystals on cooling the reaction mixture after reflux, the sparingly soluble sulfate is precipitated by treatment with ammonium sulfate. From a suspension of the complex sulfate in water copper is removed by hydrogen sulfide, and the filtrate on concentration and treatment with acetone gives shining snow-white crystals of the alkylguanylurea sulfate.

Stabilized diazoguanylurea compounds, having the general formula $RN_2NHC(=NH)NHCONHR'$, have also been prepared (86), where R is the nucleus of a diazo compound of the benzene series and R' is an alkylol or an alkoxyalkylol group.

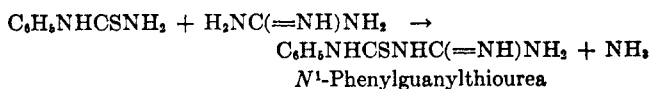
3. Guanylthiureas

Guanylthiourea was first prepared by Rathke, who obtained it by heating thiourea with thiophosgene at 100–110°C. or with phosphorus pentachloride at 100°C. (100).

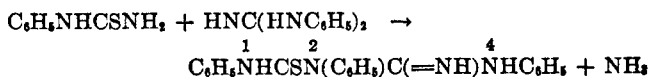
Bamberger in 1883 obtained better results by digesting dicyandiamide or a guanylurea salt with hydrogen sulfide water at 60–70°C. for several days (4). The method was, however, studied in detail much later (171).

A further modification of the method consists in heating dicyandiamide or a substituted dicyandiamide in a methanol solution of hydrogen sulfide at 78–80°C. By this method N^4 -(4-chlorophenyl)- and N^4 -(4-iodophenyl)guanylthiureas have been prepared in addition to N^4 -isopropyl- and N^4 -(*n*-butyl)guanylthiureas (17).

Phenylguanylthiourea has been prepared by heating a mixture of phenylthiourea and guanidine carbonate (3).



N^1, N^2, N^4 -Triphenylguanylthiourea was prepared by the action of phenylthiourea on diphenylguanidine in benzene solution (101).

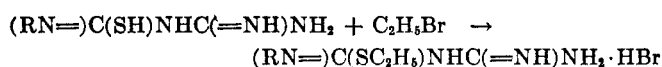


Condensation of guanidine with various alkyl and

aryl isothiocyanates in alcoholic solution gives *N*¹-alkyl(or aryl)guanylylthioureas with good yields in the aliphatic but not in the aromatic series. Salts of *N*¹-methyl-, *N*¹-ethyl-, *N*¹-propyl-, *N*¹-isobutyl-, *N*¹-allyl-, *N*¹-isoamyl-, *N*¹-phenethyl-, *N*¹-(*p*-hydroxyphenyl)-, *N*¹-(*p*-dimethylaminophenyl)guanylylthioureas, and of *p*-phenylenebisguanylylthiourea, prepared in this manner, have been described (172).



(*S*-Ethyl)guanylylthiourea bromide and (*S*-ethyl-*N*¹-methyl)guanylylthiourea bromide have also been prepared by boiling a mixture of the corresponding guanylylthiourea or its carbonate and ethyl bromide either alone or in anhydrous ethanol (170, 171).



R = H or CH₃.

C. PROPERTIES OF BIGUANIDES AND GUANYLUREAS

The properties which primarily call for attention in connection with the complex-forming capacity of ligands are their behavior as bases, acids, zwitter ions, or polar molecules. Comparatively weaker bases and weaker acids are known to form more or less strong complexes. Too strong a base readily combines with a hydrogen ion in preference to a metal ion and shows a great tendency to occur as a simple cation. Too strong an acid readily parts with its hydrogen ion to exist as a free simple anion with little tendency to share electrons with a metal ion. Too weak a base is rather averse to share electrons with a hydrogen ion or a metal ion and tends to remain more or less as a free molecule. Too weak an acid in a similar manner remains practically undissociated, with little tendency to part with its hydrogen ion for sharing electrons with a metal ion.

Biguanides and guanylureas are moderately strong bases and form well-defined salts. Many so-called acid salts of biguanides are also known, whose formation can presumably be attributed to a comparatively weak character of biguanide as a diacid base (50, 101).

Of the many known salts of biguanide some typical examples (where BH = C₂H₇N₅, a molecule of biguanide) are: the carbonate, BH·H₂CO₃, prismatic crystals, sparingly soluble in alcohol; the chlorides, BH·HCl, glistening needles, m.p. 235°C., and BH·2HCl, large plates, m.p. 248°C.; the nitrates, BH·HNO₃, glistening prisms, m.p. 192°C., and BH·2HNO₃, needles; the sulfates, BH·H₂SO₄·H₂O, rhombic crystals, and (BH)₂·H₂SO₄ (99, 101).

The use of biguanide sulfate, C₂H₇N₅·H₂SO₄·1.5H₂O, has been suggested as a primary standard for acid-base titration (103).

The free anhydrobase, C₂H₇N₅, crystallizes from absolute alcohol in glistening prisms (99).

Guanylurea generally behaves as a monacid base

and, except for its acid sulfate, forms in most cases normal salts with one equivalent of acid. The free (anhydro) guanylurea base crystallizes from alcohol in lustrous prisms, containing alcohol of crystallization; it melts at 105°C. and evolves ammonia on boiling with water (70, 175). With sulfuric acid it forms the acid salt, C₂H₆ON₄·H₂SO₄·2H₂O (175), which loses all its water at 100°C. The chloride and the nitrate have the composition C₂H₆ON₄·HCl·0.5H₂O and C₂H₆ON₄·HNO₃, respectively (5, 74).

Guanylylthiourea closely resembles guanylurea, though it is a much weaker base than the latter. Its hydrochloride, C₂H₆SN₄·HCl, readily hydrolyzes in aqueous solution, giving an acid reaction (100).

A quantitative measure of the basic character of ligands is given by the value of the dissociation constants of their conjugate acids, the protonated ligands BgH₂⁺ or BgH₃⁺⁺ as the case may be (where BgH = a molecule of any biguanide). The dissociation constants *K*_{a'} and *K*_{a''} of the first and the second protonated biguanide and its several substituted derivatives have been determined by the usual pH method (32, 106, 160, 167) and from their ultraviolet absorption spectra (54) within a certain range of pH values. The results obtained by different workers are collected in table 1.

TABLE 1

The dissociation constants of protonated ligands
*K*_{a'} = (BgH)(H⁺)/(BgH₂⁺); *K*_{a''} = (BgH₂⁺)(H⁺)/(BgH₃⁺⁺)

Substance	p <i>K</i> _{a'}	p <i>K</i> _{a''}	Temperature	Reference
			°C.	
Biguanide.....	11.5	2.9	32	(32)
	12.8	3.1	25	(54)
<i>N</i> ¹ -Methylbiguanide.....	11.4	3.0	32	(32)
<i>N</i> ¹ -Ethylbiguanide.....	11.5	3.1	32	(32)
<i>N</i> ¹ -(2-Hydroxyethyl)biguanide.....	11.5	2.8	32	(167)
<i>N</i> ¹ -(2-Methoxyethyl)biguanide.....	11.5	3.0	32	(167)
<i>N</i> ¹ -(<i>n</i> -Propyl)biguanide.....	11.35	3.1	32	(160)
<i>N</i> ¹ -(3-Hydroxypropyl)biguanide.....	11.5	3.0	32	(167)
<i>N</i> ¹ -(3-Methoxypropyl)biguanide.....	11.4	3.1	32	(167)
<i>N</i> ¹ -Isopropylbiguanide.....	11.35	3.1	32	(160)
<i>N</i> ¹ -(<i>n</i> -Butyl)biguanide.....	11.3	2.9	32	(160)
<i>N</i> ¹ -(<i>n</i> -Hexyl)biguanide.....	11.4	3.3	32	(160)
<i>N</i> ¹ -Cyclohexylbiguanide.....	11.4	3.2	32	(160)
<i>N</i> ¹ , <i>N</i> ¹ -Dimethylbiguanide.....	11.5	2.8	32	(32)
<i>N</i> ¹ , <i>N</i> ¹ -Diethylbiguanide.....	11.7	2.5	32	(32)
<i>N</i> ¹ -Phenylbiguanide.....	10.7	2.2	32	(32)
<i>N</i> ¹ -(<i>p</i> -Chlorophenyl)biguanide.....	10.4	2.2	25	(54)
<i>N</i> ¹ -Benzylbiguanide.....	11.25	2.7	32	(160)
<i>N</i> ¹ -(<i>p</i> -Tolyl)biguanide.....	11.8	2.6	32	(160)
<i>N</i> ¹ -(<i>p</i> -Phenetyl)biguanide.....	11.8	2.7	32	(160)
<i>N</i> ¹ -(1-Naphthyl)biguanide.....	10.2	2.05	32	(32)
<i>N</i> ¹ -Isopropyl- <i>N</i> ⁴ -phenylbiguanide.....	11.5	1.9	25	(54)
<i>N</i> ¹ -(<i>p</i> -Chlorophenyl)- <i>N</i> ⁴ -isopropylbiguanide.....	10.4	2.3	25	(54)
<i>N</i> ¹ -(<i>p</i> -Chlorophenyl)- <i>N</i> ⁴ -isopropylbiguanide.....	10.2	2.3	32	(106)
<i>N</i> ¹ -(<i>p</i> -Bromophenyl)- <i>N</i> ⁴ -isopropylbiguanide.....	11.4	2.2	25	(54)
<i>N</i> ¹ -(<i>p</i> -Iodophenyl)- <i>N</i> ⁴ -isopropylbiguanide.....	11.0	2.2	25	(54)
<i>N</i> ¹ -(<i>p</i> -Chlorophenyl)- <i>N</i> ⁴ -isopropyl- <i>N</i> ¹ -methylbiguanide.....	12.8	2.4	25	(54)
<i>N</i> ¹ -(<i>p</i> -Chlorophenyl)- <i>N</i> ⁴ -isopropyl- <i>N</i> ⁴ -methylbiguanide.....	11.8	2.3	25	(54)
<i>N</i> ¹ -(<i>p</i> -Chlorophenyl)- <i>N</i> ⁴ -isopropyl- <i>N</i> ⁴ -methylbiguanide.....	12.2	2.0	25	(54)

The conductivity of the free biguanide base and of its nitrate in aqueous solution within a wide range of concentration has been measured and the degree of dissociation of the base, $\text{BH}_3(\text{OH})_2 \rightleftharpoons \text{BH}_3\text{OH}^+ + \text{OH}^-$, calculated (178). The values obtained are comparable to those of barium hydroxide. The second dissociation constant of the base has also been determined by conductometric and potentiometric titration of its aqueous solution by strong acids. The mean value of the constant $K_{a''}$ for $\text{BH}_3\text{OH}^+ \rightleftharpoons \text{BH}_3^{++} + \text{OH}^-$ is given by 2.24×10^{-10} at 25°C . (178).

The dibiguanides, $\text{R}(\text{C}_2\text{H}_5\text{N}_3)_2$, can similarly give four dissociation constants, $K_{a'}$, $K_{a''}$, $K_{a'''}$, and $K_{a''''}$. The values determined for ethylene-, *m*-phenylene-, and hexamethylenedibiguanides ($\text{R} = \text{C}_2\text{H}_4$, C_6H_4 , and C_6H_{12} , respectively), are given below.

Dibiguanide	$\text{p}K_{a'}$	$\text{p}K_{a''}$	$\text{p}K_{a'''}$	$\text{p}K_{a''''}$	Temperature $^\circ\text{C}$.	Reference
<i>N</i> ¹ , <i>N</i> ¹ -Ethylenedibiguanide	11.8	11.3	2.9	1.8	32	(32)
<i>N</i> ¹ , <i>N</i> ¹ -(<i>m</i> -Phenylene)dibiguanide	11.4	9.9	2.15	1.4	32	(32)
<i>N</i> ¹ , <i>N</i> ¹ -Hexamethylenedibiguanide	11.5	10.75	3.5	2.3	32	(160)

A consideration of the dissociation constant ($K_{a'}$) values of the first protonated biguanide and its substituted products shows that their basic strengths do not differ greatly from one another except in the case of a few mono- and disubstituted biguanides containing an aryl, phenyl, or naphthyl group, in which it is appreciably lower. On the whole, biguanides are much stronger bases than ammonia ($\text{p}K_{a'} = 9.2$). They approach more or less the values for alkylamines ($\text{p}K_{a'} = 10.5$ – 11.0). Compared to alkylenediamines like ethylenediamine and propylenediamine with $\text{p}K_{a'}$ and $\text{p}K_{a''}$ values of the order of 10.0 and 7.0, respectively, biguanides are stronger as monoacid bases but considerably weaker as diacid ones, and in the latter capacity they are weaker than even aniline ($\text{p}K_{a'} = 4.43$). This is possibly related to their ampholytic character, which enables them to form inner-metallic complexes with many metallic ions (36).

Table 2 shows the $\text{p}K_{a'}$ and $\text{p}K_{a''}$ values for some guanylureas.

TABLE 2

The dissociation constants of protonated guanylureas at 32°C . $K_{a'} = (\text{GuH})(\text{H}^+)/(\text{GuH}_2^+)$; $K_{a''} = (\text{GuH}_2^+)(\text{H}^+)/(\text{GuH}_3^{++})$ (GuH = a molecule of any guanylurea)

Substance	$\text{p}K_{a'}$	$\text{p}K_{a''}$	Reference
Guanylurea	8.2	1.8	(44)
<i>N</i> ¹ -Methylguanylurea	10.4	2.9	(44)
<i>N</i> ¹ -Ethylguanylurea	11.15	3.2	(44)
<i>N</i> ¹ -Isobutylguanylurea	9.8	2.8	(44)
<i>N</i> ¹ -Isoamylguanylurea	10.3	2.9	(44)
<i>N</i> ¹ -(<i>n</i> -Hexyl)guanylurea	10.8	3.25	(44)

The $\text{p}K_{a'}$ values of guanylureas indicate that the unsubstituted simple guanylurea is a weaker base than ammonia, whereas the *N*¹-alkylguanylureas are much stronger bases and approach the biguanides in this respect.

III. METAL COMPLEXES OF BIGUANIDES AND GUANYLUREAS

A. GENERAL PROPERTIES

Biguanides and guanylureas combine with many elements of the transition series to give highly colored chelate complexes of the inner-metallic type. Both these groups of compounds function as bidentate ligands with a replaceable hydrogen atom in a potentially acidic or salt-forming imino group and also have coördinating amino groups for the chelation of metal ions. In conformity with their bidentate character the maximum number of molecules of these ligands (dibiguanides being excluded) required for the formation of a square planar complex is two; for an octahedral one it is three. Compounds containing only one molecule of the ligand in the case of divalent metals forming planar complexes, and two molecules of the ligand in the case of trivalent and tetravalent metals forming octahedral complexes, are also known. Table 3 provides a list of the known metal complexes of biguanides and table 4 lists the metal complexes of guanylureas and guanylthiourea.

It is interesting to note that *N*¹-arylguanylureas or their derivatives fail to give any colored complexes with metal ions (78).

With each type of ligand the color of the metal complex varies with the nature of the metal ion and its valency, as well as with the number of the ligand molecules in the complex. The color is also slightly modified by substitution in the ligand molecule. Table 5 gives a summary of the color of the metal complexes of biguanides and guanylureas together with the wavelengths of their absorptivity maxima and their molar absorptivity, as determined in aqueous solution at room temperature in some cases.

The infrared spectra of more than a dozen biguanide (substituted) complexes of copper(II), nickel(II), and palladium(II) in the spectral region of 2–15 microns have been published by Sadtler Research Laboratories, but their interpretation is lacking (116, 155).

In color the metal complexes of guanylurea resemble more or less closely the corresponding complexes of biguanide. The metal complexes of guanylthiourea, on the other hand, show somewhat darker colors.

The metal complexes of biguanides are comparatively more stable than those of the guanylureas (34, 44, 109, 114).

The metal complexes of these ligands are usually cationic in nature, and the anhydrobases form hy-

TABLE 3
The known metal complexes of biguanides*

Biguanide	Metal Ion											
	V ^{IV}	Cr ^{III}	Mn ^{III} and Mn ^{IV}	Co ^{II}	Co ^{III}	Ni ^{II}	Cu ^{II}	Zn ^{II}	Pd ^{II}	Ag ^{III}	Re ^V	Os ^{VI}
Biguanide	+	+	+	+	+	+	+	+	+		+	+
N ¹ -Methylbiguanide	+				+	+	+	+	+			
N ¹ -Ethylbiguanide	+				+	+	+	+	+			
N ¹ -(<i>n</i> -Propyl)biguanide						+	+					
N ¹ -Isopropylbiguanide						+	+					
N ¹ -(<i>n</i> -Butyl)biguanide						+	+					
N ¹ -(<i>n</i> -Hexyl)biguanide		+				+	+					
N ¹ ,N ¹ -Dimethylbiguanide	+					+	+		+			
N ¹ ,N ¹ -Diethylbiguanide						+	+		+			
N ¹ -(2-Hydroxyethyl)biguanide		+				+	+		+			
N ¹ -(3-Hydroxypropyl)biguanide						+	+		+			
N ¹ -(2-Hydroxypropyl)biguanide						+	+		+			
N ¹ -(2-Methoxyethyl)biguanide						+	+		+			
N ¹ -(3-Methoxypropyl)biguanide						+	+		+			
N ¹ ,N ¹ -Ethylenedibiguanide	+	+	+	+	+	+	+	+	+	+		
N ¹ N ¹ -Hexamethylenedibiguanide	+	+	+	+	+	+	+	+	+	+		
N ¹ -Phenylbiguanide		+				+	+		+			
N ¹ -Benzylbiguanide		+				+	+		+			
N ¹ -(<i>p</i> -Tolyl)biguanide						+	+		+			
N ¹ -(<i>p</i> -Phenetyl)biguanide						+	+		+			
N ¹ -(<i>p</i> -Acetylamino)phenyl)biguanide						+	+		+			
N ¹ -(4-Sulfophenyl)biguanide				+	+	+	+		+			
N ¹ -(<i>o</i> -Phenylene)biguanide				+	+	+	+	+	+			
N ¹ -(<i>p</i> -Sulfamoyl)phenyl)biguanide					+	+	+		+			
N ¹ -(1-Naphthyl)biguanide						+	+		+			
N ¹ -(2-Sulfo-1-naphthyl)biguanide					+	+	+		+			
N ¹ -Methyl-N ¹ -phenylbiguanide						+	+		+			
N ¹ ,N ⁴ -Diphenylbiguanide						+	+		+			
N ⁴ -Ethyl-N ¹ -phenylbiguanide						+	+		+			
N ⁴ ,N ⁶ -Diethyl-N ¹ -phenylbiguanide						+	+		+			
N ¹ -(<i>p</i> -Chlorophenyl)-N ⁴ -isopropylbiguanide					+	+	+		+			
N ¹ ,N ¹ -(<i>m</i> -Phenylene)dibiguanide		+		+	+	+	+		+			
N ¹ ,N ¹ -(<i>p</i> -Phenylene)dibiguanide		+				+	+		+			
Piperazinedibiguanide						+	+		+			

* Plus signs indicate the occurrence of complexes.

dioxides and salts. In most cases the solubility of the complexes of the biguanide series is comparatively less than that of the corresponding complexes of the guanylurea series (cf. Sections IV and VI). All known metal complexes of guanylthiourea, on the other hand, are practically insoluble (cf. Section VII).

TABLE 4
The known metal complexes of guanylureas*
Guanylurea = H₂NCONHC(=NH)NH₂

Guanylurea	Metal Ions					
	Cr ^{III}	Co ^{III}	Ni ^{II}	Cu ^{II}	Zn ^{II}	Pd ^{II}
Guanylurea		+	+	+	+	+
N ¹ -Methylguanylurea	+	+	+	+	+	+
N ¹ -Ethylguanylurea	+	+	+	+	+	+
N ¹ -Isopropylguanylurea			+	+		
N ¹ -(<i>n</i> -Butyl)guanylurea	+	+	+	+		+
N ¹ -Isobutylguanylurea	+	+	+	+		+
N ¹ -Isoamylguanylurea	+	+	+	+		+
N ¹ -(<i>n</i> -Hexyl)guanylurea	+	+	+	+		+
N ¹ -(2-Hydroxyethyl)-guanylurea				+		
N ¹ -Benzylguanylurea			+	+		
N ⁴ -Phenylguanylurea		+	+	+		
Guanylthiourea		+	+	+		+

* Plus signs indicate the occurrence of complexes.

The magnetic properties of the metal complexes of all these ligands are in keeping with their nature as inner-metallic penetration or lower-level complexes, except in the case of manganese(IV) biguanide and rhenium(V) biguanide complexes, which show rather anomalous magnetic behavior. The values of the magnetic moment of all the metal atoms, excepting that of rhenium(V), in these complexes agree closely with what might be expected theoretically on the basis of Pauling's valence-bond theory (92, 93; cf. Sections IV, VI, and VII).

A summary of the properties and constitution of the complex compounds of some metallic elements with biguanides and guanylureas was reported by Rây in 1955 (116).

B. STRUCTURE

Though the complex compounds of biguanide with copper(II) and nickel(II) were described more than three quarters of a century earlier (49, 71, 101, 154, 173), their structures formed a subject of controversy for a long time. The earliest interpretation was due to Tschugaeff (182) and to Ley and Müller (82).

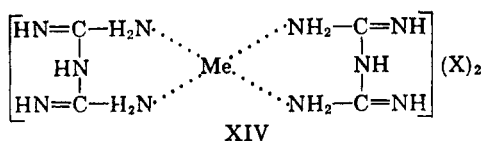
From a consideration of the complex-forming capacity of acid imides and related compounds, Tschugaeff

TABLE 5

Color and absorption of the metal complexes of biguanides and guanylureas
 $\lambda_{\max.}$ = wavelength for absorptivity maximum; ϵ = molar absorptivity

Metal	Complex with Biguanide	Complex with Guanylurea	Complex with Guanylthiourea
Vanadium(IV).....	Bluish green to light green		
Chromium(III):			
Tris complexes.....	Crimson (base); yellow (salt); $\lambda_{\max.}$ = 485 m μ ; ϵ = 102.9 (pH, 6.0) (159)	Orange-red to rose-red	
Bis complexes.....	Violet-red to rose-red; $\lambda_{\max.}$ = 490 m μ ; ϵ = 75 for diaquo complex (ClO ₄) (8a)		
Manganese(III).....	Chocolate-red (base); yellow (salt)		
Manganese(IV).....	Dark red to chocolate-red		
Cobalt(II).....	Yellow and red		Brown
Cobalt(III):			
Tris complexes.....	Dark red (base); yellow (salt); $\lambda_{\max.}$ = 480 m μ ; ϵ = 231.5 (pH, 6.0) (159)	Dark rose-red; $\lambda_{\max.}$ = 485 m μ ; ϵ = 201.7 (pH, 7.5) (48a)	Chocolate-brown
Bis complexes.....	Red to red-violet; yellow; bright green (rare)	Yellow	Scarlet-red
Nickel(II).....	Orange-yellow to yellow; $\lambda_{\max.}$ = 460-470 m μ ; ϵ = 49-67 (pH, 8) (109)	Yellow; $\lambda_{\max.}$ = 440 m μ ; ϵ = 47-55 (pH, 7.5) for alkylguanylureas (44)	Orange
Copper(II):			
Uni complexes.....	Blue; $\lambda_{\max.}$ = 660 m μ ; ϵ_1 = 35-47 (pH, 4.25) (114)	Blue; $\lambda_{\max.}$ = 660 m μ ; ϵ_1 = 32-38 at optimum pH (44)	Brown
Bis complexes.....	Rose-red; violet-red; rarely green; $\lambda_{\max.}$ = 520 m μ ; ϵ_1 = 38.5-48 (pH, 7) (114)	Red-violet; $\lambda_{\max.}$ = 540 m μ ; ϵ_1 = 38-43 (pH, 7.5) (44)	
Zinc.....	White	White	
Palladium(II).....	Light yellow	Light yellow	Crimson (base); chocolate (salt)
Silver(III).....	Orange-red to purple-red with ethylenedibiguanide only		
Rhenium(V).....	Rose-violet (base); brownish yellow (salts)		
Osmium(VI).....	Yellow		

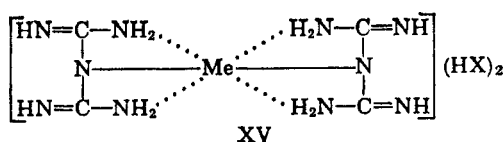
(182) represented the metal biguanides as coordination complexes having the structure shown in formula XIV. This formula, however, does not represent the complex as an inner-metallic salt and can neither ac-



Me = Cu or Ni; X = a univalent anion.

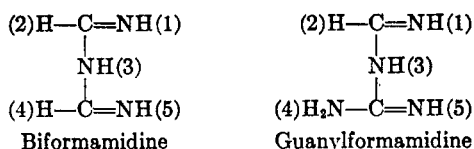
count for the formation of the complex anhydrobases of the composition $\text{Me}^{\text{II}}(\text{C}_2\text{H}_6\text{N}_6)_2$ or $\text{Me}^{\text{III}}(\text{C}_2\text{H}_6\text{N}_6)_3$, nor for the great stability of the metal complexes of biguanides, as shown by later workers (116, 146).

Ley and Müller (82) formulated the metal complexes of biguanides as inner-metallic salts and represented them by structure XV, in which the metal atom replaces the hydrogen of the central imino group of the biguanide molecule and simultaneously coordinates with the nitrogen atoms of the two amino groups at the end. The structure was suggested by the analogous behavior of acid



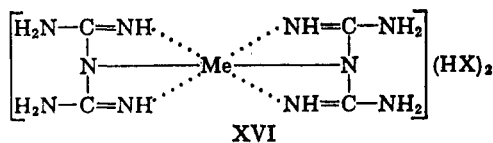
imides in forming metal complexes of similar character, particularly by the observation of the authors that bi-

formamide and guanylformamide retain their complex-forming power even when substituted by phenyl groups at positions 2, 4, and 5.



In the structure suggested by Ley and Müller each biguanide molecule functions as a tridentate ligand, giving rise to a rather unlikely pair of adjacent four-membered rings. Besides, the formation of octahedral biguanide complexes of cobalt(III) and chromium(III) of the composition $[\text{Me}(\text{C}_2\text{H}_7\text{N}_6)]^{3+}$, as described by later workers (128, 146), cannot be accounted for except on the basis of the bidentate character of the ligand.

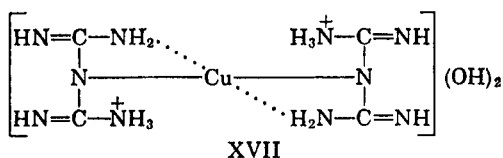
A somewhat similar structure (XVI) for the metal complexes of biguanides was advanced by Slotta and Tschesche (170). From the facts that the complex-



forming capacity of the biguanide is not affected by substitution in position 1 or 5, or in both the 1- and

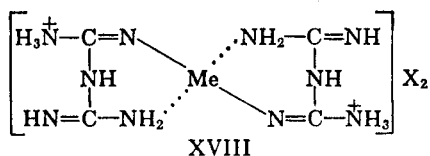
the 5-position of its molecule, while this is completely inhibited by simultaneous substitution in positions 1, 2, and 3 of the molecule, the authors concluded that in metal complexes of biguanides the hydrogen atom of the central imino group of the biguanide molecule is replaced by the metal atom, to which the nitrogen atoms of the other two imino groups are linked by auxiliary valency. The structure, however, suffers from the same defects as those of Ley and Müller's formula, and in addition has the potential capacity to make the molecule behave as a cation of valency higher than what is actually observed.

Traube and Glaubitt (180) from a study of the solubility of copper(II) hydroxide in solutions of guanylurea and biguanide came to a similar conclusion and suggested structure XVII for the copper(II) biguanide complex.

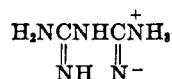


As in the previous two cases the authors assume the formation of four-membered rings, which, as is well known, is not likely to give rise to a stable complex like copper(II) biguanide.

A study of the preparation and properties of the chromium(III) tris(biguanide) complexes led Ray and Saha (146) to suggest structure XVIII for the metal complexes of these biguanides, where Me =



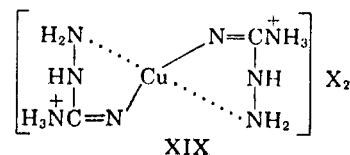
a bivalent metal atom; for a trivalent metal mostly three biguanide molecules are thus linked to one and the same metal atom. In this structure the hydrogen atom of an imino (=NH) group in each biguanide molecule is replaced by the metal atom and one of the two amino groups is linked to the metal atom by a coordinate bond, thus forming a six-membered ring. The other amino group of each biguanide molecule acts as a basic group and can combine with water or acids to form a complex base or its salts. It might also be assumed that the biguanide molecule reacts in its tautomeric zwitter-ion form (36) with the metal ion.



The cationic complexes of such chelating ligands have been termed inner-metallic salts of the third order (132).

Several evidences have been advanced in favor of

structure XVIII: (1) The cationic copper(II) complexes of aminoguanidine, described by Thiele (179), have been



assigned structure XIX. A similar structure might, therefore, be assigned to the biguanide complexes (146).

(2) The formation of copper(II) complexes by *N*¹-(*p*-chlorophenyl)-*N*⁵,*N*⁶-diethyl-*N*¹-methylbiguanide (31, 116) provides evidence for the replacement of a hydrogen atom in one of the imino (=NH) groups of the biguanide molecule by the copper atom. The central imino (—NH—) group is considered unreactive for this purpose, as it cannot give rise to a stable ring.

(3) The reaction of complex chromium(III) and cobalt(III) biguanide bases with mercury(II) chloride in aqueous solution, giving rise to sparingly soluble compounds of the composition, Cr($\bar{\text{B}}\text{HgCl}$)₃ and Co($\bar{\text{B}}\text{HgCl}$)₃·HgCl₂ (150), where $\bar{\text{B}}$ = C₂H₅N₅, furnishes evidence regarding the presence of only one free amino (—NH₂) group in each biguanide molecule bound to the metal atom. On the other hand, the formation of sparingly soluble compounds of the infusible white precipitate type of the composition $\bar{\text{B}}(\text{HgCl})_2$ from the free biguanide base and mercury(II) chloride suggests the reactivity of both the amino groups in a biguanide molecule. Furthermore, the fact that cobalt(III) tris(ethylenediamine) fails to react in a similar manner with mercury(II) chloride is regarded as evidence for the inertness of bound —NH₂ groups (150).

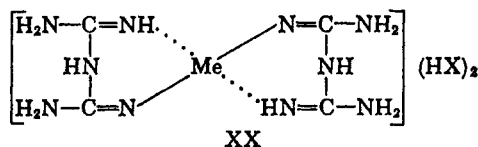
(4) The formation of cobalt(III) biguanide silver hydroxide, Co($\bar{\text{B}}\text{-AgOH}$)₃·aq, where $\bar{\text{B}}$ = C₂H₅N₅, provides another instance in support of this conclusion (150).

(5) A considerably higher molecular rotation (± 2100° approx.) of optically active enantiomers of complex cobalt(III) tris(biguanide) salts, [Co(BH)₃]₃X₃, as against that of the enantiomers of cobalt(III) tris(ethylenediamine) salts (± 600° approx.), is believed to furnish evidence of a much lower order of symmetry in the molecule of the former, due presumably to an unsymmetrical bonding of the symmetrical biguanide molecule in the complex (129).

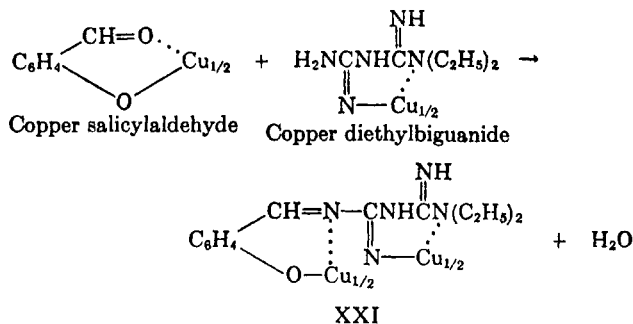
(6) A structural formula similar to XVIII for the biguanide complexes of bivalent metals has also been suggested by Stumpf (176, 181).

An alternative structure (XX) has been suggested by Curd and Rose (29) on the basis of a symmetrical disposition of the biguanide molecules in a planar structure in its copper(II) complex by analogy with copper(II) phthalocyanine. But this would make the complex cation with four free amino groups show a higher valency than that which is actually observed.

For the same reason a complex chromium(III) or cobalt(III) biguanide base of this structure would react with a much larger number of mercury(II) chloride molecules than is found in the products actually isolated (150).



In metal complexes of biguanide substituted at N^1 - and/or N^5 -positions it has been assumed that the comparatively less basic of the two groups in those positions coordinates with the metal atom. Thus salts of metal complexes of phenylbiguanide behave more or less as ammonium salts and not like those of aniline. This indicates the presence of a free amino ($-\text{NH}_2$) group of each biguanide molecule occurring in the complex, for salt formation (136). Further support to this assumption has been derived from a study of the reaction of copper(II) N^1, N^1 -diethylbiguanide, which might otherwise exist in two isomeric forms owing to a difference in the disposition of metal-ligand bonds. A solution of this complex copper(II) base in methanol, when heated with a solution of copper(II) salicylaldehyde in the same solvent, gives a sand-colored crystalline precipitate having the composition and structure shown in formula XXI (116, 137).

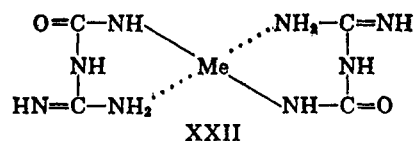


The slow decomposition of the complex copper(II) N^1, N^1 -diethylbiguanide salts in aqueous solution with separation of copper(II) oxide, indicating the weakness of the copper-nitrogen coordination bond, is also in favor of the assumption that this bond links the metal with the nitrogen atom of the $-\text{N}(\text{CH}_3)_2$ group (116, 137).

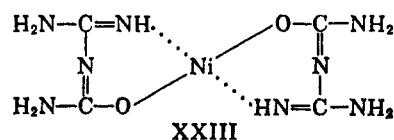
In view of the close resemblance in properties of the metal complexes of biguanide and guanylurea, a similar structure may be assigned to both.

Tschugaeff (182), on the basis of Schiff's investigation of the metal complexes of biurets, represented the metal complexes of guanylurea by structure XXII (where Me = a divalent metal) and suggested a similar formula also for the biguanide complexes (cf. formula XIV).

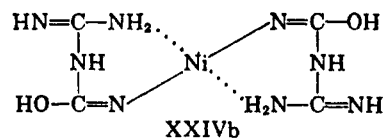
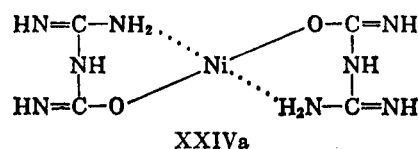
A configuration represented by formula XXIII



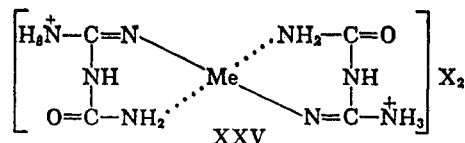
was given to nickel(II) guanylurea by Weinland (186), assuming a tautomeric structure of the ligand.



Dumont (41) has, however, proposed structures XXIVa and XXIVb for nickel(II) guanylurea complexes.



Rāy and Bandopadhyay (118), by analogy with the structure (XVIII) of metal complexes of biguanide proposed by Rāy and Saha (146), have represented the constitution of metal complexes of guanylureas by formula XXV (in which Me = a divalent metal).



A very close resemblance in the absorption spectra of the corresponding biguanide and guanylurea complexes of metals like copper(II), nickel(II), cobalt(III), etc., speaks strongly in support of this view (cf. table 5 and Sections V and VIII).

The structural analogy of the cobalt(III) biguanide complex to that of biuret has also been deduced in a similar manner by Kato (75) from a similarity of their absorption curves.

Slotta and Tschesche (170) observed that guanylurea substituted at the N^1 - or N^4 -position by a methyl group loses its complex-forming character. This could not, however, be confirmed by Dutta and Rāy (46, 47), who have described a large number of metal complexes of methylguanylurea and of other alkylguanylureas.

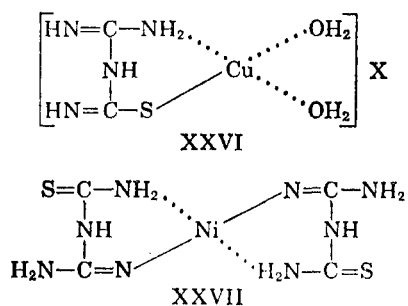
On the other hand, Kundu and Rāy (78, 116) have shown that substituted guanylureas having a phenyl group or a derivative thereof at the N^1 -position, i.e., adjacent to the $-\text{CO}-$ group, lose their complex-forming power altogether. A possible explanation of

this behavior has been suggested by the authors (78) on the assumption that the N^1 -atom, being situated between the two electron-attracting groups, carbonyl and phenyl, loses much of its basic (coördinating) character.

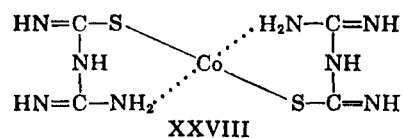
Metal complexes of guanylthiourea differ in certain cases from those of guanylurea in their color and other properties. It is believed that this ligand can react in either of its tautomeric forms (A or B) to give rise to inner-metallic complexes of different structures, depending upon the nature of the metal (97, 126).



The copper(II) complex of the ligand is brown, while that of nickel(II) is orange, resembling the complexes of nickel(II) guanylurea and nickel(II) biguanide. The brown color of the copper(II) complex suggests the presence of a copper-sulfur bond, which accounts for the rapid decomposition of the complex into copper sulfide on warming with dilute acid or alkali solution. The nickel complex, on the other hand, is unaffected by boiling alkali solution. Furthermore, while the copper complex contains only one molecule of guanylthiourea per copper atom, the nickel atom combines as usual with two molecules of the ligand. Their structures are, therefore, represented by formulas XXVI and XXVII, where $X = \text{OH}$ or $\frac{1}{2}\text{SO}_4$.



Both cobalt(II) and cobalt(III) guanylthioureas, having the composition $\text{Co}(\text{C}_2\text{H}_6\text{SN}_4)_2 \cdot 3\text{H}_2\text{O}$ and $\text{Co}(\text{C}_2\text{H}_6\text{SN}_4)_3 \cdot 3\text{H}_2\text{O}$, respectively, are brown, and are decomposed by warm alkali with the formation of black cobalt sulfide. This suggests the presence of a cobalt-sulfur bond in these molecules. The structure of the cobalt(II) complex, for instance, is represented by formula XXVIII. The palladium(II) complex behaves like the cobalt(II) complex and, unlike that of nickel(II), is believed to contain metal-sulfur bonds (97).



IV. METAL COMPLEXES OF BIGUANIDES

A. COPPER(II) BIGUANIDES

The earliest observation about the formation of copper(II) biguanide complexes was made by Rathke (101), who prepared the copper base and its sulfate. Subsequently a large number of other salts, as well as copper(II) complexes of many substituted biguanides, have been described. In all these compounds a copper(II) ion is associated with two units of the ligand forming the complex. They are, therefore, named copper(II) bis(biguanide) complexes. They form red or rose-red crystals.

But copper has also been found to form 4-covalent complexes containing only one unit of the ligand bound to a copper(II) ion. In a few instances they have been found to give rise to a binuclear configuration. All the unibiguanide copper(II) complexes are blue or dark blue in color (33, 162).

Copper(II) dibiguanide complexes, containing only one unit of the ligand per copper(II) ion, like the bis(biguanide) complexes, are red or rose-red in color (cf. table 10).

1. Bis(biguanide) complexes

The composition of the copper(II) bis(biguanide) complexes can be represented by the general formulas $[\text{Cu}(\text{Bg})_2]$ and $[\text{Cu}(\text{BgH})_2]\text{X}_2$, where BgH = a molecule of biguanide or substituted biguanide and X = OH or any univalent anion or an equivalent of any polyvalent anion. They all form red, rose-red, or red-violet crystals. The sulfates, as a rule, are sparingly soluble in water. Most of the complex bases behave in a similar manner. They are all paramagnetic with a moment value of 1.73–1.84 Bohr magnetons, as expected (149, 163). The value is lower than that of the simple copper(II) ion of 1.9–2.2 Bohr magnetons, indicating a square planar configuration with dsp^2 hybrid bonds (149). Measurements of equivalent conductivities of some of these copper(II) bis(biguanide) salts (117, 122) and of their molecular weights in isolated cases (117, 122) demonstrate the bipoisitive character of the complex copper(II) bis(biguanide) ion. They are all decomposed by acids, but are more or less stable toward alkalis.

The complex bis(biguanide) hydroxides are generally prepared by the action of an ammoniacal copper(II) salt solution on an alkaline solution of the biguanide sulfate concerned. The anhydrobase, $\text{Cu}(\text{Bg})_2$, is formed from the hydroxide at 110°C . with loss of water. A few complex bases, which are extremely soluble in water, are prepared from their sulfates by the action of barium hydroxide solution (162). The salts are usually prepared by heating the complex bases with solutions of ammonium salts at 60 – 70°C . for some time on the water bath, or by treating

TABLE 6

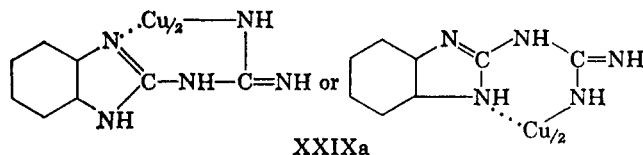
The known copper(II) bis(biguanide) complexes
 BH = a molecule of biguanide; B'H = a molecule of a substituted biguanide

Ligand	Complex ^(a)	References
Biguanide..... C ₂ H ₇ N ₃	[Cu(B) ₂], [Cu(BH) ₂]X ₂ X = OH, F (4), Cl (2), Br (2), I (3), SCN, NO ₃ (1), NO ₂ (2), H ₂ PO ₄ (2), ‡CO ₃ (4), ‡SO ₃ (4), ‡SO ₄ (3), ‡S ₂ O ₃ (3), ‡S ₂ O ₄ (2), ‡CrO ₄ (3) X = ‡M ₂ O ₄ (4) Equivalent conductivity for the chloride at 35°C.: Λ _∞ = 144.6 mhos	(2, 71, 101, 117, 151, 181)
N ¹ -Methylbiguanide..... CH ₃ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = OH (1.5), Cl (2.5), ‡SO ₄	(35, 154)
N ¹ -Ethylbiguanide..... C ₂ H ₅ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = Cl (0.5), ‡SO ₄	(35, 49)
N ¹ -(n-Propyl)biguanide..... C ₃ H ₇ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = Cl (2.5), ‡SO ₄	(159)
N ¹ -Isopropylbiguanide..... C ₃ H ₇ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = ‡SO ₄ (0.5)	(159)
N ¹ -(n-Butyl)biguanide..... C ₄ H ₉ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = OH (0.5), Cl (1.5), ‡SO ₄	(159)
N ¹ -(n-Hexyl)biguanide..... C ₆ H ₁₃ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = OH, Cl (2), NO ₃ (4), ‡SO ₄ (2)	(42)
N ¹ -(2-Hydroxyethyl)biguanide..... HOCH ₂ CH ₂ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = OH (2.5), Cl (2), Br (0.5), I (2.5), NO ₃ (3.5), NO ₂ (2), CH ₃ COO (4.5), ‡CO ₃ (2), ‡SO ₄ (5), ‡S ₂ O ₃ (1), ‡S ₂ O ₄ (1), ‡HPO ₄ (2.5), ‡HA ₂ O ₄ (4), ‡CrO ₄ (3) The base is highly soluble in water.	(162)
N ¹ -(3-Hydroxypropyl)biguanide..... HOC ₂ H ₄ C ₃ H ₆ N ₃	[Cu(B') ₂]·0.5H ₂ O, [Cu(B'H) ₂]X ₂ X = Cl, NO ₃ (2), ‡SO ₄ (4), ‡S ₂ O ₃ (3), ‡S ₂ O ₄ (1), ‡CrO ₄ (4), ‡HPO ₄ (3.5) The base is highly soluble in water.	(162)
N ¹ -(2-Hydroxypropyl)biguanide..... HOC ₂ H ₄ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH (4), Cl (3), Br (1.5), I (2), NO ₃ (5), NO ₂ (4), ‡CO ₃ (4), ‡SO ₄ (3), ‡S ₂ O ₃ (3), ‡S ₂ O ₄ (1), ‡CrO ₄ (3), ‡HPO ₄ (3) The base is highly soluble in water.	(162)
N ¹ -(2-Methoxyethyl)biguanide..... CH ₃ OC ₂ H ₄ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH (0.5), Cl (0.5), NO ₃ (1.5), ‡SO ₄ (1) The base is highly soluble in water.	(162)
N ¹ -(3-Methoxypropyl)biguanide..... CH ₃ OC ₃ H ₆ C ₃ H ₆ N ₃	[Cu(B') ₂]·0.5H ₂ O, [Cu(B'H) ₂]X ₂ X = Cl, NO ₃ (1), ‡SO ₄ (0.5) The base is sparingly soluble in water.	(162)
N ¹ -(2-Sulfoethyl)biguanide..... HO ₂ SC ₂ H ₄ C ₃ H ₆ N ₃	[Cu(B') ₂]·2.5H ₂ O; loses all water at 100°C.	(159)
N ¹ ,N ¹ -Dimethylbiguanide..... (CH ₃) ₂ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = Cl (2.5), ‡SO ₄	(35)
N ¹ ,N ¹ -Diethylbiguanide..... (C ₂ H ₅) ₂ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = Cl (1.5), Br, I, NO ₃ , ‡SO ₄ (3) X ₂ = OH, Cl (1) Salts mostly decompose in aqueous solution with separation of copper(II) oxide.	(35, 137)
N ¹ -Phenylbiguanide..... C ₆ H ₅ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = OH, Cl (6, 3), Br (2), I (2), SCN (1), NO ₃ (1), NO ₂ (1), ClO ₄ , BrO ₃ , IO ₃ , ‡SO ₄ (4, 5), ‡S ₂ O ₃ (2), ‡S ₂ O ₄ (1, 0), ‡CrO ₄ (1) [Cu(B') ₂]·H ₂ O, [Cu(B'H) ₂]SO ₄ ·2H ₂ O	(122, 173)
o-Phenylenebiguanide..... C ₆ H ₄ C ₃ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = Cl (1.5), Br (2.5), I (2), NO ₃ (1.5), NO ₂ (2), ‡SO ₄ (3), ‡S ₂ O ₄ (1.5), ‡CrO ₄ (3)	(39)
N ¹ -Benzylbiguanide..... C ₆ H ₅ CH ₂ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B'H) ₂]X ₂ X = OH, Cl (5), Br, I, NO ₃ (1), ‡SO ₄	(108)
N ¹ -(p-Tolyl)biguanide..... p-CH ₃ C ₆ H ₄ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH, Cl (5), Br, I, NO ₃ (1), ‡SO ₄	(87)
N ¹ -(p-Phenetyl)biguanide..... p-C ₂ H ₅ OC ₆ H ₄ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH (3), Cl (4.5), Br (2), I, ‡SO ₄	(55)
N ¹ -(p-Acetylamino)phenylbiguanide..... p-CH ₃ CONHC ₆ H ₄ C ₃ H ₆ N ₃	[Cu(B') ₂]·0.5H ₂ O, [Cu(B'H) ₂]X ₂ X = Cl (4), ‡SO ₄ (4)	(134)
N ¹ -(4-Sulfo)phenylbiguanide..... 4-HO ₂ SC ₆ H ₄ C ₃ H ₆ N ₃	[Cu(B') ₂]·H ₂ O (also with 1.5 H ₂ O), soluble in alkalis [Cu(B') ₂]K ₂ ·H ₂ O or [Cu(B') ₂]Na ₂ ·2.5H ₂ O, where B'H = B'	(132, 153)
N ¹ -(p-Sulfamoyl)phenylbiguanide..... p-H ₂ NO ₂ SC ₆ H ₄ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH (4), Cl (1.5), ‡SO ₄ (1.5)	(159)
N ¹ -Methyl-N ¹ -phenylbiguanide..... C ₆ H ₅ (CH ₃)C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH, Cl (1), Br (1), I (4), NO ₃ , ‡SO ₄ (4)	(58)
N ¹ -(1-Naphthyl)biguanide..... C ₁₀ H ₇ C ₃ H ₆ N ₃	[Cu(B') ₂], [Cu(B') ₂]·H ₂ O, [Cu(B'H) ₂]X ₂ X = Cl (1.5), Br (1), I, SCN, NO ₃ , ‡CO, ‡SO ₄ (7), ‡S ₂ O ₃ (2), ‡S ₂ O ₄ (2)	(144)
N ¹ -(2-Sulfo-1-naphthyl)biguanide..... HO ₂ SC ₁₀ H ₇ C ₃ H ₆ N ₃	[Cu(B') ₂], soluble in alkalis [Cu(B') ₂]K ₂ ·4H ₂ O or [Cu(B') ₂]Na ₂ ·5H ₂ O, where B'H = B'	(132)
N ¹ ,N ¹ -Diphenylbiguanide..... (C ₆ H ₅) ₂ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = OH (2), Cl (1.5), ‡SO ₄ (1)	(96)
N ¹ -Ethyl-N ¹ -phenylbiguanide..... C ₆ H ₅ (C ₂ H ₅)C ₃ H ₆ N ₃	[Cu(B'H) ₂](OH) ₂ ·H ₂ O	(98)
N ¹ -(p-Chlorophenyl)-N ¹ -isopropylbiguanide..... p-ClC ₆ H ₄ (C ₃ H ₇)C ₃ H ₆ N ₃	[Cu(B'H) ₂](OH) ₂ ·0.5H ₂ O	(104)
N ¹ ,N ¹ -Diethyl-N ¹ -phenylbiguanide..... C ₆ H ₅ (C ₂ H ₅) ₂ C ₃ H ₆ N ₃	[Cu(B'H) ₂]X ₂ X = Cl (3), ‡SO ₄ (1)	(98)

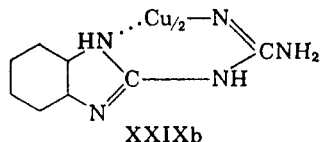
(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

the complex bases with an adequate amount of dilute acids. The insoluble complex sulfates are obtained directly by the addition of an ammoniacal copper(II) sulfate solution to that of the biguanide sulfate or chloride. Many salts, which are sparingly soluble in water, have been prepared by double decomposition from the complex chloride and the corresponding alkali salt in aqueous solution. Table 6 furnishes a list of the known copper(II) bis(biguanide) complexes.

The copper(II) complex of *o*-phenylenebiguanide has been represented by structure XXIXa, differing from that of other bis(biguanide) complexes, in view of the unusual constitution of the ligand itself (39).



The constitution of the complex is, however, better represented by structure XXIXb, in conformity with that of the biguanide complexes in general. The complex copper(II) base is olive-brown and its sulfate is green (39). The ligand, therefore, behaves



more like an iminazole than a biguanide derivative.

Polyhalides of copper(II) bis(biguanide) complexes

A number of sparingly soluble or insoluble copper(II) bis(biguanide) polyhalides have been prepared by reaction between the solution of a copper(II) bis(biguanide) halide and that of iodine in potassium chloride, potassium bromide, or potassium iodide, as the case may be, using either of the solutions in excess. Many of these compounds are iridescent and show the

phenomenon of dichroism with metallic luster (119). Their composition and properties are given in table 7.

Two different modifications of some copper(II) bis(biguanide) complexes

Copper(II) bis(phenylbiguanide) base and many of its salts have been found to occur in two forms, α and β , differing in color, melting point, and solubility (122). The phenomenon is believed to be due either to a difference in the crystal form or to the occurrence of isomerism in a planar structure, owing to the unsymmetrical nature of the ligand. The view that the two varieties are related as *cis* (α) and *trans* (β) isomers has, however, been preferred (122). Their properties are summarized in table 8.

Copper(II) bis(1-naphthylbiguanide) dichloride, $[\text{Cu}(\text{C}_{10}\text{H}_7\text{C}_2\text{H}_4\text{N}_5)_2]\text{Cl}_2$, has been obtained in two differently colored crystals, chocolate-red and blue-violet. In aqueous solution, however, both give a light red color (144).

Copper(II) bis[N^1 -(4-sulfophenyl)biguanide] has also been found to occur in two forms, red-violet and green (132, 153). The red form changes to the green variety on digestion with hot concentrated ammonia solution. The red variety contains one molecule of water and the green form contains 1.5 H_2O per molecule. Both show the identical magnetic moment value of 1.84 Bohr magnetons (132).

Two different modifications, red and blue, of copper(II) bis[N^1 -(*p*-chlorophenyl)- N^5 -isopropylbiguanide] have been reported. Both the compounds are soluble in alcohol, but sparingly soluble in water. The blue variety changes into the red form when heated in alcoholic solution (102).

Two varieties of copper(II) bis(N^1,N^1 -diethylbiguanide), red and blue-violet (137), are also known; they are sparingly soluble in water but dissolve readily in methanol, ethanol, and acetone. The red variety melts at 199–200°C. and slowly changes into the blue-

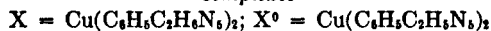
TABLE 7

Polyhalides of copper(II) bis(biguanide) complexes
 $\text{X} = \text{Cu}(\text{C}_2\text{H}_7\text{N}_5)_2$

	Compound	Method of Preparation	Properties
1.	$[\text{X}]\text{I}_2 \cdot [\text{X}]\text{Cl}_{12} \cdot 2\text{H}_2\text{O}$	$[\text{X}]\text{Cl}_2$ in excess and iodine in potassium iodide	Dark red, silky crystals; slowly loses iodine on keeping
2.	$[\text{X}]\text{I}_2 \cdot [\text{X}]\text{Br}_{12}$	$[\text{X}]\text{Br}_2$ in excess and iodine in potassium iodide; or $[\text{X}]\text{I}_2$ and an excess of iodine in potassium bromide	Bright red, needle-shaped crystals; slowly loses iodine on keeping; isomeric with compound No. 5
3.	$[\text{X}]\text{I}_2 \cdot 2\text{H}_2\text{O}$; also with $3\text{H}_2\text{O}$	$[\text{X}]\text{I}_2$ and iodine in potassium iodide; $[\text{X}]\text{Cl}_2$ or $[\text{X}]\text{Br}_2$ and an excess of iodine in potassium iodide	Dark green, needle-shaped crystals
4.	$[\text{X}]\text{Br}_2 \cdot [\text{X}]\text{Br}_{12} \cdot 5.5\text{H}_2\text{O}$; also with $2\text{H}_2\text{O}$	$[\text{X}]\text{Cl}_2$ or $[\text{X}]\text{Br}_2$ and iodine in potassium bromide	Yellowish red, silky crystals
5.	$[\text{X}]\text{Br}_2 \cdot [\text{X}]\text{I}_2$	$[\text{X}]\text{I}_2$ and an excess of iodine in potassium bromide	Green, needle-shaped, silky crystals; changes readily to compound No. 2; a case of either dimorphism or isomerism due to the transfer of a molecule of iodine from I_2 to bromide ion
6.	$[\text{X}]\text{Cl}_2 \cdot [\text{X}]\text{Cl}_{12} \cdot 4\text{H}_2\text{O}$	$[\text{X}]\text{Cl}_2$ in excess and iodine in potassium chloride; $[\text{X}]\text{Cl}_2$ or $[\text{X}]\text{Br}_2$ and an excess of iodine in potassium chloride	Greenish black crystals changing readily to a yellowish brown, granular product of identical composition; dimorphous; does not lose more than 35 per cent of iodine even at 140°C.

TABLE 8

Properties of the α - and β -forms of copper(II) bis(biguanide) complexes



Compound	Properties	
	α -Form	β -Form
[X](OH),	Light pink crystals; insoluble in water; changes into the β -form when moist	Dark red crystals; insoluble in water
[X ⁰],	Light pink; soluble in methanol, ethanol, and acetone; insoluble in chloroform or benzene; melts 155°C. (d.); molecular weight (by boiling point in methanol) = 382.3; calculated value, 415.5	Dark red crystals; more soluble in alcohol and acetone than the α -form; melting point 165°C.; molecular weight = 382
[X]Cl ₂ ,	Contains 6 H ₂ O; blue-violet crystals; solubility (28°C.) = 2.1088 g. per 100 g. of solution; changes to the β -form on rapid heating at 102–103°C.; in contact with water changes to the β -form after several days; loses all water without change on slow heating and melts at 170°C. (d.); presence of moisture is necessary for transformation; equivalent conductivity, Λ_{∞} (28°C.) = 117.9 mhos; degree of dissociation (cryoscopic) = 0.7	Contains 3 H ₂ O; red crystals; solubility (28°C.) = 1.6055 g. per 100 g. of solution; melting point 210°C.; Λ_{∞} (28°C.) = 117.5 mhos; degree of dissociation (cryoscopic) = 0.9
[X]Br ₂ ·2H ₂ O,	Light pink crystals; solubility (28°C.) = 1.71 g. per 100 g. of solution; gradually changes to the β -form in the presence of moisture	Deep rose-red crystals; solubility (28°C.) = 1.55 g. per 100 g. of solution
[X]I ₂ ·2H ₂ O,	Light pink crystals; sparingly soluble in water; changes to the β -form on digestion with boiling water	Brown crystals; difficultly soluble in water
[X](NO ₃) ₂ ,	Violet crystals; solubility (28°C.) = 0.4988 g. per 100 g. of solution; gradually changes to the β -form in contact with water; Λ_{∞} (28°C.) = 110.5 mhos	Red crystals; contains 1 H ₂ O; solubility (28°C.) = 0.2923 g. per 100 g. of solution
[X](NO ₃) ₂ ,	Red-violet crystals; contains 1 H ₂ O; solubility (28°C.) = 0.096 g. per 100 g. of solution; changes into the β -form rapidly in the presence of moisture	Dark violet crystals; solubility (28°C.) = 0.0457 g. per 100 g. of solution
[X] ₂ SO ₄ ,	Contains 4 H ₂ O; sparingly soluble pink crystals; changes rapidly into the β -form when heated with water	Contains 5 H ₂ O; sparingly soluble, violet-red crystals
[X] ₂ S ₂ O ₈ ,	Pink crystals; sparingly soluble in water; changes readily to the β -form when heated with water	Red crystals; sparingly soluble in water; contains 1 H ₂ O

violet form when kept in contact with water. The blue-violet variety, on the other hand, changes into the red form when heated at 160–162°C. Both show the same magnetic moment value of 1.68 Bohr magnetons (137).

Copper(II) bis(biguanide) complexes in analytical work

Precipitation of copper(II) bis(biguanide) sulfate from solution has been employed for the estimation of copper on both the macro and the semimicro scale

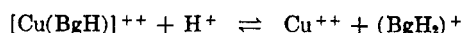
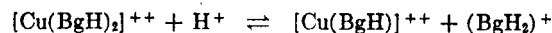
(145). The precipitate formed in the cold (10°C.) is dried at 50–60°C. and weighed as $[\text{Cu}(\text{C}_2\text{H}_7\text{N}_6)_2]\text{SO}_4 \cdot 3\text{H}_2\text{O}$. Zinc, cadmium, magnesium, alkali metals, molybdate, and tungstate do not interfere. Nitrates and an excess of ammonium salts should be absent. The method has also been employed for the volumetric estimation of copper, using rubeanic acid as an external indicator (145).

Copper(II) bis(biguanide) chloride has been used as a reagent for the estimation of mercury by precipitating it from cold (15–20°C.) neutral solutions containing potassium iodide. The precipitate is dried at 105°C. and weighed as $[\text{Cu}(\text{C}_2\text{H}_7\text{N}_6)_2]\text{HgI}_4$. Many cations and anions interfere. Good results are obtained only by careful observance of specified conditions (12).

2. Unibiguanide complexes

(a) Mononuclear

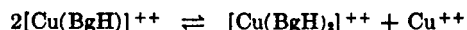
The observation that the red-violet color of the copper(II) bis(biguanide) complexes in aqueous solution changes gradually to deep blue with progressive addition of acid has led to the isolation of unibiguanide copper(II) complexes (33). The color change has been explained on the basis of stepwise decomposition:



BgH = a molecule of any biguanide.

The unibiguanide complexes are, therefore, stable in acid solutions only within a certain limit and are decomposed by excess acid. The coordination number of the copper(II) atom is satisfied finally by water molecules, anions, or other ligands, as the case may be. Formation of unibiguanide copper(II) complexes by mixing equimolecular proportions of copper(II) bis(biguanide) chloride and copper(II) chloride in aqueous solution has also been demonstrated from a study of their absorption spectra (33, 114).

The general method of preparing unibiguanide copper complexes consists in treating a solution of the copper bis(biguanide) salt, either alone or previously mixed with an equimolecular quantity of the corresponding copper(II) salt, with a dilute acid having the same anion, until the color of the solution becomes deep blue at about pH 3.5–4.5. The crystals obtained on cooling can be recrystallized from very dilute acid solution (pH, 3.5). In aqueous solution the copper(II) unibiguanide complexes suffer a reversible change into the corresponding bis(biguanide) complexes and simple copper(II) ion (33, 34, 114, 162).



The complex glycine and alanine copper(II) biguanide salts of the composition $[\text{Cu}(\text{Gn or An})(\text{BgH})]\text{X} \cdot aq$ (where GnH or AnH is a molecule of glycine or alanine, BgH = a molecule of any biguanide, and X =

Cl or Br) have been prepared by mixing solutions of copper(II) bis(biguanide) chloride (or bromide), copper(II) chloride (or bromide), and glycine or alanine in molar proportions of 1:1:2, respectively. The solution on concentration on the water bath and subsequent cooling deposits deep blue-violet crystals of the complex amino acid copper(II) biguanide salt. The product can be recrystallized from hot water without change. These salts can also be prepared by treating the particular unibiguanide copper(II) complex with the amino acid in molar proportions in aqueous solution at a pH of about 6-7 (33). Their absorption spectra show that they are not molecular compounds of copper(II) bis(biguanide) salt and copper(II) glycine or copper(II) alanine, but contain a univalent complex cation of the composition noted above (33). They furnish instances of heterochelate copper(II) compounds.

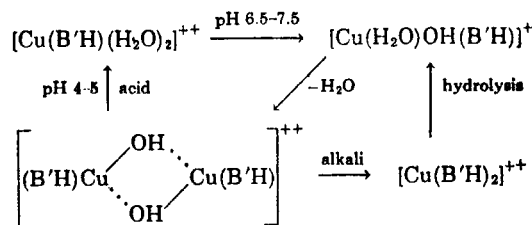
Measurements of magnetic susceptibilities of most of the copper(II) unibiguanide complexes show that their magnetic moment values vary from 1.70 to 1.86 Bohr magnetons, except in the case of a few heterochelate compounds which give somewhat higher values of about 1.99 Bohr magnetons (33, 163).

(b) Binuclear

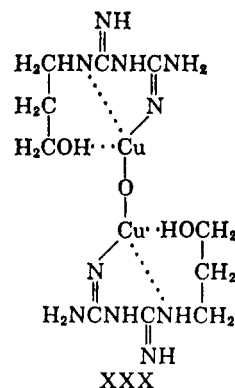
Copper(II) bis(2-hydroxyethylbiguanide) and bis(2-hydroxypropylbiguanide) salts suffer hydrolysis in boiling aqueous solution or suspension with the formation of ultramarine-like, deep blue, insoluble, crystalline binuclear complexes. For complete conversion the solution or the suspension of the bis(biguanide) salts is heated on the water bath for 6-8 hr. (162). The complex binuclear sulfates are, however, more readily obtained by refluxing for about 4 hr. a mixture of dicyandiamide, ethanamine or 2-hydroxypropylamine, and copper(II) sulfate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) with water in proportions employed for the preparation of the corresponding copper(II) bis(2-hydroxyethylbiguanide) or bis(2-hydroxypropylbiguanide) sulfate (162).

The binuclear diol complexes have also been prepared from an aqueous solution of the corresponding copper(II) (2-hydroxyethyl)biguanide salts by neutralization with alkali to pH 6-7. The solution turns deep blue and dark blue crystals of the complex diol compound separate from it. The binuclear diol-copper(II) complexes are believed to occupy an intermediate position between the corresponding unibiguanide and bis(biguanide) complexes. An excess of alkali solution changes them into bis(biguanide) complexes with separation of some copper(II) hydroxide (162).

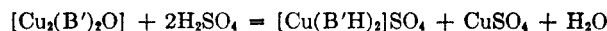
A brick-red crystalline product of composition $\text{CuO} \cdot \text{CuB}'_2$, where $\text{B}'\text{H} = \text{HOC}_3\text{H}_6\text{C}_2\text{H}_6\text{N}_6$, has been described. The compound is named μ -oxodicopper(II) bis[N^1 -(3-hydroxypropyl)biguanide], to which formula XXX has been assigned (162). The substance was prepared in a manner similar to that followed in the



case of the diol-dicopper(II) complexes described before (162). The compound is unaffected by alkalis,



but is changed into the corresponding bis(biguanide) complex by treatment with an ammonium salt solution or by the controlled action of dilute acids (162).



All the binuclear copper(II) complexes are insoluble or sparingly soluble in water. The diol complexes are changed by alkali solution into the corresponding bis(biguanide) bases with separation of some copper(II) hydroxide. They show a magnetic moment value of 1.67-1.73 Bohr magnetons (163).

All the known unibiguanide complexes of copper(II) (mononuclear and binuclear) are included in table 9.

3. Dibiguanide complexes

Copper(II) complexes of several dibiguanides—namely, ethylene-, hexamethylene-, *m*-phenylene-, *p*-phenylene-, and piperazinedibiguanides—have been described (table 10). Being a quadridentate ligand, a molecule of a dibiguanide combines with one atom of copper to form a square planar complex. They are prepared like the bis(biguanide) complexes and show more or less similar properties. The dibiguanide copper(II) complexes are, as a rule, much less soluble than the bis(biguanide) complexes, are somewhat more stable toward acids, and are not affected by alkalis.

Dittler (37) described a rose-red copper(II) ethylenebiguanide sulfate of a different composition, $\text{Cu}(\text{C}_4\text{H}_8\text{N}_6)_2 \cdot \text{H}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$. A similar composition, but with 1 H_2O , was assigned to the compound also by Dubský, Langer, and Strnad (39), assuming the ligand to be a monobiguanide, derived from ethylenediamine and dicyandiamide with loss of one molecule of ammonia.

TABLE 9

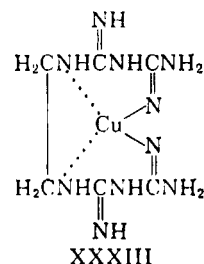
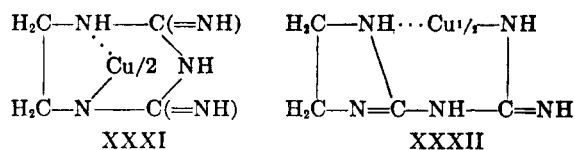
The known copper(II) unibiguanide complexes
 BH = a molecule of biguanide; B'H = a molecule of any substituted biguanide; GnH = a molecule of glycine;
 AnH = a molecule of alanine

Ligand	Complex ^(a)	Reference
Biguanide.....	[Cu(H ₂ O) ₅ (BH)]Cl ₂ ·2H ₂ O	(33)
C ₃ H ₇ N ₅		
N ¹ -Methylbiguanide.....	[CuCl ₂ (B'H)] ₂	(33)
CH ₃ C ₂ H ₄ N ₅	[Cu(H ₂ O) ₅ (B'H)]SO ₄	
N ¹ -Ethylbiguanide.....	[CuCl ₂ (B'H)]·0.5H ₂ O	(33)
C ₂ H ₅ C ₂ H ₄ N ₅		
N ¹ ,N ¹ -Dimethylbiguanide.....	[CuX ₂ (B'H)]·0.5H ₂ O	(33)
(CH ₃) ₂ C ₂ H ₄ N ₅	X = Cl, †SO ₄	
N ¹ ,N ¹ -Diethylbiguanide.....	[CuCl ₂ (B'H)]·0.5H ₂ O	(33)
(C ₂ H ₅) ₂ C ₂ H ₄ N ₅		
N ¹ -(2-Hydroxyethyl)biguanide..	[Cu(H ₂ O) ₅ (B'H)]X ₂	(162)
HOC ₂ H ₄ C ₂ H ₄ N ₅	X = Cl, †SO ₄	
	[Cu ₂ (OH) ₂ (B'H) ₂]X ₂	
	X = Cl, Br, I, NO ₂ , NO ₃ , †SO ₄ , †S ₂ O ₈ , †HPO ₄ , †HAsO ₄	
N ¹ -(2-Hydroxypropyl)biguanide	[Cu ₂ (OH) ₂ (B'H) ₂]X ₂	(162)
HOC ₃ H ₆ C ₂ H ₄ N ₅	X = Cl (2), Br, I, NO ₂ (1), NO ₃ (1), †SO ₄	
N ¹ -Benzylbiguanide.....	[CuCl ₂ (B'H)]·0.5H ₂ O	(108)
C ₆ H ₅ CH ₂ C ₂ H ₄ N ₅		
Biguanide + glycine.....	[Cu(Gn)(BH)]X	(33)
C ₃ H ₇ N ₅ + H ₂ NCH ₂ COOH	X = Cl (1.5), Br (2), I (1)	
Biguanide + alanine.....	[Cu(An)(BH)]Cl·3H ₂ O	(33)
C ₃ H ₇ N ₅ + H ₂ NC ₂ H ₄ COOH		
N ¹ -Methylbiguanide + glycine..	[Cu(Gn)(B'H)]Cl·0.5H ₂ O	(33)
N ¹ -Ethylbiguanide + glycine..	[Cu(Gn)(B'H)]Cl·6.5H ₂ O	(33)
N ¹ -Ethylbiguanide + alanine..	[Cu(An)(B'H)]Cl·2H ₂ O	(33)

^(a) The figure inside the parentheses after an anion denotes the number of water molecules in the crystals.

This has, however, been shown to be erroneous, and it has been proved that the ligand is a true dibiguanide (22). The correct composition of the complex copper(II) salt (sulfate) of the ligand is represented by [CuC₂H₄(C₂H₄N₅)₂]SO₄·2.5H₂O (22, 140), and the structures XXXI (37) and XXXII (39), suggested by the earlier workers, have been replaced by XXXIII (140).

p-Phenylenedibiguanide and piperazinedibiguanide complexes of bivalent metals (copper, nickel) present



difficulties of structural representation in view of their apparent bridging of para positions of the ring by bond formation with the metal atom, unless, of course, a dimeric or polymeric structure for the complexes be assumed. An x-ray study of their crystal structure will be of considerable interest in this connection.

B. NICKEL(II) BIGUANIDES

1. Bis(biguanide) complexes

Like copper(II), nickel(II) forms bis(biguanide) and dibiguanide complexes, but no unibiguanide nickel complexes have been described. In this respect the nickel(II) complexes differ from those of copper(II). Though the formation of a nickel(II) biguanide complex was noticed as early as in 1878 (100), very little attention was paid to the subject for a long time. Hydrated nickel(II) biguanide base and its sulfate (53), and the anhydrobase, chloride, and sulfate of phenylbiguanide (173), are the few compounds described by earlier workers. Mention may also be made of the nickel(II) complex of *o*-phenylenebiguanide reported by Ziegelbauer (188). A large number of nickel(II) bis(biguanides) and dibiguanides have, however, been prepared within the last two decades. In table 11 are

TABLE 10

The known copper(II) dibiguanide complexes
 B'H₂ = a molecule of any particular dibiguanide

Ligand	Complex	References
N ¹ ,N ¹ -Ethylenedibiguanide.....	[Cu(B'')]·H ₂ O, rose-red, sparingly soluble in water; [Cu(B''H ₂)]X ₂	(22, 37, 39, 140)
C ₃ H ₄ (C ₂ H ₄ N ₅) ₂	X = Cl (1.5), Br (1.5), I (1.5), SCN (1.5), NO ₂ (1.5), NO ₃ (1.5), †SO ₄ (2.5), †S ₂ O ₈ (2.5); rose-red, silky crystals	
	Equivalent conductivity (32°C.) of the chloride = 134.6 mhos	
N ¹ ,N ¹ -Hexamethylenedibiguanide.....	[Cu(B''H ₂)]X ₂	(43)
C ₆ H ₁₂ (C ₂ H ₄ N ₅) ₂	X = OH (1), Cl (4), SCN (1.5), CH ₃ COO (6), †SO ₄ (4); rose-violet crystals, insoluble in water	
N ¹ ,N ¹ -(<i>m</i> -Phenylene)dibiguanide.....	[Cu(B'')], [Cu(B''H ₂)]X ₂	(152)
C ₆ H ₄ (C ₂ H ₄ N ₅) ₂	X = OH, Cl (1.5), Br (2), I, SCN (1), †SO ₄ (0.5), †S ₂ O ₈ (2.5); rose-violet crystals	
	Λ _∞ (32.6°C.) of the chloride = 137.4 mhos	
N ¹ ,N ¹ -(<i>p</i> -Phenylene)dibiguanide.....	[Cu(B''H ₂)]X ₂	(134)
C ₆ H ₄ (C ₂ H ₄ N ₅) ₂	X = OH (6.5), Cl (3), †SO ₄ (2.5); violet, crystalline powder, insoluble in water	
Piperazinedibiguanide.....	[Cu(B'')], [Cu(B''H ₂)]X ₂	(125)
C ₄ H ₈ (C ₂ H ₄ N ₅) ₂	X = OH (3), Cl (4), NO ₂ (1), †SO ₄ (5.5); red-violet crystalline powder, almost insoluble in water	

TABLE 11

The known nickel(II) bis(biguanide) complexes

BH = a molecule of biguanide; B'H = a molecule of a substituted biguanide

Ligand	Complex ^(a)	References
Biguanide..... C ₂ H ₇ N ₃	[Ni(B) ₂], [Ni(BH) ₂]X ₂ X = OH, F (4), Cl (2), Br (1.5), I, SCN, ClO ₃ (1), BrO ₃ (1.5), IO ₃ (0.5), ClO ₄ , MnO ₄ , BF ₄ , NO ₃ (1), NO ₂ (1), $\frac{1}{2}$ CO ₃ (2), $\frac{1}{2}$ IO ₃ (7.5), $\frac{1}{2}$ SO ₄ (3), $\frac{1}{2}$ SO ₄ (3), $\frac{1}{2}$ S ₂ O ₈ (2), $\frac{1}{2}$ S ₂ O ₈ (2), $\frac{1}{2}$ SeO ₄ (3), $\frac{1}{2}$ CrO ₄ (3), $\frac{1}{2}$ Fe(CN) ₆ (4), $\frac{1}{2}$ Fe(CN) ₆ (8), $\frac{1}{2}$ [Fe(CN) ₅ NO] (1), $\frac{1}{2}$ Co(CN) ₆ (6), $\frac{1}{2}$ Co(NO ₂) ₆ (18), $\frac{1}{2}$ HgI ₄ [Ni(BH) ₂]F ₂ ·NH ₄ F·2HF·3.5H ₂ O [Ni(BH) ₂] ₂ (Na or NH ₄) ₂ Mo ₇ O ₂₄ (4) Δ _∞ (25°C.) = 122.9 mhos (chloride) χ _g for [Ni(B) ₂] = -0.149 × 10 ⁻⁶ χ _g for [Ni(BH) ₂](OH) ₂ = -0.2212 × 10 ⁻⁶	(53, 100, 143, 151, 177, 181)
N ¹ -Methylbiguanide..... CH ₃ C ₂ H ₅ N ₃	[Ni(B'H) ₂]Cl ₂ ·4.5H ₂ O	(35)
N ¹ -Ethylbiguanide..... C ₂ H ₅ C ₂ H ₅ N ₃	[Ni(B'H) ₂]Cl ₂ ·0.5H ₂ O	(35)
N ¹ -Propylbiguanide..... C ₃ H ₇ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B'H) ₂]X ₂ X = OH (2.5), Cl (1.5), $\frac{1}{2}$ SO ₄ (1)	(159)
N ¹ -Isopropylbiguanide..... C ₃ H ₇ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B'H) ₂]SO ₄	(159)
N ¹ -(n-Butyl)biguanide..... C ₄ H ₉ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B'H) ₂]X ₂ X = Cl (1), $\frac{1}{2}$ SO ₄ (1.5)	(159)
N ¹ -Hexylbiguanide..... C ₆ H ₁₃ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B'H) ₂]X ₂ ·2H ₂ O X = Cl, NO ₃ , $\frac{1}{2}$ SO ₄	(42)
N ¹ ,N ¹ -Dimethylbiguanide..... (CH ₃) ₂ C ₂ H ₅ N ₃	[Ni(B'H) ₂]Cl ₂ ·0.5H ₂ O	(35)
N ¹ ,N ¹ -Diethylbiguanide..... (C ₂ H ₅) ₂ C ₂ H ₅ N ₃	[Ni(B'H) ₂]Cl ₂ ·0.5H ₂ O	(35)
N ¹ -(2-Hydroxyethyl)biguanide..... HOC ₂ H ₄ C ₂ H ₅ N ₃	[Ni(B'H) ₂]X ₂ X = OH (0.5), Cl, Br, I, NO ₃ , $\frac{1}{2}$ CO ₃ , $\frac{1}{2}$ SO ₄ (5.5), $\frac{1}{2}$ S ₂ O ₈ (2.5), $\frac{1}{2}$ S ₂ O ₈ (2), $\frac{1}{2}$ CrO ₄ (3) χ _g (sulfate) = -0.2040 × 10 ⁻⁶	(164)
N ¹ -(3-Hydroxypropyl)biguanide..... HOC ₃ H ₆ C ₂ H ₅ N ₃	[Ni(B') ₂]·0.5H ₂ O, [Ni(B'H) ₂]X ₂ X = Cl (0.5), I (1), NO ₃ (1), $\frac{1}{2}$ SO ₄ (3.5), $\frac{1}{2}$ S ₂ O ₈ (3.5), $\frac{1}{2}$ S ₂ O ₈ (1), $\frac{1}{2}$ CrO ₄ (4) χ _g (sulfate) = -0.4547 × 10 ⁻⁶	(164)
N ¹ -(2-Hydroxypropyl)biguanide..... HOC ₂ H ₄ C ₂ H ₅ N ₃	[Ni(B'H) ₂]X ₂ X = OH (1.5), Cl (4.5), I (1), NO ₃ (2), $\frac{1}{2}$ SO ₄ (3), $\frac{1}{2}$ S ₂ O ₈ (3.5), $\frac{1}{2}$ S ₂ O ₈ (3), $\frac{1}{2}$ CrO ₄ (8) χ _g (sulfate) = -0.3430 × 10 ⁻⁶	(164)
N ¹ -(2-Methoxyethyl)biguanide..... CH ₃ OC ₂ H ₄ C ₂ H ₅ N ₃	[Ni(B') ₂]·0.5H ₂ O, [Ni(B'H) ₂]X ₂ X = Cl (1), NO ₃ (1), $\frac{1}{2}$ SO ₄ (1) χ _g (sulfate) = -0.4186 × 10 ⁻⁶	(164)
N ¹ -(3-Methoxypropyl)biguanide..... CH ₃ OC ₃ H ₆ C ₂ H ₅ N ₃	[Ni(B') ₂]·0.5H ₂ O, [Ni(B'H) ₂]X ₂ X = Cl, NO ₃ (1), $\frac{1}{2}$ SO ₄ (0.5) χ _g (sulfate) = -0.4075 × 10 ⁻⁶	(164)
N ¹ -(2-Sulfoethyl)biguanide..... HO ₂ SC ₂ H ₄ C ₂ H ₅ N ₃	[Ni(B') ₂]·2.5H ₂ O; loses water at 100°C.	(159)
N ¹ -Phenylbiguanide..... C ₆ H ₅ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B') ₂]·0.5H ₂ O, [Ni(B'H) ₂]X ₂ X = Cl (2.5), Br (2), I (1), SCN, NO ₃ (1), NO ₂ (1), ClO ₃ , BrO ₃ , IO ₃ (2), $\frac{1}{2}$ SO ₄ (1), $\frac{1}{2}$ SO ₄ (2), $\frac{1}{2}$ S ₂ O ₈ , $\frac{1}{2}$ S ₂ O ₈	(123, 173)
N ¹ -(o-Phenylene)biguanide..... C ₆ H ₄ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B') ₂]·3H ₂ O (chocolate), [Ni(B'H) ₂]SO ₄ ·4H ₂ O (red-brown)	(39, 188)
N ¹ -Benzylbiguanide..... C ₆ H ₅ CH ₂ C ₂ H ₅ N ₃	[Ni(B') ₂]·0.5H ₂ O, [Ni(B'H) ₂]X ₂ X = Cl (2), $\frac{1}{2}$ SO ₄ (0.5)	(108)
N ¹ -(p-Tolyl)biguanide..... p-CH ₃ C ₆ H ₄ C ₂ H ₅ N ₃	[Ni(B'H) ₂]X ₂ X = OH, Cl (3), Br (1), I, NO ₃ (1), $\frac{1}{2}$ SO ₄ (3)	(57)
N ¹ -(p-Acetylamino)phenyl)biguanide..... p-CH ₃ CONHC ₆ H ₄ C ₂ H ₅ N ₃	[Ni(B'H) ₂]X ₂ X = OH, Cl (3), $\frac{1}{2}$ SO ₄	(134)
N ¹ -(4-Sulfo)phenyl)biguanide..... 4-HO ₂ SC ₆ H ₄ C ₂ H ₅ N ₃	[Ni(B') ₂]·2H ₂ O, soluble in alkali; [Ni(B*) ₂]K ₂ ·3.5H ₂ O or [Ni(B*) ₂]Na ₂ ·3H ₂ O, where B*H = B'	(132)
N ¹ -(p-Sulfamoyl)phenyl)biguanide..... p-H ₂ NSO ₂ C ₆ H ₄ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B'H) ₂]X ₂ X = OH, Cl (0.5), NO ₃ (1.5), $\frac{1}{2}$ SO ₄ (2.5)	(159)
N ¹ -Methyl-N ¹ -phenylbiguanide..... C ₆ H ₅ (CH ₃)C ₂ H ₅ N ₃	[Ni(B'II) ₂]X ₂ X = OH, Cl (3), Br (2), I (2), $\frac{1}{2}$ SO ₄ (2)	(56)
N ¹ -(1-Naphthyl)biguanide..... C ₁₀ H ₇ C ₂ H ₅ N ₃	[Ni(B') ₂], [Ni(B') ₂]·1.2H ₂ O, [Ni(B') ₂]·2.5H ₂ O, [Ni(B'H) ₂]X ₂ X = Cl (2), $\frac{1}{2}$ SO ₄ (1)	(144)
N ¹ -(2-Sulfo-1-naphthyl)biguanide..... o-HO ₂ SC ₁₀ H ₇ C ₂ H ₅ N ₃	[Ni(B'H) ₂](OH) ₂ ·3H ₂ O, soluble in alkalis; [Ni(B*) ₂]K ₂ ·2H ₂ O or [Ni(B*) ₂]Na ₂ ·2H ₂ O where B*H = B'	(132)
N ¹ ,N ¹ -Diphenylbiguanide..... (C ₆ H ₅) ₂ C ₂ H ₅ N ₃	[Ni(B'H) ₂]X ₂ X = OH (1.5), Cl (2), $\frac{1}{2}$ SO ₄ (1.5) χ _g (hydroxide) = -1.096 × 10 ⁻⁶	(98)
N ¹ -Ethyl-N ¹ -phenylbiguanide..... C ₆ H ₅ (C ₂ H ₅)C ₂ H ₅ N ₃	[Ni(B'H) ₂](OH) ₂	(98)
N ¹ -(p-Chlorophenyl)-N ¹ -isopropylbiguanide..... p-ClC ₆ H ₄ (C ₃ H ₇)C ₂ H ₅ N ₃	[Ni(B') ₂]·H ₂ O	(104)
N ¹ ,N ¹ -Diethyl-N ¹ -phenylbiguanide..... C ₆ H ₅ (C ₂ H ₅) ₂ C ₂ H ₅ N ₃	[Ni(B'H) ₂]X ₂ X = OH (0.5), Cl (2.5), $\frac{1}{2}$ SO ₄ (1) χ _g (hydroxide) = -0.453 × 10 ⁻⁶	(98)

(a) The figure in parentheses after an anion indicates the number of water molecules in the crystals.

recorded all the known nickel(II) bis(biguanide) complexes.

The preparation of the complex nickel(II) biguanide bases and their salts resembles closely that of copper(II) bis(biguanides). Most nickel(II) biguanide complexes are either orange or yellow; a few are red. They also resemble the corresponding copper(II) complexes in solubility; all are decomposed by acids but unaffected by alkalis. As a rule, all nickel(II) biguanide complexes are diamagnetic. This furnishes evidence of their square planar structure with dsp^2 hybrid bonds (92).

Nickel(II) *o*-phenylenebiguanide has a somewhat different composition and structure, resembling its copper(II) analog (Section IV,A,1; references 39 and 188).

Nickel(II) bis(biguanide) polyhalides

Like its copper analog nickel(II) bis(biguanide) forms a number of highly colored polyhalides. They have been prepared like the corresponding copper(II) compounds from solutions of nickel(II) biguanide halides and of iodine in potassium chloride, potassium bromide, or potassium iodide, as the case may be (119, 143). Their composition and properties are given in table 12.

As shown in table 12, in many of these cases different methods of preparation led to products with different amounts of water of crystallization in the molecule.

Different modifications of some nickel(II) bis(biguanides)

A number of nickel(II) bis(biguanide) complexes are known to occur in two or more modifications differing mainly in color. This difference is believed to arise in many cases from a difference in their molecular configurations, related as *cis-trans* isomers, but the phenomenon may as well be due to polymorphism. No definite conclusion is, however, possible without an x-ray study of their crystal structure. Table 13 gives a summary of these compounds, where the dif-

ferent varieties are designated as α , β , and γ .

Nickel(II) bis(biguanide) complex in analysis

Nickel has been estimated volumetrically by precipitation as nickel(II) bis(biguanide) hydroxide, $[\text{Ni}(\text{C}_2\text{H}_7\text{N}_3)_2](\text{OH})_2$, followed by titration with a standard acid in the presence of an indicator (85). The method permits the estimation of nickel when mixed with metals like beryllium, zirconium, iron, aluminum, chromium, titanium, uranium, antimony, bismuth, and arsenic, after precipitation as above in the presence of tartaric acid as a masking agent (85).

2. Dibiguanide complexes

Nickel(II) dibiguanide complexes resemble the corresponding copper(II) complexes in composition and general properties and are prepared in a similar manner. Like its bis(biguanide) complexes, all dibiguanide complexes of nickel(II) are orange-red or yellow, but they are comparatively less soluble and more stable. The complex nickel(II) ethylenedibiguanide base, however, has not been isolated in a pure state. The known nickel(II) dibiguanide complexes are listed in table 14.

Nickel(II) ethylenedibiguanide, like the corresponding copper(II) complex, was previously represented by a different composition and structure, as the ligand was then believed to be a monobiguanide derivative (see Section IV,A,1; references 37 and 39).

C. PALLADIUM(II) BIGUANIDES

Palladium(II) biguanide complexes are very similar to those of nickel(II) in composition and properties. The metal forms only bis(biguanides) and dibiguanides with square planar structure. They are invariably diamagnetic and form light yellow, silky crystals. The palladium(II) complexes are comparatively less soluble and more stable than the corresponding nickel(II) compounds. The known palladium(II) biguanides and dibiguanides are listed in table 15.

Thiocyanates of palladium(II) biguanide complexes,

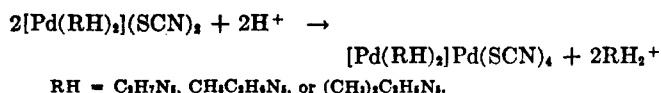
TABLE 12
Polyhalides of nickel(II) biguanide complexes
 $\text{X} = \text{Ni}(\text{C}_2\text{H}_7\text{N}_3)_2$

Compound	Method of Preparation	Properties
$[\text{X}]_2^{\text{Cl}} \cdot 3\text{H}_2\text{O}$	$[\text{X}]\text{Cl}_2$ in excess and iodine in potassium iodide	Dark green, needle-shaped crystals; sparingly soluble in water and insoluble in alcohol; changes to iodotriiodide with an excess of KI_3
$[\text{X}]_2^{\text{Br}} \cdot 2\text{H}_2\text{O}$	$[\text{X}]\text{Br}_2$ and requisite amount of iodine in potassium iodide	Brownish black, silky, needle-shaped crystals; sparingly soluble in water
$[\text{X}]_2^{\text{I}} \cdot 1.5\text{H}_2\text{O}$ and $[\text{X}]_2^{\text{I}} \cdot \text{H}_2\text{O}$	$[\text{X}]\text{Cl}_2$, $[\text{X}]\text{Br}_2$, or $[\text{X}]\text{I}_2$ and an excess of iodine in potassium iodide; or $[\text{X}]\text{I}_2$ in excess and iodine in potassium iodide	Brownish black or green, needle-shaped crystals; sparingly soluble in water but readily soluble in alcohol
$[\text{X}]\text{Br}_2 \cdot [\text{X}]_2^{\text{Br}}$, with 0.5, 1.5, and 3.5 H_2O	$[\text{X}]\text{Cl}_2$ and iodine in potassium bromide; $[\text{X}]\text{Br}_2$ in excess and iodine in potassium bromide; $[\text{X}]\text{I}_2$ and an excess of iodine in potassium bromide	Greenish black, needle-shaped, fine crystals
$[\text{X}]\text{Cl}_2 \cdot [\text{X}]_2^{\text{Cl}}$, with 6 and 8.5 H_2O	$[\text{X}]\text{Cl}_2$ and iodine in potassium chloride with either in excess	Greenish yellow, silky, needle-shaped crystals with a bronze luster; sparingly soluble in water

TABLE 13
Different modifications of some nickel(II) bis(biguanides)

Compound	α -Form	β -Form	γ -Form
Nickel <i>N</i> ¹ -phenylbiguanide. [Ni(B ¹ H) ₂] ₂ (123)	Occurs also with 0.5 H ₂ O; red; insoluble in water; soluble in alcohol and acetone; changes rapidly to the β -form; decomposes without melting at 255°C.	Yellow; insoluble in water, alcohol, and acetone; decomposes without melting at 265°C.	Occurs also with 0.5 H ₂ O; deep yellow; obtained from the moist α -variety on keeping; insoluble in water, alcohol, or acetone; decomposes without melting at 263°C.; believed to be a molecular compound or solid solution of α - and β -forms
Nickel <i>N</i> ¹ -(<i>p</i> -tolyl)biguanide base and salts (57): [Ni(B ¹ H) ₂](OH) ₂	Light orange; insoluble in water	Pink; changes to the α -form on warming with water; insoluble in water	Yellow; insoluble in water; changes to the α -form in presence of a drop of dilute acetic acid
[Ni(B ¹ H) ₂]Cl ₂ ·3H ₂ O.	Buff-colored; insoluble in water	—	Orange-yellow; insoluble in water
[Ni(B ¹ H) ₂]Br ₂ ·H ₂ O.	Buff-colored; insoluble in water	—	Orange-yellow; insoluble in water
[Ni(B ¹ H) ₂]SO ₄ ·3H ₂ O.	Buff-colored; insoluble in water	—	Orange-yellow; insoluble in water
Nickel <i>N</i> ¹ -(<i>p</i> -phenetyl)biguanide base and salts (55): [Ni(B ¹ H) ₂](OH) ₂	Buff-colored; insoluble in water; changes on drying to the β -variety	Orange; insoluble in water	—
[Ni(B ¹ H) ₂]Cl ₂ ·3H ₂ O.	Light yellow; moderately soluble in hot water	Brick-red; insoluble in water; slowly changes to the α -form when moist	—
[Ni(B ¹ H) ₂]SO ₄	Contains 3 H ₂ O; reddish cream; insoluble in water	Contains 2 H ₂ O; brick-red; insoluble in water	—
Nickel <i>N</i> ¹ -(1-naphthyl)biguanide. [Ni(B ¹ H) ₂] ₂ (144)	Also occurs with 1 H ₂ O; flesh-colored; insoluble in water; sparingly soluble in alcohol; dissolves in pyridine to a red solution	Occurs also with 2.5 H ₂ O; yellow; insoluble in water; soluble in pyridine and warm alcohol to a yellow solution	Occurs with 2 H ₂ O only; buff-colored; insoluble in water; sparingly soluble in alcohol; dissolves in pyridine to a yellow solution
Sodium salt of nickel <i>N</i> ¹ -(2-sulfo-1-naphthyl)-biguanide. [Ni(O ₂ SC ₁₀ H ₆ C ₂ H ₃ N ₃) ₂]Na ₂ ·7H ₂ O (132)	Yellow crystals; soluble in water with partial hydrolysis	Red crystals; soluble in water with partial hydrolysis	

such as those of biguanide, methylbiguanide, and dimethylbiguanide, on treatment with dilute sulfuric acid (pH 2) suffer rearrangement with the formation of insoluble, brownish red, silky crystals of palladium(II) bis(biguanide) thiocyanatopalladite (107, 139).



D. COBALT(II) BIGUANIDES

Rathke (100) observed the formation of a yellow

cobalt(II) biguanide complex but failed to isolate it in a pure state. Cobalt(II) complexes of biguanide and ethylenedibiguanide were first prepared by Rây and Ghosh (140). These form greenish yellow, silky crystals, sparingly soluble in water. In this respect they resemble more or less the corresponding nickel complexes. But the cobalt(II) biguanides are rather unstable and are readily oxidized in moist air to form cobalt(III) compounds. They are also readily decomposed by acids.

Cobalt(II) bis(biguanide) sulfate, [Co(BH)₂]₂SO₄·4H₂O, is obtained as a greenish yellow, silky precipitate

TABLE 14
The known nickel(II) dibiguanide complexes
B¹H₂ = a molecule of a dibiguanide

Ligand	Complex ^(a)	References
<i>N</i> ¹ , <i>N</i> ¹ -Ethylenedibiguanide. C ₂ H ₆ (C ₂ H ₄ N ₃) ₂	[Ni(B ¹ H ₂)]X ₂ X = Cl (1.5), Br (2.5), I (1.5), SCN (1.5), NO ₂ (1.5), NO ₃ (1.5), $\frac{1}{2}$ SO ₄ (2), $\frac{1}{2}$ S ₂ O ₈ (2.5) Λ_{∞} (34°C.) for the chloride = 138.5 mhos χ_g (chloride) = -0.4436 × 10 ⁻⁶	(39, 140)
<i>N</i> ¹ , <i>N</i> ¹ -Hexamethylenedibiguanide. C ₆ H ₁₂ (C ₂ H ₆ N ₃) ₂	[Ni(B ¹ H ₂ -)]X ₂ X = OH, Cl (4), $\frac{1}{2}$ SO ₄ (4)	(43)
<i>N</i> ¹ , <i>N</i> ¹ -(<i>m</i> -Phenylene)dibiguanide. C ₆ H ₄ (C ₂ H ₆ N ₃) ₂	[Ni(B ¹ H ₂)] ₂ [Ni(B ¹ H ₂)]X ₂ X = OH, OH (2), $\frac{1}{2}$ SO ₄ (5)	(152)
<i>N</i> ¹ , <i>N</i> ¹ -(<i>p</i> -Phenylene)dibiguanide. C ₆ H ₄ (C ₂ H ₆ N ₃) ₂	[Ni(B ¹ H ₂)] ₂ [Ni(B ¹ H ₂)]X ₂ X = OH (1.5), Cl (3), $\frac{1}{2}$ SO ₄ (2)	(134)
Piperasinedibiguanide. C ₂ H ₅ (C ₂ H ₅ N ₃) ₂	[Ni(B ¹ H ₂)] ₂ [Ni(B ¹ H ₂)]X ₂ X = OH (1.5), Cl (7.5), $\frac{1}{2}$ SO ₄ (4.5); orange; insoluble in water; all lose water at 110°C. [Ni(B ¹ H ₂)](OH) ₂ ·Ni(OH) ₂ ·5H ₂ O; buff-colored; insoluble in water, loses 5 H ₂ O at 110°C. χ_g (30°C.) = 4.31 × 10 ⁻⁶ Magnetic moment = 2.48 Bohr magnetons	(125)

^(a) A figure in parentheses after an anion indicates the number of water molecules in the crystals.

TABLE 15

*The known palladium(II) biguanide complexes*BH = a molecule of biguanide; B'H = a molecule of a substituted biguanide; B'H₂ = a molecule of a dibiguanide

Ligand	Complex ^(a)	Reference
Biguanide..... C ₂ H ₇ N ₃	[Pd(B) ₂], [Pd(BH) ₂]X ₂ X = OH, Cl (2), Br (1), I (2), SCN (1), NO ₂ , †SO ₄ (3), †S ₂ O ₄ (3), Pd(SCN) ₂ , PdCl ₂ , PdCl ₄ (5) A _∞ (28°C.) for the chloride = 120.76 mhos χ _g (hydroxide) = -0.259 × 10 ⁻⁶	(139)
N ¹ -Methylbiguanide..... CH ₃ C ₂ H ₆ N ₃	[Pd(B'H) ₂]X ₂ X = OH (0.5), Cl (3), SCN (2), NO ₂ (1.5), †SO ₄ (1), Pd(SCN) ₂ A _∞ (30°C.) for the chloride = 112 mhos A _∞ for the sulfate = 107 mhos	(107)
N ¹ -Ethylbiguanide..... C ₂ H ₅ C ₂ H ₆ N ₃	[Pd(B'H) ₂]X ₂ X = OH (1), Cl (2), NO ₂ , †SO ₄ (1) A _∞ (30°C.) for the chloride = 120 mhos	(107)
N ¹ ,N ¹ -Dimethylbiguanide..... (CH ₃) ₂ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂]X ₂ , [Pd(B' ₂ H) ₂]X ₂ X = Cl (2), SCN (1.5), NO ₂ (0.5), Pd(SCN) ₂ A _∞ (30°C.) for the chloride = 113 mhos	(107)
N ¹ -(2-Hydroxyethyl)biguanide..... HOC ₂ H ₄ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂], [Pd(B' ₂ H) ₂]X ₂ X = OH (1.5), Cl (0.5), NO ₂ (0.5), †SO ₄ (2)	(165)
N ¹ -(3-Hydroxypropyl)biguanide..... HOC ₃ H ₆ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂]·0.5H ₂ O, [Pd(B' ₂ H) ₂]X ₂ X = Cl (1), †SO ₄ (3)	(165)
N ¹ -(2-Methoxyethyl)biguanide..... CH ₃ OC ₂ H ₄ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂]SO ₄ ·H ₂ O	(165)
N ¹ -(3-Methoxypropyl)biguanide..... CH ₃ OC ₃ H ₆ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂]SO ₄ ·2H ₂ O	(165)
N ¹ -Phenylbiguanide..... C ₆ H ₅ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂], [Pd(B' ₂ H) ₂]X ₂ X = Cl (1.5), NO ₂ (1), †SO ₄ (1)	(107)
N ¹ -Benzylbiguanide..... C ₆ H ₅ CH ₂ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂], [Pd(B' ₂ H) ₂]X ₂ X = Cl (2), †SO ₄ (1.5)	(107)
N ¹ ,N ⁴ -Diphenylbiguanide..... (C ₆ H ₅) ₂ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂]X ₂ X = OH (3), Cl (1.5), †SO ₄ (1.5)	(98)
N ¹ ,N ⁴ -Diethyl-N ¹ -phenylbiguanide..... C ₂ H ₅ (C ₆ H ₅) ₂ C ₂ H ₆ N ₃	[Pd(B' ₁ H) ₂](OH) ₂	(98)
N ¹ ,N ¹ -Ethylenedibiguanide..... C ₂ H ₄ (C ₂ H ₆ N ₃) ₂	[Pd(B' ₁ H) ₂], [Pd(B' ₂ H) ₂]X ₂ X = OH, Cl (4), †SO ₄ (3) All compounds are insoluble in water	(107)

^(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

by the addition of a cold ammoniacal solution of biguanide sulfate to one of cobalt chloride in the presence of ammonium sulfate. It loses its water of crystallization at 105°C. The corresponding complex base, [Co(BH)₂](OH)₂, is precipitated in the form of silky yellow flakes by using an excess of sodium hydroxide solution in place of ammonia. The complex base is fairly stable in the dry state, but undergoes slow oxidation in moist air. At 70°C. it loses water and changes to the anhydrobase, [Co(B)₂]. Their magnetic susceptibility values at 30°C. are given below (141).

χ_g (sulfate) = 6.787 × 10⁻⁶; magnetic moment =
2.75 Bohr magnetons

χ_g (hydroxide) = 8.268 × 10⁻⁶; magnetic moment =
2.49 Bohr magnetons

Cobalt(II) ethylenedibiguanide sulfate, [CoC₂H₄(C₂H₆N₃)₂]SO₄·2.5H₂O, is obtained similarly as a very sparingly soluble, greenish yellow, silky precipitate from an ammoniacal solution of ethylenedibiguanide sulfate and one of cobalt chloride. It loses one molecule of water at 80°C. On treatment with very dilute sodium hydroxide solution, the complex sulfate changes to the light yellow anhydrobase in a rather impure form (140). The complex sulfate at 26°C. gives a magnetic suscepti-

bility value of χ_g = 6.81 × 10⁻⁶; its magnetic moment = 2.74 Bohr magnetons (141).

The values of the magnetic moment of these yellow cobalt(II) biguanide complexes differ considerably from that of cobalt(II) ion (5.04 Bohr magnetons) in simple cobalt(II) salts. They are, however, much nearer the theoretical value for a 4-covalent cobalt(II) complex of the penetration type with square planar structure containing *dsp*² hybrid bonds. On the basis of Pauling's theory (92, 93) a complex cobalt(II) compound of this type should have a moment of 1.73 Bohr magnetons, corresponding to the spin moment of one unpaired electron. The higher values for the magnetic moment of 2.5–2.75 Bohr magnetons found in the case of cobalt(II) biguanides have been attributed by Rây and Ghosh (141) to an incomplete quenching of the orbital moment of the unpaired electron of the cobalt(II) ion in the complexes, which really possess a square planar configuration with *dsp*² bonds.

On the other hand, cobalt(II) with N¹-(4-sulfo-phenyl)biguanide and with N¹-(*m*-phenylene)dibiguanide has been found to form red paramagnetic complexes, the values of whose magnetic moment approach that of the simple cobalt(II) ion.

Cobalt(II) N¹-(4-sulfo-phenyl)biguanide, [Co(HO₃S-C₆H₄C₂H₆N₃)₂]·5H₂O, forms quite stable, beautiful,

vermillion-red crystals with a magnetic moment of 4.97 Bohr magnetons; χ_g (27°C.) = 15.0×10^{-6} . It is sparingly soluble in water, but dissolves in aqueous alkali to form a yellow solution which readily turns red, owing to oxidation (132).

Cobalt(II) *N*¹-(*m*-phenylene)dibiguanide chloride, $[\text{CoC}_6\text{H}_4(\text{C}_2\text{H}_5\text{N}_5)_2]\text{Cl}_2 \cdot 3\text{H}_2\text{O}$, likewise forms vermillion-red crystals; it is fairly stable in dry air, but is oxidized readily when moist. It also shows an effective moment value of 4.84 Bohr magnetons; χ_g (30°C.) = 16.11×10^{-6} (127).

Both of these red cobalt(II) complexes lose all their water molecules at 100°C. without any appreciable change in color and values for the magnetic moment (159). These red cobalt(II) biguanides might be regarded as either ionic complexes or outer-level covalent complexes having tetrahedral (*sp*³) or square planar (*sp*²*d*) configuration with practically unquenched moment (88, 127).

A grayish brown cobalt(II) *o*-phenylenebiguanide, $[\text{Co}(\text{C}_8\text{H}_8\text{N}_5)_2] \cdot 2\text{H}_2\text{O}$, with a structure analogous to those of the corresponding copper and nickel compounds, has also been described (39).

E. COBALT(III) BIGUANIDES

Complex compounds of biguanides with cobalt(III) were very little studied until the last two decades. In 1896 Ziegelbauer (188) described a red cobalt(III) *o*-phenylenebiguanide of the composition $\text{Co}(\text{C}_8\text{H}_8\text{N}_5)_3 \cdot 3.5\text{H}_2\text{O}$. The same compound in the anhydrous state, as well as a red-brown acetate, $\text{Co}(\text{C}_8\text{H}_8\text{N}_5)_3 \cdot 5\text{CH}_3\text{COOH} \cdot \text{H}_2\text{O}$, were prepared and analyzed as late as 1938 (39). Strictly speaking, *o*-phenylenebiguanide is more a benzimidazole derivative than a true biguanide. A systematic study of cobalt(III) biguanide complexes, leading to the preparation of a large variety of these compounds, has subsequently been made. These can be classified under three main groups: (1) tris(biguanide) complexes; (2) bis(biguanide) complexes; (3) dibiguanide complexes. As a tripositive cobalt atom invariably forms octahedral complexes, those of the bis(biguanide) and dibiguanide groups contain also other ligands for the saturation of the coordination number of the metal atom. In the case of dibiguanide complexes this is often realized by the formation of binuclear structure.

The complex cobalt(III) biguanide bases are usually dark red to rose-red, and their salts are red, orange-red, or golden-yellow. The compounds are all diamagnetic, which is characteristic of all octahedral cobalt(III) complexes with *d*²*sp*³ hybrid bonds (121, 161).

1. Tris(biguanide) complexes

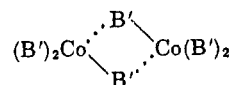
Cobalt(III) tris(biguanide) bases have usually been prepared by oxidizing a mixture of cobalt chloride, biguanide sulfate, or substituted biguanide sulfate, as

the case may be, in strongly alkaline solution with a vigorous current of air. The yellow cobalt(II) biguanide, which separates first, is slowly oxidized and gradually passes into solution with a red color. Oxidation with air may, however, be avoided by evaporating on the water bath a concentrated alkaline solution of hexamminecobalt(III) chloride and the biguanide sulfate concerned (166).

All complex cobalt(III) tris(biguanide) bases, except that of (2-hydroxyethyl)biguanide, are more or less sparingly soluble. From these bases the corresponding salts are prepared by neutralization with suitable acids, or by digesting with ammonium salts on the water bath.

The known cobalt(III) tris(biguanide) complexes are summarized in table 16.

In alcoholic solution the anhydrous cobalt(III) tris(phenylbiguanide) base, $\text{Co}(\text{C}_6\text{H}_5\text{C}_2\text{H}_4\text{N}_5)_3$, has been found to give a molecular weight of 1000–1200 (ebullioscopic method), which is nearly twice its normal value of 590. The dihydrate in the same solvent shows a still higher value of about 1700 against its normal value of 626. The phenomenon has been attributed to the formation of polynuclear complexes by polymerization. For the anhydrobase a dimeric formula with a binuclear structure has been suggested (121).



Optically active modifications of cobalt(III) tris(biguanide) complexes

Rây and Dutt (129) accomplished the resolution of cobalt(III) tris(biguanide) chloride, $[\text{Co}(\text{C}_2\text{H}_7\text{N}_5)]\text{Cl}_3$, into its optically active enantiomers by converting the complex chloride into *d*-tartrate chloride, *d*-tartrate, or *d*-camphorsulfonate. The diastereomers, containing the respective anions, were isolated in the pure state by fractional crystallization of the partial racemates, the *l*-salt being less soluble in all cases.

The phenomenon of "asymmetric transformation of the second order," as described by Kühn (76), was observed during the fractional crystallization of the *d*-tartrate chloride. Further evidence regarding the phenomenon was derived from the study of the "addition curve," as described by Jamieson and Turner (72). It expresses the rotation as a function of the acid-base ratio.

In a solution of the *d*-tartrate chloride of the racemoid complex it has been shown that there is an equilibrium between the dextrorotatory and the levorotatory forms, with the former in slight excess. The first crop of crystals separating from this solution consisted of pure levorotatory diastereomer. From the dextrorotatory mother liquor the pure dextrorotatory

TABLE 16

The known cobalt(III) tris(biguanide) complexes

BH = a molecule of biguanide; B'H = a molecule of a substituted biguanide; B*H = B'

Ligand	Complex ^(a)	References
Biguanide..... C ₂ H ₇ N ₃	[Co(B) ₃], [Co(B) ₂]·2H ₂ O, [Co(BH) ₃]X ₃ X = F, Cl, Br, I, SCN, I ₂ (13; black), BF ₄ , ClO ₄ , IO ₃ , ClO ₃ , NO ₃ , NO ₂ , HS, HS ₂ , ‡CO ₂ , ‡C ₂ O ₄ , ‡SO ₄ (3.5), ‡SO ₄ (3.5), ‡S ₂ O ₈ , ‡S ₂ O ₈ , ‡SeO ₄ (3.5), ‡IO ₄ (3), ‡CrO ₄ (4), ‡HPO ₄ (3), <i>d</i> -C ₁₀ H ₁₁ OSO ₄ , ‡(Cl·IO ₄) X ₃ = Cl·CO ₂ , Cl·SeO ₄ , (OH)SO ₄ , Cl·S ₂ O ₈ (2.5), Cl·CrO ₄ , Cl·HPO ₄ , Cl· <i>d</i> -C ₄ H ₉ O ₄ Δ ₁₉₃₄ (25°C.) for the base = 92.0 mhos α (cryoscopic) = 0.87 in 0.267% solution Λ _∞ (25°C.) for the chloride = 138.5 mhos α (cryoscopic) = 0.98 in 0.5784% solution	(119, 128, 129)
N ¹ -Methylbiguanide..... CH ₃ C ₂ H ₆ N ₃	[Co(B'H) ₃]X ₃ X = Cl, ‡SO ₄ (1.5)	(104)
N ¹ -Ethylbiguanide..... C ₂ H ₅ C ₂ H ₆ N ₃	[Co(B'H) ₃](SO ₄) ₂ ·1.5H ₂ O	(104)
N ¹ -(<i>n</i> -Hexyl)biguanide..... C ₆ H ₁₃ C ₂ H ₆ N ₃	[Co(B'H) ₃](OH) ₃	(42)
N ¹ -(2-Hydroxyethyl)biguanide..... HOC ₂ H ₄ C ₂ H ₆ N ₃	[Co(B'H) ₃](SO ₄) ₂ ·4H ₂ O; very soluble in water	(166)
N ¹ ,N ¹ -Dimethylbiguanide..... (CH ₃) ₂ C ₂ H ₆ N ₃	[Co(B' ¹) ₃]·0.5H ₂ O	(104)
N ¹ ,N ¹ -Diethylbiguanide..... (C ₂ H ₅) ₂ C ₂ H ₆ N ₃	[Co(B' ¹) ₃]·2.5H ₂ O	(104)
N ¹ -Phenylbiguanide..... C ₆ H ₅ C ₂ H ₆ N ₃	[Co(B' ¹) ₃], [Co(B' ¹) ₂]·3H ₂ O (insoluble in water and alcohol), [Co(B' ¹) ₂]·2H ₂ O (insoluble in water but soluble in alcohol and acetone), [Co(B'H) ₃]X ₃ X = Cl (2.5), Br (1), I (1), SCN (3), NO ₂ (0.5), NO ₃ (0.5), ‡CO ₂ (1), ‡SO ₄ (5), ‡S ₂ O ₈ (3.5), ‡S ₂ O ₈ (1), ‡CrO ₄ (1) X ₃ = Cl· <i>d</i> -C ₄ H ₉ O ₄ Λ _∞ (35°C.) for the chloride = 141.3 mhos α (cryoscopic) = 0.75 in 0.5342% solution of the chloride X _g = -0.5501 × 10 ⁻⁴	(121, (168))
N ¹ -Benzylbiguanide..... C ₆ H ₅ CH ₂ C ₂ H ₆ N ₃	[Co(B'H) ₃]X ₃ X = OH, Cl (3), ‡SO ₄ (5)	(108)
N ¹ -(4-Sulfophenyl)biguanide..... 4-HSO ₃ C ₆ H ₄ C ₂ H ₆ N ₃	[Co(B' ¹) ₃]·5H ₂ O, [Co(B' ¹) ₂]·7H ₂ O, K ₃ [Co(B* ¹) ₃]·3H ₂ O (B*H = B')	(133, 153)
N ¹ -(<i>o</i> -Phenylene)biguanide..... C ₆ H ₄ C ₂ H ₆ N ₃	[Co(B' ¹) ₃], [Co(B' ¹) ₂]·3.5H ₂ O, [Co(B' ¹) ₂]·5CH ₂ COOH·H ₂ O	(39, 188)
N ¹ -(2-Sulfo-1-naphthyl)biguanide..... <i>o</i> -HO ₂ SC ₁₀ H ₇ C ₂ H ₆ N ₃	[Co(B' ¹) ₃]·6H ₂ O, Na ₃ [Co(B* ¹) ₃]·2H ₂ O, K ₃ [Co(B* ¹) ₃]·5H ₂ O	(133)
N ¹ -(<i>p</i> -Chlorophenyl)-N ¹ -isopropylbiguanide..... <i>p</i> -ClC ₆ H ₄ (C ₃ H ₇)C ₂ H ₆ N ₃	[Co(B' ¹) ₃]·2H ₂ O	(104)

(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

form was obtained by repeated fractional precipitation with alcohol. The slow rate of transformation in solution leading to an equilibrium, suggested thereby, was verified by experiments with a freshly prepared solution of the *d*-tartrate chloride of the racemoid complex, as well as of their levorotatory and dextrorotatory enantiomers.

From a measurement of the specific rotations of the freshly prepared solutions of the levorotatory and the dextrorotatory forms, as well as of the same solutions after sufficient time had been allowed for equilibrium when no further change in their rotation occurred, the equilibrium compositions of the solutions were determined. From this the equilibrium constant for the transformation *l*-salt \rightleftharpoons *d*-salt was calculated for two different temperatures, 25°C. and 46.1°C. A value of 923 cal. as the heat of transformation from the *l*-salt to the *d*-salt was thus obtained from the temperature variation of the equilibrium constant. The free-energy changes for the process were found to be given by 89.1 cal. at 25°C. and 30.4 cal. at 46.1°C. The two equilibrium constants are given as $K_{25} = 1.16$ and $K_{46.1} = 1.05$ (129).

From a solution of the *d*-tartrate of the racemoid complex, both the levorotatory and the dextrorotatory forms can be obtained in the pure state by the normal process of fractionation only as the least and the most soluble fraction, respectively, owing to their favorable solubility and stability relationships (129).

From the pure levorotatory and the dextrorotatory forms of these diastereomers pure optically active enantiomers of the complex cobalt(III) tris(biguanide) chloride, nitrate, and sulfate were prepared. The average molecular rotation of all these active salts at 31°C. has a value of about $\pm 2110^\circ$ per cobalt atom (129). The salts in the solid state retain their optical activity unchanged even after a year, but in solution above 25°C. they slowly lose their activity by racemization (129).

The same authors (130) have determined the kinetics of racemization of *l*- and *d*-cobalt(III) tris(biguanide) *d*-tartrate chloride, as well as of the pure enantiomers, *l*- and *d*-cobalt(III) tris(biguanide) chloride, in aqueous solution at different temperatures, and the activation energy in each case was calculated from the temperature coefficient of the rate constant. The values

found for the activation energy are 22,310 and 21,350 cal. per mole for the *l*- and the *d*-diastereomer, respectively, and 13,930 cal. per mole for the pure active enantiomers of the complex chloride. Many simple and complex foreign cations, including the hydrogen ion, when added to the solution retard the inversion rate of the active cobalt(III) tris(biguanide) chloride, which is more or less completely inhibited by calcium, copper(II), manganese(II), and hydrogen ions even when present in very small quantities. Anions have generally no effect on the rate of transformation, excepting for hydroxide ion, which exercises a powerful accelerating effect on the rate of racemization (130).

From a consideration of the kinetics of racemization of the cobalt(III) tris(biguanide) complexes and a critical examination of the previously suggested theories regarding the mechanism of racemization of optically active coordination complexes, Rây and Dutt (131) have suggested a new mechanism for the process on the basis of intramolecular rearrangement of the chelating groups. This does not admit of the opening of any chelate rings or of any of the metal-ligand bonds even for a moment. According to this view, when a molecule is activated by the addition of energy two pairs of octahedral bonds, holding any two of the three chelating groups, rotate along their own planes in opposite directions through an angle of 45° . The bond angles between the planes of two pairs remain, however, unchanged at 90° during the process. The activated molecule with its distorted octahedron, on the removal of excess energy, can then return to the normal octahedral state either by retracing its previous steps to regenerate the original active form, or by a further rotation through 45° of the displaced chelating pairs in the same direction as before to degenerate into the mirror-image enantiomer of its former structure. Since the two enantiomers have equal energy content, both are formed with equal ease. The mechanism proposed by Rây and Dutt is illustrated in figure 1.

Cobalt(III) tris(phenylbiguanide) chloride has also been resolved into its optical enantiomers through the fractional crystallization of its *d*-tartrate chloride. The levorotatory diastereomer, being less soluble, separates out first. The dextrorotatory form is obtained

from the mother liquor. Their molecular rotation is given by $[M]_D^{25} = \pm 288^\circ$. From the two diastereomers the optically active pure dextrorotatory and levorotatory components of the cobalt(III) tris(phenylbiguanide) chloride, sulfate, and nitrate were prepared with an average molecular rotation, $[M]_D^{25}$, equal to $\pm 2469^\circ$. The kinetics of racemization of the complex levorotatory chloride was also measured at different temperatures and the activation energy for the change, calculated from the temperature coefficient of the rate constant, was found to be 9700 cal. per mole (168). This is much lower than that for cobalt(III) tris(biguanide) chloride (13,930 cal.).

2. Bis(biguanide) complexes

Several bis(biguanide) complexes of cobalt(III) have been described, which necessarily contain other ligands as well to saturate the coordination number (six) of the metal atom. With two identical or different monodentate ligands in the complex, some new varieties of the bis(biguanide) complex have been obtained. These are mainly diamminocobalt(III), hydroxoquoocobalt(III), and dicyanocobalt(III) bis(biguanide) complexes. The charge on the complex ion varies of course with the nature of the monodentate ligand present.

In the case of diammine and hydroxoquo complexes two series of compounds, related to each other as cis-trans isomers, have been isolated.

The cis series of these compounds was studied by Rây and Ghosh (138). The diamminocobalt(III) bis(biguanide) sulfate, $[\text{Co}(\text{NH}_3)_2(\text{C}_2\text{H}_7\text{N}_5)_2](\text{SO}_4)_3 \cdot 12\text{H}_2\text{O}$, was obtained by the oxidation of cobalt(II) bis(biguanide) suspended in concentrated ammonia solution with a current of air. The filtrate, on neutralization with dilute sulfuric acid and cooling, deposited red crystals of the complex sulfate after a day or two. On the passage of a current of air through the filtrate until all ammonia had been removed, the color of the solution turned violet. This solution, after neutralization with dilute sulfuric acid and standing for a day or two in the cold, deposited beautiful, needle-shaped, violet crystals of the hydroxoquoocobalt(III) bis(biguanide) sulfate, $[\text{Co}(\text{H}_2\text{O})(\text{OH})(\text{C}_2\text{H}_7\text{N}_5)_2]\text{SO}_4 \cdot 2.5$

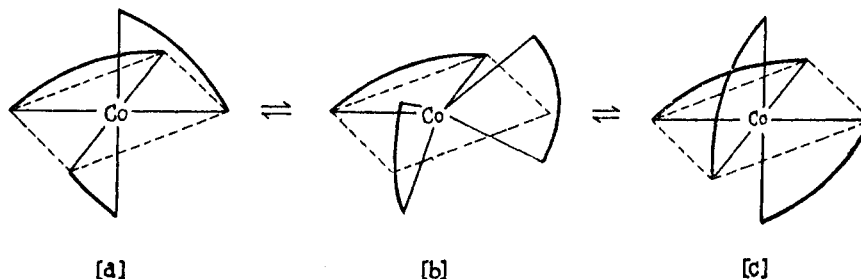
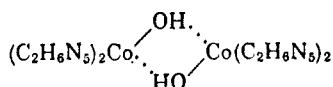


FIG. 1. Racemization of active cobalt(III) biguanide complexes. (a) Dextrorotatory form (octahedral); (b) intermediate form (distorted octahedral); (c) levorotatory form (octahedral).

H₂O (138). This complex hydroxoquo sulfate loses 3.5 H₂O when heated to 80°C. and is thereby converted to the brown-violet sulfatohydroxocobalt(III) bis(biguanide), [Co(OH)(SO₄)(C₂H₇N₅)₂]. On exposure to moist air the latter changes back to the original violet hydroxoquo complex (138).

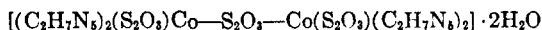
A series of other salts of the hydroxoquo complex, viz., the chloride (1H₂O), the nitrate, the sulfite, the thiosulfate (1H₂O), and the dithionate (1H₂O), have been prepared and the equivalent conductivity of the chloride determined (138). Δ_∞(25°C.) for the chloride = 120.6 mhos.

The complex base, [Co(H₂O)(OH)(C₂H₇N₅)₂](OH)₂·H₂O, is precipitated in the form of dark violet crystals by the action of alkali on the solution of the complex chloride. At 80°C. it loses all water, including even that inside the complex, to form a dark violet product of the composition Co(OH)(C₂H₆N₅)₂, which is represented as a binuclear diol complex having the structure:



This is regarded as evidence for the cis configuration of these hydroxoquo complexes and consequently of the parent diammine complex (138). The formation of an oxalatocobalt(III) bis(biguanide) oxalate, [Co(C₂O₄)(C₂H₇N₅)₂]₂C₂O₄·4H₂O, from the hydroxoquo base and oxalic acid, which loses all its water at 95°C. without any change, is also cited as additional evidence in support of this conclusion (142).

The violet crystals of hydroxoquo cobalt(III) bis(biguanide) thiosulfate (1H₂O), formed by precipitation from a solution of the complex chloride with that of sodium thiosulfate, change immediately into a bright green, insoluble product with an excess of the precipitant (thiosulfate). The same change also occurs slowly on shaking the violet crystals with water alone and more rapidly upon the addition of a trace of acid. The product has the composition Co₂(S₂O₃)₃(C₂H₇N₅)₄·2H₂O and loses all its water at 90°C. without any change. It does not react with a solution of barium chloride in the cold, and for this reason is represented by a binuclear structure (138).



But no definite conclusion is possible without an analysis of its structure by physical methods.

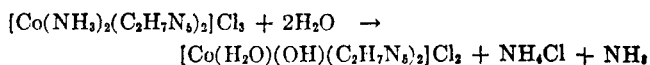
The trans series of these diammine and hydroxoquo complexes was investigated by Rây and Majumdar (142), and a number of basic and normal *trans*-diamminecobalt(III) bis(biguanide) salts have been described. These by deamination and dehydration, followed in certain cases by hydrolysis, have led to the formation of hydroxoamine-, acidohydroxo-, hydroxo-aquo-, diacido-, and diaquo cobalt(III) bis(biguanide)

salts. The trans configuration of the series was deduced from a consideration of the composition and properties of the hydroxoquo cobalt(III) bis(biguanide) oxalate in the series, as well as from the difference in properties of the compounds of this series from those of the cis series.

The parent compound of the trans series, the diamminecobalt(III) bis(biguanide) hydroxide sulfate, [Co(NH₃)₂(C₂H₇N₅)₂](OH)SO₄·2H₂O, is obtained in the form of rectangular red crystals by passing a current of air through a mixture of biguanide sulfate and cobalt chloride in 6 N ammonia solution. The compound loses water and ammonia to give the hydroxoamminecobalt(III) bis(biguanide) sulfate, [Co(NH₃)(OH)(C₂H₇N₅)₂]-SO₄, at 90°C. and the sulfatohydroxocobalt(III) bis(biguanide), [Co(OH)(C₂H₇N₅)₂SO₄], at 100°C. (142).

From the diamminecobalt(III) bis(biguanide) hydroxide sulfate, the corresponding nitrate hydroxide (1.5H₂O) and the chloride hydroxide, and from the latter by deamination at 80°C. the chlorohydroxocobalt(III) bis(biguanide) chloride, [Co(OH)Cl(C₂H₇N₅)₂]Cl, were obtained (142). Suitable treatment of the diammine complex with dilute acids or ammonium salts led further to the preparation of its sulfate chloride (1H₂O), sulfate (12H₂O), chloride (2H₂O), and nitrate (1H₂O), besides the sulfate bromide and the sulfate iodide of somewhat different composition, [Co(NH₃)₂(C₂H₇N₅)₂Br₄(I₄)SO₄·3.5H₂O (142).

The sulfate of the diammine complex, when dried at 110°C., gave by deamination sulfatocobalt(III) bis(biguanide) sulfate, [Co(SO₄)(C₂H₇N₅)₂]₂SO₄. In a similar manner the chloride of the diammine complex gave the dichlorocobalt(III) bis(biguanide) chloride, [CoCl₂(C₂H₇N₅)₂]Cl. The equivalent conductivity for the complex diammine chloride gave a rather high value of 178.8 mhos, indicating hydrolysis into a hydroxoquo complex (142).



The *trans*-hydroxoquo cobalt(III) bis(biguanide) sulfate, [Co(H₂O)(OH)(C₂H₇N₅)₂]SO₄·2H₂O, was obtained in the form of very soluble, red crystals from the aqueous solution of the sulfatohydroxocobalt(III) bis(biguanide) by hydrolysis. The corresponding chloride (1H₂O) was prepared similarly by the hydrolysis of chlorohydroxocobalt(III) bis(biguanide) chloride, to which it changes back by dehydration at 80°C. The oxalate (4H₂O) of the hydroxoquo complex was prepared by neutralization of the complex base with oxalic acid in the form of highly soluble, prismatic, rose-colored crystals. The base was obtained in aqueous solution from the solution of its sulfate and barium hydroxide solution (142).

The hydrolysis of dichlorocobalt(III) bis(biguanide) gave the chloride of the diaquo complex, [Co(H₂O)₂-

(C₂H₇N₅)₂Cl₃, which was found to revert back to its parent dichloro complex upon dehydration at 110°C. The corresponding sulfate of the diaquo complex was obtained in a similar manner from the hydrolysis of sulfatocobalt(III) bis(biguanide) sulfate (142).

The characteristic properties of the *cis* and *trans* isomers of some of the typical cobalt(III) bis(biguanide) complexes are summarized in table 17.

The properties of the diamminecobalt(III) bis(biguanide) complexes suggest that in their solutions there is evidently an equilibrium among the diammine, hydroxoquo, and diaquo complexes, any of which may separate from the solution under circumstances favorable for its occurrence in high concentration. There is scope for physicochemical studies in this connection.

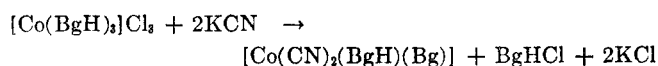
Oxidation of cobalt(II) bis(biguanide) sulfate suspended in an aqueous solution of methylamine, ethylamine, or *n*-propylamine with a current of air has also led to the preparation of the corresponding bis(alkylamine)cobalt(III) bis(biguanide) sulfate hydroxides, which crystallize with 4, 3, and 5.5 molecules of water, respectively. They can be represented by the general formula [Co(RNH₂)₂(B'H)₂](OH)SO₄. With benzylamine a normal sulfate of the composition [Co(RNH₂)₂(B'H)₂](SO₄)₃·10H₂O has been obtained (106).

Using pyridine in place of the amines Ghosh and Gupta (58) have similarly prepared the dipyridinecobalt(III) bis(biguanide) hydroxide, [Co(C₅H₅N)₂(C₂H₇N₅)₂](OH)₃, in the form of red crystals. From the complex hydroxide a number of its salts like the chloride dihydroxide (0.5H₂O), the chloride dibromide (2H₂O), the iodide (2H₂O), the nitrate, the sulfate (12H₂O), the thiosulfate (6H₂O), and the oxalate (8H₂O) have been obtained. The equivalent conductivity for the nitrate at 35°C. is given by Λ_∞ = 156.3 mhos. The solution of the red thiosulfate, like the thiosulfate of the hydroxoquo cobalt(III) bis(biguanide) complex, gives a precipitate of the green, binuclear, thiosulfato

(bridge) compound by treatment with an excess of thiosulfate solution or a trace of acetic acid (138). The solution of the complex oxalate, when heated to 60°C. in the presence of a little sulfuric acid, changes gradually in color from red to violet with elimination of pyridine and deposits, on cooling, violet crystals of oxalatocobalt(III) bis(biguanide) oxalate, identical with that obtained from the *cis*-hydroxoquo complex (142). Unlike the diamminecobalt(III) bis(biguanide) complex, the dipyridine complex does not readily hydrolyze to give rise to hydroxoquo and diaquo complexes. From an examination of the properties of the thiosulfate and oxalate salts of the dipyridine complex a *cis* configuration might be assumed for its structure, though a *trans* configuration is preferred by Ghosh and Gupta (58).

In a similar manner oxidation of cobalt(II) bis(*n*-hexylbiguanide) and of cobalt(II) bis(benzylbiguanide) sulfate in the presence of aqueous pyridine has led to the preparation of dipyridinecobalt(III) bis(*n*-hexylbiguanide) hydroxide, [Co(C₅H₅N)₂(C₆H₁₃C₂H₆N₅)₂](OH)₃, in violet crystals (42), and of dipyridinecobalt(III) bis(benzylbiguanide) sulfate, [Co(C₅H₅N)₂(C₆H₅CH₂C₂H₆N₅)₂](SO₄)₃·2.5H₂O in the form of red-violet crystals (108).

Sengupta and Rây (161) have recently described a number of dicyanocobalt(III) bis(biguanide) complexes in which biguanide and several substituted biguanides occur as chelating ligands. These were obtained in the form of sparingly soluble, golden-yellow, shining, silky crystals by heating on the water bath a mixture of a cobalt(III) tris(biguanide) complex and potassium cyanide in aqueous solution. The reaction is represented as follows, where BgH is a molecule of any biguanide:



From the complex bases a number of their soluble salts were obtained by digestion with ammonium

TABLE 17
Cobalt(III) bis(biguanide) complexes (*cis* and *trans*)
BH = C₂H₇N₅

Compound	Properties	
	<i>Cis</i> form	<i>Trans</i> form
[Co(NH ₃) ₂ (BH) ₂](SO ₄) ₃ ·12H ₂ O	Red crystals; soluble in water; solution readily turns violet, forming hydroxoquo complex by hydrolysis, and reacts alkaline	Light rose-red, prismatic needles; solution neutral to litmus
[Co(H ₂ O)(OH)(BH) ₂](OH) ₃	Contains 1 H ₂ O; dark violet, needle-shaped crystals; insoluble in water; forms binuclear bridge compound at 80°C.; gives with oxalic acid blue-violet, prismatic crystals, insoluble in water, of [Co(C ₂ O ₄)(BH) ₂](C ₂ O ₄)·4H ₂ O	Forms red solution; not isolated in the solid state; gives with oxalic acid highly soluble, rose-red, prismatic crystals of an oxalate (4 H ₂ O) which reacts acid to litmus in solution
[Co(H ₂ O)(OH)(BH) ₂](SO ₄)	Contains 2.5 H ₂ O; rectangular, violet prisms; sparingly soluble in hot water	Contains 2 H ₂ O; red crystals; very soluble in water; solution reacts alkaline to litmus
[Co(H ₂ O)(OH)(BH) ₂](Cl) ₃ ·H ₂ O	Violet prisms; soluble in water; gives with Na ₂ S ₂ O ₄ solution a violet thiosulfate, sparingly soluble in water; turns in presence of a trace of acid into the insoluble, binuclear, green complex	Red-violet, needle-shaped crystals; soluble in water; solution reacts alkaline; does not react with Na ₂ S ₂ O ₄ solution unless acidified, when it gives the insoluble green product

salts, and the addition of suitable alkali salts to the solution of the fairly soluble dicyanocobalt(III) bis(biguanide) chlorides led to the separation of many other sparingly soluble salts of the cobalt(III) complex. Like cobalt(III) complexes in general, all these dicyanocobalt(III) bis(biguanide) compounds are diamagnetic (161). They are, however, decomposed by acids (161).

Table 18 provides a list of the known dicyanocobalt(III) bis(biguanide) complexes.

TABLE 18

The known dicyanocobalt(III) bis(biguanides)
BH = a molecule of biguanide; B'H = a molecule of a substituted biguanide

Biguanide Ligand	Complex ^(a)	Reference
Biguanide..... C ₂ H ₅ N ₃	[Co(CN) ₂ B(BH)], [Co(CN) ₂ (BH) ₂]X X = Cl, NO ₃ , SCN, $\frac{1}{2}$ SO ₄ (1) Λ_{∞} (35°C.) for the chloride = 128 mhos χ_g (base) = -0.5224×10^{-4} χ_g (sulfate) = -0.1821×10^{-4}	(161)
N ¹ -Methylbiguanide..... CH ₃ C ₂ H ₅ N ₃	[Co(CN) ₂ (B'H) ₂]X X = OH (1), Cl (1.5), $\frac{1}{2}$ SO ₄ (2.5) Λ_{∞} (35°C.) for the chloride = 129.9 mhos χ_g (base) = -0.5055×10^{-4}	(161)
N ¹ ,N ¹ -Dimethylbiguanide (CH ₃) ₂ C ₂ H ₅ N ₃	[Co(CN) ₂ (B'H) ₂]X X = OH, $\frac{1}{2}$ SO ₄	(161)
N ¹ -Ethylbiguanide..... C ₂ H ₅ C ₂ H ₅ N ₃	[Co(CN) ₂ (B'H) ₂]X X = OH, $\frac{1}{2}$ SO ₄ (2)	(161)
N ¹ ,N ¹ -Diethylbiguanide... (C ₂ H ₅) ₂ C ₂ H ₅ N ₃	[Co(CN) ₂ B'(B'H)], [Co(CN) ₂ (B'H) ₂] $\frac{1}{2}$ SO ₄ · H ₂ O	(161)
N ¹ -(n-Hexyl)biguanide... C ₆ H ₁₃ C ₂ H ₅ N ₃	[Co(CN) ₂ (B'H) ₂]X X = OH (1), $\frac{1}{2}$ SO ₄ (2.5)	(161)
N ¹ -Phenylbiguanide..... C ₆ H ₅ C ₂ H ₅ N ₃	[Co(CN) ₂ (B'H) ₂]X X = OH (2.5), Cl	(161)
N ¹ -Benzylbiguanide..... C ₆ H ₅ CH ₂ C ₂ H ₅ N ₃	[Co(CN) ₂ (B'H) ₂]X X = OH, Cl (2.5), $\frac{1}{2}$ SO ₄ (5) Λ_{∞} (35°C.) for the chloride = 127.3 mhos χ_g (base) = -0.2391×10^{-4}	(161)

(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

3. Dibiguanide complexes

With dibiguanides the tripositive cobalt ion combines to form the binuclear dicobalt(III) tris(dibiguanide) complexes, besides the mononuclear cobalt(III) dibiguanide complexes containing one molecule of a quadridentate dibiguanide ligand along with two other monodentate ligands for saturation of the coordination number of the metal.

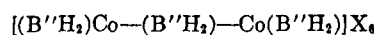
Dicobalt(III) tris(ethylenedibiguanide) hydroxide, [Co₂{C₂H₄(C₂H₅N₃)₂]₃(OH)₆, was prepared by digesting on the water bath a solution of hexamminecobalt(III) chloride, [Co(NH₃)₆]Cl₃, with one of ethylenedibiguanide sulfate in alkaline (5 per cent sodium hydroxide) solution. The complex base separated from the solution in the form of insoluble dark red crystals after the evolution of ammonia had ceased. The action of dilute acids on the complex base led to the prepara-

tion of its chloride (12H₂O), nitrate (9H₂O), and sulfate (12H₂O) in the form of insoluble reddish brown crystals (108).

In a similar manner dicobalt(III) tris(hexamethylenedibiguanide) hydroxide, [Co₂{C₆H₁₃(C₂H₅N₃)₂]₃(OH)₆, has been prepared from hexamminecobalt(III) chloride and an alkaline solution of hexamethylenedibiguanide sulfate in the form of insoluble, dark red crystals (43).

Dicobalt(III) tris(*m*-phenylenedibiguanide) hydroxide, [Co₂{C₆H₄(C₂H₅N₃)₂]₃(OH)₆ · 10H₂O, was obtained in the form of insoluble red crystals by oxidizing with air a mixture of cobalt(II) chloride (CoCl₂ · 6H₂O) and an excess of *m*-phenylenedibiguanide chloride in concentrated ammonia solution, followed by treatment with an excess of concentrated potassium hydroxide solution. The complex base, when treated with the requisite amount of appropriate dilute acids, gave salts like the chloride (13H₂O), the nitrate, and the sulfate (25H₂O) in the form of orange-red crystals (127). The chloride in aqueous solution gave an equivalent conductivity, Λ_{∞} (35°C.), of 129.1 mhos (127).

The constitution of these binuclear dicobalt(III) complexes is represented as follows, with a dibiguanide molecule serving as a bridge between the two metal atoms:



where B''H₂ = a molecule of the dibiguanide and X = OH, Cl, or $\frac{1}{2}$ SO₄. The quadridentate dibiguanide molecule at the center satisfies two cis positions of each octahedral cobalt atom on its two opposite sides (127). These binuclear dicobalt(III) tris(dibiguanide) salts may, therefore, be capable of being resolved into their optically active enantiomers, or they may, like meso-tartaric acid, possess an internally compensated inactive configuration.

A number of mononuclear cobalt(III) complexes of these dibiguanides, containing two other identical or different monodentate ligands, have also been described (108, 127).

The oxidation of cobalt(II) ethylenedibiguanide sulfate, suspended in aqueous ammonia, methylamine, or ethylamine, with air or hydrogen peroxide has led to the preparation of the diammine-, bis(methylamine)-, and bis(ethylamine)cobalt(III) ethylenedibiguanide sulfate hydroxide with 4, 4.5, and 3.5 molecules of water, respectively. With benzylamine the complex separated as a normal sulfate with 12 molecules of water. They all form rose-red crystals, soluble in water, and can be represented by the general formula [Co(Am)₂C₂H₄(C₂H₅N₃)₂]X₃ · aq, where Am = ammonia or an amine and X = OH and/or $\frac{1}{2}$ SO₄ (108).

When pyridine was employed in place of ammonia or an amine, highly soluble, brownish violet crystals of hydroxypyridinecobalt(III) ethylenedibiguanide sul-

fate, $[\text{Co}(\text{C}_6\text{H}_5\text{N})(\text{OH})\text{C}_2\text{H}_4(\text{C}_2\text{H}_5\text{N}_6)_2]\text{SO}_4 \cdot 3.5\text{H}_2\text{O}$, were obtained (108).

Oxidation of a mixture of cobalt chloride and *m*-phenylenedibiguanide hydrochloride in concentrated ammonia solution with air, followed by neutralization with dilute hydrochloric acid, has led to the preparation of diamminecobalt(III) *m*-phenylenedibiguanide chloride. It forms dark brown crystals, which suffer dehydration at 90°C. and deamination at 105°C. to give dichlorocobalt(III) *m*-phenylenedibiguanide chloride, $[\text{CoCl}_2\text{C}_6\text{H}_4(\text{C}_2\text{H}_5\text{N}_6)_2]\text{Cl}$. The equivalent conductivity in aqueous solution of the diammine chloride, Λ_{∞} (35°C.), is 148.05 mhos (127). From a solution of the complex diammine chloride the corresponding nitrate (1H₂O) and sulfate (12H₂O) are precipitated by the addition of ammonium nitrate and ammonium sulfate, respectively; with caustic potassium hydroxide solution the insoluble chocolate-brown hydroxide (5H₂O) is formed (127).

A solution of the complex diamminecobalt(III) *m*-phenylenedibiguanide chloride, when digested with concentrated potassium hydroxide, gave, with loss of ammonia, pale brown crystals of a diaquo base, $[\text{Co}(\text{H}_2\text{O})_2\text{C}_6\text{H}_4(\text{C}_2\text{H}_5\text{N}_6)_2](\text{OH})_3 \cdot \text{H}_2\text{O}$. On treatment with dilute hydrochloric acid it gave red-brown crystals of the diaquo chloride with an equivalent conductivity in aqueous solution of Λ_{∞} (35°C.) = 137.9 mhos. From the solution of the complex chloride sparingly soluble, orange-brown crystals of the diaquo chloride (16H₂O) and violet crystals of the oxalate (4H₂O) were obtained by the addition of alkali sulfate and oxalate, respectively (127).

Action of potassium cyanide solution on dicobalt(III) tris(ethylenedibiguanide) and tris(hexamethylenedibiguanide) chloride at the temperature of a water bath, followed by treatment with ammonium chloride, led to the preparation of dicyanocobalt(III) ethylenedibiguanide chloride (3H₂O) and of the corresponding hexamethylenedibiguanide chloride (2.5H₂O), respectively, in the form of yellow crystalline precipitates. Dicobalt(III) tris(*m*-phenylenedibiguanide) chloride under similar conditions gave orange-yellow crystals of the dicyanocobalt(III) *m*-phenylenedibiguanide hydroxide (2.5H₂O), from which by the action of ammonium sulfate the sulfate of the complex base containing nine molecules of water was prepared. The magnetic susceptibility value for the hydroxide is given by $\chi_g = 0.4635 \times 10^{-6}$ (161). All these dicyanocobalt(III) dibiguanide complexes can be represented by the general formula $[\text{Co}(\text{CN})_2(\text{B}''\text{H}_2)]\text{X} \cdot \text{aq}$, where B''H₂ = a molecule of the dibiguanide and X = OH, Cl, or $\frac{1}{2}\text{SO}_4$.

It is rather unlikely from stereochemical considerations that a molecule of hexamethylenedibiguanide might occur in a monomeric octahedral complex. In fact, even the dicyanocobalt(III) ethylenedibiguanide

chloride has been found to change more or less readily into an amorphous gummy mass after its isolation (161), indicating the formation of polymeric aggregates.

F. CHROMIUM(III) BIGUANIDES

Chromium(III) biguanide complexes were first studied by Ráy and Saha (146). These resemble closely the cobalt(III) biguanides in composition and properties, though they are comparatively less stable than the latter.

Unlike the cobalt(III) biguanides, the chromium(III) biguanide complexes are all paramagnetic with a value for the magnetic moment corresponding to the presence of three unpaired electrons, in general agreement with practically all well-defined chromium(III) compounds, both simple and complex.

1. Tris(biguanide) complexes

Chromium(III) tris(biguanide) hydrate, $[\text{Cr}(\text{C}_2\text{H}_6\text{N}_6)_3] \cdot \text{H}_2\text{O}$, has been obtained in the form of bright, crimson-red, prismatic crystals by the gradual addition of a saturated solution of chrome alum to one of biguanide sulfate in 30 per cent sodium hydroxide solution. It behaves in aqueous solution as a triacid base, stronger than ammonia. In a pH titration it gives a sharp inflection at three equivalents of perchloric acid (8a). At 150–160°C. it loses water to form the anhydrobase (146). Complexes with substituted biguanides were also prepared in a similar manner. Salts of the complex bases, particularly the chlorides, were prepared by treating the respective bases with appropriate acids or ammonium salts. The complex chlorides were then employed for the preparation of other salts by double decomposition with the corresponding alkali salts.

All chromium(III) tris(biguanide) bases are red and their salts are yellow to orange-yellow, unless the anion is colored.

The known chromium(III) tris(biguanide) complexes are listed in table 19.

2. Bis(biguanide) complexes

The chromium(III) tris(biguanide) base and its salts have been found to undergo slow hydrolysis in dilute aqueous solution, particularly on warming (146). This has led to the isolation of a series of hydroxoquo-chromium(III) bis(biguanide) complexes (147, 148). These bis(biguanide) complexes in dilute aqueous solution undergo further hydrolysis on keeping with elimination of biguanide molecules, leading finally to the separation of chromium(III) hydroxide. The sequence of the hydrolysis is represented as follows (146, 147).

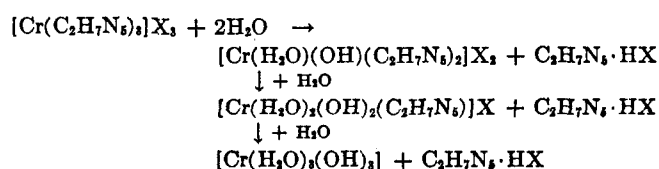


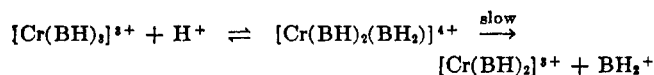
TABLE 19

The known chromium(III) tris(biguanide) complexes
 BH = a molecule of biguanide; B'H = a molecule of a
 substituted biguanide

Ligand	Complex ^(a)	References
Biguanide C ₂ H ₇ N ₃	[Cr(B) ₃], [Cr(B) ₃]·H ₂ O, [Cr(BH) ₃]X ₃ X = Cl, Br, I, J ₂ (5.5), SCN, NO ₂ , NO ₃ , HS, †CO ₂ (2), †SO ₄ (2), †S ₂ O ₄ , †CrO ₄ (5), †CrO ₄ (4), †Fe(CN) ₆ , †Co(CN) ₆ , †Cr- (SCN) ₆ , †Co(NO ₂) ₆ , C ₁₀ H ₁₅ OSO ₃ X ₃ = Cl·CO ₂ , Cl·SO ₄ (1), (OH)- SO ₄ (2.5), Cl·S ₂ O ₄ , Cl·CrO ₄ (1), Cl·HPO ₄ , Cl·[Fe(NO)(CN) ₅], (OH)(HgI ₂) ₂ , Cl(BiI ₄) ₂ , OH(SCN) ₃ (1) Λ _∞ (30°C.) for the chloride = 146 mhos α (cryoscopic) for the chloride = 0.97 in 0.72% solution α (cryoscopic) for the base = 0.75 in 0.25% solution χ _g (31°C.) for the hydrated base = 16.47 × 10 ⁻⁴ Magnetic moment = 3.86 Bohr magnetons	(119, 135, 146, 148)
N ⁴ -(n-Hexyl)biguanide . . . C ₆ H ₁₃ C ₂ H ₅ N ₃	[Cr(B'H) ₃](OH) ₃ , insoluble in water but soluble in alcohol	(42)
N ⁴ -Phenylbiguanide C ₆ H ₅ C ₂ H ₅ N ₃	[Cr(B' ¹) ₃], [Cr(B' ²) ₃]X ₃ X = OH, Cl, Br, I, NO ₂ , †SO ₄ (2), †CrO ₄ Λ _∞ (0°C.) for the chloride = 65 mhos α (0°C.) for the chloride = 0.85 in 1% solution	(136)
N ⁴ -Benzylbiguanide C ₆ H ₅ CH ₂ C ₂ H ₅ N ₃	[Cr(B' ¹) ₃]·1.5H ₂ O, [Cr(B' ²) ₃]X ₃ X = Cl, †SO ₄ (2)	(108)

^(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

The acid hydrolysis (aquation) of chromium(III) tris(biguanide) and chromium(III) tris(phenylbiguanide) complexes into the corresponding diaquobis(biguanides), recently studied by Banerjee and Chakravarty (8a), indicates a first-order dependence of the rate on both the complex and the hydrogen-ion concentrations. Under comparable conditions (complex, 0.001 M; HClO₄, 0.02 M; NaClO₄, 0.2 M; temperature, 35.5°C.) the pseudo-first-order rate constants obtained are 0.08 and 0.018 min.⁻¹, respectively, indicating greater *lability* (kinetic) of the former, which is somewhat more *stable* (thermodynamic) (8). The authors suggest that the reaction involves protonation of the complex-bound ligand at the basic imino (=NH) group which is free, followed by the actual loss of the ligand:



This mechanism accounts for all the observed facts: namely, the dependence of the rate on the concentrations of the complex and the hydrogen ions as also on the decrease in rate with decreasing basic strength of the ligand. In support of this the authors observe that in the case of the analogous change for the chromium(III) tris(ethylenediamine) complex the rate is very

much slower (155a), although this is less stable than the corresponding biguanide complex. This is expected, as in the case of the ethylenediamine complex protonation cannot occur without bond rupture because of the absence of a free basic group (8a).

These hydroxoquo chromium(III) bis(biguanide) complexes resemble the corresponding cobalt(III) complexes (138, 142). On treatment with hot sodium hydroxide solution they are all converted to chromium(III) tris(biguanide) hydroxide with separation of some chromium(III) hydroxide (147).

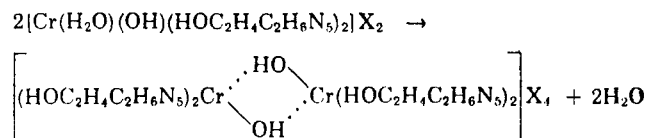
Hydroxoquo chromium(III) bis(biguanide) sulfate, [Cr(H₂O)(OH)(C₂H₇N₃)₂]SO₄, separated as a violet crystalline precipitate when a concentrated solution of chromium(III) tris(biguanide) hydroxide was heated on the water bath with a concentrated solution of ammonium sulfate. From the complex sulfate the corresponding chloride (1H₂O) was obtained by treatment with barium chloride solution. The chloride lost all its water, including the complex-bound molecule, in a vacuum over concentrated sulfuric acid and gave a chlorohydroxochromium(III) bis(biguanide) chloride, [Cr(OH)Cl(C₂H₇N₃)₂]Cl. This readily absorbed moisture, regenerating the parent hydroxoquo salt. Λ₂₀₄₈ at 28.3°C. for the chloride of the chlorohydroxo complex is given by 141.9 mhos, which indicates its reconversion into the bivalent cation of the hydroxoquo complex, but the measurement of its molecular weight in 0.32 per cent aqueous solution by the freezing-point method indicates the presence of the practically unchanged univalent cation of the chlorohydroxo complex (*i* = 1.875). From a solution of the complex hydroxoquo chromium chloride other salts of the complex, viz., the bromide, the iodide, the thiosulfate, and the chromate (1H₂O), were prepared by the action of solutions of appropriate alkali salts. The camphorsulfonate of the complex separated spontaneously from a solution of the corresponding tris(biguanide) salt upon hydrolysis. The hydroxoquo chromium(III) bis(biguanide) hydroxide and its nitrate were obtained by digestion of the complex sulfate with a solution of barium hydroxide and barium nitrate, respectively (147). The thiocyanate of the hydroxoquo complex was found to separate in the form of red-violet crystals from the mother liquor remaining after the crystallization of all tris(biguanide) thiocyanate, which was prepared by the reaction between chromium(III) tris(biguanide) sulfate and barium thiocyanate. The tris(biguanide) thiocyanate, as indicated by the cryoscopic measurement, is hydrolyzed in aqueous solution (148).

The dithiocyanatochromium(III) bis(biguanide) thiocyanate, [Cr(SCN)₂(C₂H₇N₃)₂]SCN, was obtained in the form of beautiful red crystals by heating on the water bath a mixture of concentrated solutions of chromium(III) tris(biguanide) hydroxide and ammonium thiocyanate until all free ammonia had escaped from

the solution. The measurement of its molar conductivity in aqueous solution (Λ_{1024} at 28°C. = 276.6 mhos) and of its molecular weight by the cryoscopic method in 0.37–0.75 per cent solution (molecular weight = 167–170; calculated value = 428) indicate that the substance readily undergoes hydrolysis, giving rise presumably to a diaquo derivative, $[\text{Cr}(\text{H}_2\text{O})_2(\text{C}_2\text{H}_7\text{N}_5)_2]_2(\text{SCN})_3$, in solution (148). This was confirmed by the preparation of the brick-red diaquochromium(III) bis(biguanide) nitrate ($1\text{H}_2\text{O}$) from the dithiocyanatochromium(III) bis(biguanide) thiocyanate by digestion with a concentrated solution of silver nitrate in the cold. The diaquo nitrate, however, lost all its water, including that bound inside the complex, at about 120°C., obviously with the formation of a dinitratochromium(III) bis(biguanide) nitrate (148).

Using (2-hydroxyethyl)biguanide Sengupta and Rây (166) have prepared a number of complex hydroxo-aquochromium(III) bis(biguanide) compounds: the hydroxide ($1.5\text{H}_2\text{O}$), the chloride ($2.5\text{H}_2\text{O}$), the bromide ($1\text{H}_2\text{O}$), the iodide ($0.5\text{H}_2\text{O}$), the nitrate, the sulfate ($1.5\text{H}_2\text{O}$), the thiosulfate ($1\text{H}_2\text{O}$), the dithionate ($3\text{H}_2\text{O}$), and the chromate ($1.5\text{H}_2\text{O}$). The complex sulfate was obtained in the form of rose-red crystals by adding a solution of chrome alum to an alkaline solution of (2-hydroxyethyl)biguanide sulfate and then heating the mixture on the water bath, followed by cooling and neutralization with dilute sulfuric acid. It gave a magnetic susceptibility value, $\chi_g = 13.89 \times 10^{-6}$ at 32°C.; magnetic moment = 4.19 Bohr magnetons (166). From the sulfate the free complex base and the complex chloride were obtained as usual by the action of barium hydroxide solution and barium chloride solution, respectively. The equivalent conductivity at 35°C. for the chloride is given by $\Lambda_{\infty} = 147.8$ mhos, a value which indicates partial hydrolysis. The other salts were obtained from the solution of the complex chloride by the addition of solutions of appropriate alkali salts. With the exception of the chloride, the salts are sparingly soluble in water; the complex base, on the other hand, is highly soluble. The salts lose their complex-bound water molecules even at as low a tempera-

ture as 90°C., presumably giving rise to di- μ -hydroxochromium(III) tetrakis[(2-hydroxyethyl)biguanide] salts (166).



3. Dibiguanide complexes

Like cobalt(III), chromium(III) combines with dibiguanides to form binuclear tris(dibiguanide) complexes. Several such complexes, both as bases and as salts, with ethylenedibiguanide, hexamethylenedibiguanide, *m*-phenylenedibiguanide, and *p*-phenylenedibiguanide have been described (43, 108, 127, 134). The complex binuclear tris(dibiguanide) bases were obtained as usual by the action of a saturated solution of chrome alum on a warm, strongly alkaline solution of the sulfate or chloride of the dibiguanide concerned. The complex bases form red crystals, which are sparingly soluble in water; from these bases salts were prepared in some cases as usual. Table 20 gives a list of these known dibiguanide complexes.

G. SILVER(III) BIGUANIDES

Rây and Chakravarty (124) have described a complex silver ethylenedibiguanide base and some of its salts in which the central 4-covalent silver atom occurs in the tripositive state. The salts of the violet-red base form beautiful deep red, needle-shaped crystals. They are all diamagnetic like the nickel(II) and palladium(II) biguanide complexes. The compounds are quite stable in the solid state; the nitrate can be recrystallized without change from 2 *N* nitric acid. As the electronic configuration of a tripositive silver ion resembles closely those of bivalent palladium and nickel, the authors assume that these complex tripositive silver biguanide compounds possess a square planar structure with dsp^2 hybrid bonds as in the case of the nickel(II) or palladium(II) compounds (see structure XXXIII).

Silver(III) ethylenedibiguanide sulfate, $[\text{AgC}_2\text{H}_4$ -

TABLE 20

The known chromium(III) dibiguanide complexes
 B^*H_2 = a molecule of any particular dibiguanide

Ligand	Complex ^(a)	Reference
N^1, N^1 -Ethylenedibiguanide..... $\text{C}_2\text{H}_4(\text{C}_2\text{H}_6\text{N}_5)_2$	$[\text{Cr}_2(\text{B}^*H_2)_3]X_6$ X = OH, Cl (9), $\frac{1}{2}\text{SO}_4$ (10); the salts lose water at 110°C. χ_g (30°C.) for the chloride = 8.764×10^{-6} Magnetic moment = 3.58 Bohr magnetons	(108)
N^1, N^1 -Hexamethylenedibiguanide..... $\text{C}_6\text{H}_{12}(\text{C}_2\text{H}_6\text{N}_5)_2$	$[\text{Cr}_2(\text{B}^*H_2)_3](\text{OH})_4 \cdot 1.5\text{H}_2\text{O}$; loses all the water at 120°C. to form the anhydrobase, $[\text{Cr}_2(\text{B}^*)_3]$	(43)
N^1, N^1 -(<i>m</i> -Phenylene)dibiguanide..... $\text{C}_8\text{H}_8(\text{C}_2\text{H}_6\text{N}_5)_2$	$[\text{Cr}_2(\text{B}^*H_2)_3]X_6$ X = OH (4), Cl (5), NO_3 , $\frac{1}{2}\text{SO}_4$ (11) The base loses 4 H_2O at 90°C.	(127)
N^1, N^1 -(<i>p</i> -Phenylene)dibiguanide..... $\text{C}_8\text{H}_8(\text{C}_2\text{H}_6\text{N}_5)_2$	$[\text{Cr}_2(\text{B}^*)_3] \cdot 5\text{H}_2\text{O}$; loses 3.5 H_2O at 105°C.	(134)

^(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

$(C_2H_6N_5)_2(SO_4)_2 \cdot 7H_2O$, is obtained in the form of red, silky crystals when a solution of silver sulfate mixed with one of ethylenedibiguanide sulfate is oxidized in the cold with potassium persulfate. The substance loses all its water at $80^\circ C$. It is moderately soluble in water and gives a magnetic susceptibility value, $\chi_g = -0.394 \times 10^{-6}$ (124).

The complex base, $[AgC_2H_4(C_2H_6N_5)_2](OH)_2 \cdot 3H_2O$, obtained from the sulfate by treatment with a cold 15 per cent solution of sodium or potassium hydroxide, forms microcrystals of violet-red color, resembling those of potassium permanganate. It is sparingly soluble in cold water and reacts strongly alkaline to litmus. $\chi_g = -0.393 \times 10^{-6}$ (124).

The complex nitrate and the perchlorate ($1.5H_2O$) are prepared by treating the moist base with a cold solution of 1 *N* nitric acid and 60 per cent perchloric acid, respectively. While the complex nitrate is moderately soluble in water, the perchlorate is highly soluble. χ_g for the nitrate = -0.402×10^{-6} (124).

The rate of decomposition of the complex silver(III) ethylenedibiguanide nitrate has been studied at different pH values at 25° , 35° , and $45^\circ C$. The reaction, which is pH dependent, is believed to occur in a complicated manner. It has been suggested that in aqueous solution the decomposition proceeds mainly through some intermediate stage with the formation of bivalent silver and hydrogen peroxide, while the direct decomposition of Ag^{3+} to Ag^+ predominates in acid solutions (158).

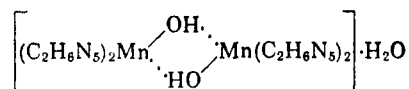
H. MANGANESE BIGUANIDES

Ray and Rây (111, 112) have recently described a number of quite stable biguanide complexes of trivalent and tetravalent manganese. They form cationic complexes containing two bidentate biguanide molecules or one quadridentate dibiguanide ligand. Gen-

erally speaking, they may, therefore, be regarded as complexes of the bis(biguanide) series. The tripositive manganese forms hydroxoquo bis(biguanide) and hydroxoquo dibiguanide complexes, besides the diaquo dibiguanide complex, while in the tetrapositive state it invariably forms dihydroxo bis(biguanide) and dihydroxo dibiguanide complexes.

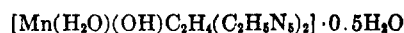
1. Manganese(III) complexes

Di- μ -hydroxomanganese(III) tetrakis(biguanide),



has been prepared by oxidizing with a brisk current of air a mixture of manganese(II) sulfate and a strongly alkaline solution of biguanide sulfate. The manganese hydroxide, first formed in suspension, is gradually oxidized and converted into dark, chocolate-colored, glistening crystals of the dihydroxo compound. The same product results when a freshly prepared solution of manganese(III) acetate is treated with an alkaline solution of biguanide (111).

When ethylenedibiguanide was substituted in the above preparation, dark chocolate-red crystals of hydroxoquo manganese(III) ethylenedibiguanide complex were obtained (111):



The hydroxoquo manganese(III) ethylenedibiguanide in dilute acetic acid solution changes to diaquomanganese(III) ethylenedibiguanide acetate, from which the sulfate, selenate, and chromate of the diaquo complex were prepared (111). The composition and properties of the known manganese(III) biguanide complexes are summarized in table 21.

With the exception of hydroxoquo manganese(III)

TABLE 21

The known manganese(III) biguanide complexes

BH = a molecule of biguanide; B^{*}H₂ = a molecule of a dibiguanide

Complex	Properties	Reference
Di- μ -hydroxomanganese tetrakis(biguanide) $[Mn(OH)_2(BH)_4] \cdot H_2O$	Chocolate-colored crystals; insoluble in water; loses water at $90^\circ C$.; hydrolyses in contact with water and reacts strongly alkaline to litmus; gives a violet solution in syrupy phosphoric acid χ_g ($30^\circ C$.) = 31.9×10^{-6} Magnetic moment = 4.70 Bohr magnetons	(111)
Hydroxoquo manganese ethylenedibiguanide $[Mn(H_2O)(OH)(B^*H_2)] \cdot 0.5H_2O$	Chocolate-red crystals; sparingly soluble in water; loses 0.5 H_2O at $90^\circ C$.; aqueous solution strongly alkaline to litmus and hydrolyses to the diaquo complex χ_g ($30^\circ C$.) = 12.68×10^{-6} Magnetic moment = 3.22 Bohr magnetons	(111)
Diaquomanganese ethylenedibiguanide sulfate $[Mn(H_2O)_2(B^*H_2)]_2(SO_4)_2 \cdot 6H_2O$	Yellow, silky crystals; almost insoluble in water; loses water at $80^\circ C$., giving $[Mn(H_2O)(SO_4)(B^*H_2)]_2SO_4$ χ_g ($29^\circ C$.) = 16.12×10^{-6} Magnetic moment = 4.57 Bohr magnetons	(111)
Diaquomanganese ethylenedibiguanide selenate $[Mn(H_2O)_2(B^*H_2)]_2(SeO_4)_2 \cdot 6H_2O$	Resembles the sulfate in properties; does not decompose even in boiling water	(111)
Diaquomanganese ethylenedibiguanide chromate $[Mn(H_2O)_2(B^*H_2)]_2(CrO_4)_2 \cdot 5H_2O$	Brownish yellow, silky crystals; sparingly soluble in water χ_g ($30^\circ C$.) = 14.16×10^{-6} Magnetic moment = 4.58 Bohr magnetons	(111)

ethylenedibiguanide the compounds show a value for the magnetic moment more or less in agreement with the theoretical value of 4.9 Bohr magnetons on the basis of spin-only effective formula for an ionic or outer-level tripositive manganese complex without any electron pairing. The lower moment value of 3.22 Bohr magnetons for the hydroxo-aquamanganese(III) ethylenedibiguanide suggests that it must be regarded as an inner-level complex with d^2sp^3 octahedral bonds, but with an incomplete quenching of its orbital moment (93).

2. Manganese(IV) complexes

Dihydroxomanganese(IV) bis(biguanide) hydroxide, $[\text{Mn}(\text{OH})_2(\text{C}_2\text{H}_7\text{N}_5)_2](\text{OH})_2$, has been obtained in the form of dark red crystals by the action of potassium permanganate on an alkaline solution of biguanide sulfate. Oxidation of a mixture of manganese(II) sulfate and biguanide sulfate in alkaline solution with hydrogen peroxide or sodium persulfate also serves as alternative methods of preparation. By treating a solution of the complex hydroxide in dilute acetic or nitric acid with solutions of appropriate alkali salts, the following salts of the complex base have been prepared (112): nitrate, sulfate ($4.5\text{H}_2\text{O}$), hydrogen phosphate ($1.5\text{H}_2\text{O}$), oxalate ($0.5\text{H}_2\text{O}$), iodate ($2\text{H}_2\text{O}$), chromate ($3\text{H}_2\text{O}$), fluoberyl-late ($3.5\text{H}_2\text{O}$).

The nitrate forms dark, chocolate-colored, shining crystals, readily soluble in water. The equivalent conductivity of its solution at 29°C . is $\Lambda_\infty = 130.2$ mhos. The sulfate forms a snuff-colored crystalline powder, sparingly soluble in water; it loses $4.5 \text{H}_2\text{O}$ at 90°C . The iodate also loses $2 \text{H}_2\text{O}$ in a vacuum (112).

An alcoholic solution of ethylenedibiguanide sulfate, when treated with solutions of manganese(II) sulfate and sodium persulfate, gave sparingly soluble, reddish brown crystals of dihydroxomanganese(IV) ethylenedibiguanide hydrate, $[\text{Mn}(\text{OH})_2\text{C}_2\text{H}_4(\text{C}_2\text{H}_5\text{N}_5)_2] \cdot 1.5\text{H}_2\text{O}$ (112).

Action of potassium permanganate on an alkaline solution of hexamethylenedibiguanide sulfate also led to the formation of dihydroxomanganese(IV) hexamethylenedibiguanide hydroxide, $[\text{Mn}(\text{OH})_2\text{C}_6\text{H}_{12}(\text{C}_2\text{H}_5\text{N}_5)_2](\text{OH})_2 \cdot 2\text{H}_2\text{O}$, in the form of insoluble, dark red crystals (43).

The magnetic susceptibility of all these dihydroxomanganese(IV) biguanide complexes has been measured at about 30°C . and their effective moment values have been found to lie between 2.0 and 2.83 Bohr magnetons, values which are much lower than the theoretical spin-only value of 3.87 Bohr magnetons for an ionic or covalent complex of tetrapositive manganese. A study of the variation of the magnetic susceptibility of dihydroxomanganese(IV) bis(biguanide) nitrate with temperature shows a linear decrease of its value for the effective moment from room temperature (300°K .)

down to 140°K . A much higher effective moment value of 3.41 Bohr magnetons has, however, been reported for the complex nitrate in aqueous solution. A consideration of these facts has led to the conclusion that in the manganese(IV) biguanide complexes the bonds are of the covalent d^2sp^3 type with some metal-metal linkage in the solid crystalline state (112).

I. VANADIUM(IV) BIGUANIDES

Tetrapositive vanadium has been found to combine with biguanides to form vanadyl biguanides which may be represented as sixfold, and in some cases also as fivefold, coordination complexes, assuming that the oxygen atom satisfies only one coordination position (9). All these compounds contain the vanadyl group, VO^{++} . These oxovanadium complexes with biguanides and dibiguanides are prepared by the reaction between vanadyl sulfate and an excess of biguanides in alkaline solution. The products form bluish green to light green, insoluble, crystalline powders. The complexes with alkyl biguanides are more or less hydrolyzed in contact with water. The compounds can be heated to 110°C . without decomposition, but all are decomposed by acids (9). Their composition and values for the magnetic moment are given in table 22.

TABLE 22

The known vanadium(IV) biguanide complexes
 BH = a molecule of biguanide; B'H = a molecule of a substituted biguanide; B'H₂ = a molecule of a dibiguanide

Ligand	Complex	Reference
Biguanide..... $\text{C}_2\text{H}_7\text{N}_5$	$[\text{VO}(\text{H}_2\text{O})\text{B}_2]$ $\chi_g = 3.95 \times 10^{-4}$ Magnetic moment = 1.75 Bohr magnetons	(9)
N ¹ -Methylbiguanide..... $\text{CH}_3\text{C}_2\text{H}_6\text{N}_5$	$[\text{VOB}'_2]$ $\chi_g = 3.21 \times 10^{-4}$ Magnetic moment = 1.62 Bohr magnetons	(9)
N ¹ -Ethylbiguanide..... $\text{C}_2\text{H}_5\text{C}_2\text{H}_6\text{N}_5$	$[\text{VOB}'_2]$ $\chi_g = 2.17 \times 10^{-4}$ Magnetic moment = 1.45 Bohr magnetons	(9)
N ¹ ,N ¹ -Dimethylbiguanide..... $(\text{CH}_3)_2\text{C}_2\text{H}_6\text{N}_5$	$[\text{VOB}'_2]$ $\chi_g = 2.74 \times 10^{-4}$ Magnetic moment = 1.60 Bohr magnetons	(9)
N ¹ -(n-Hexyl)biguanide..... $\text{C}_6\text{H}_{13}\text{C}_2\text{H}_6\text{N}_5$	$[\text{VO}(\text{H}_2\text{O})\text{B}'_2]$ $\chi_g = 2.37 \times 10^{-4}$ Magnetic moment = 1.81 Bohr magnetons	(9)
N ¹ ,N ¹ -Ethylenedibiguanide..... $\text{C}_4\text{H}_{11}(\text{C}_2\text{H}_5\text{N}_5)_2$	$[\text{VO}(\text{H}_2\text{O})\text{B}''_2] \cdot 0.5\text{H}_2\text{O}$ $\chi_g = 4.36 \times 10^{-4}$ Magnetic moment = 1.94 Bohr magnetons	(9)
N ¹ ,N ¹ -Hexamethylenedibiguanide..... $\text{C}_6\text{H}_{11}(\text{C}_2\text{H}_5\text{N}_5)_2$	$[\text{VO}(\text{H}_2\text{O})\text{B}''_2] \cdot 1.5\text{H}_2\text{O}$; loses $1.5 \text{H}_2\text{O}$ at 110°C . $\chi_g = 1.81 \times 10^{-4}$ Magnetic moment = 1.50 Bohr magnetons	(9)

A tetrapositive vanadium either in its simple or in its complex compounds should show a moment value of 1.73 Bohr magnetons, corresponding to the presence

of one unpaired electron on the basis of spin-only formula. Some of these vanadyl biguanide compounds, however, show a moment value of 1.48–1.62 Bohr magnetons. The lower values possibly arise from an exchange interaction leading to the formation of a metal-metal bond to a certain extent.

J. RHENIUM(V) BIGUANIDES

Ray and Rây (113) have recently reported the preparation of a rhenium(V) biguanide complex, oxohydroxorhenium bis(biguanide) hydroxide, $[\text{ReO}(\text{OH})(\text{C}_2\text{H}_7\text{N}_5)_2](\text{OH})_2$. This was obtained in the form of shining, rose-violet crystals by treating a strongly alkaline solution of biguanide sulfate with one of potassium hexachlororhenite, K_2ReCl_6 . Rhenium(IV) is oxidized by air during the reaction to rhenium(V). On treatment with ammonium salts or neutralization with dilute acids the complex base yielded a number of salts of the composition $[\text{ReO}_2(\text{C}_2\text{H}_7\text{N}_5)_2]\text{X}$, where $\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{SCN}, \text{NO}_3, \text{CH}_3\text{COO}, \frac{1}{2}\text{CO}_3, \frac{1}{2}\text{C}_2\text{O}_4, \frac{1}{2}\text{SO}_4$, and $\frac{1}{2}\text{HPO}_4$ (113). It is, therefore, quite likely that during neutralization or salt formation the base suffers a change, owing to the transfer of a proton from the complex to the outer zone, giving $[\text{ReO}_2(\text{C}_2\text{H}_7\text{N}_5)_2]\text{OH}\cdot\text{H}_2\text{O}$.

The salts of the dioxorhenium(V) biguanide complex form yellowish brown, silky crystals, sparingly soluble in water. The complex acetate at room temperature shows a molar conductivity of 74.76 mhos. The valence state of rhenium in both the base and its salts has been determined by their reaction with hydrogen peroxide in acid solution, followed by titration with permanganate. Both the base and its salts have been found to be diamagnetic. This is rather anomalous for a hexavalent pentapositive rhenium complex. Formation of a rhenium-rhenium bond has been suggested as an explanation (113).

K. OSMIUM(VI) BIGUANIDE

A solution of osmium tetroxide, OsO_4 , in concentrated hydrochloric acid, when treated with an alkaline solution of biguanide sulfate, was found to give a yellow crystalline precipitate, having the composition $[\text{OsO}_2(\text{C}_2\text{H}_6\text{N}_5)_2]$, of osmyl bis(biguanide) with hexapositive osmium. The product suffered no change even when heated to 130°C . for several hours. On digestion with hot concentrated hydrochloric acid it dissolved to form an olive-green solution from which, upon the addition of biguanide sulfate, sparingly soluble, olive-green crystals of the osmyl bis(biguanide) sulfate, $[\text{OsO}_2(\text{C}_2\text{H}_7\text{N}_5)_2]\text{SO}_4\cdot\text{H}_2\text{O}$, gradually separated out (110).

In the absence of any determination of the valence state of osmium the alternative formulas with tetrapositive osmium—viz., $[\text{Os}(\text{OH})_2(\text{C}_2\text{H}_6\text{N}_5)_2]$ and $[\text{Os}(\text{OH})_2(\text{C}_2\text{H}_7\text{N}_5)_2]\text{SO}_4\cdot\text{H}_2\text{O}$ —might as well be suggested. But as the yellow anhydrobase does not lose any weight

even at 130°C ., the formation of a dihydroxoosmium(IV) bis(biguanide) complex is rather unlikely.

L. ZINC BIGUANIDES

A number of zinc biguanide compounds containing biguanide, methylbiguanide, ethylbiguanide, and ethylenedibiguanide have been recently described (115). They have the formulas $[\text{Zn}(\text{C}_2\text{H}_6\text{N}_5)_2]$, $[\text{Zn}(\text{CH}_3\text{C}_7\text{H}_5\text{N}_5)_2]$, $[\text{Zn}(\text{C}_2\text{H}_5\text{C}_2\text{H}_5\text{N}_5)_2]$, and $[\text{ZnC}_2\text{H}_4(\text{C}_2\text{H}_5\text{N}_5)_2]\cdot\text{H}_2\text{O}$, respectively. These compounds are prepared by the action of sodium zincate on biguanides in strongly alkaline solutions. They form white, silky crystals, but are readily hydrolyzed by water with separation of zinc hydroxide; the zinc alkylbiguanides are the least stable and the zinc ethylenedibiguanide is the most stable in this respect. They can, however, be recrystallized from a hot solution of an alkali containing a little of the chelating ligand.

V. STABILITY OF METAL-BIGUANIDE COMPLEXES

In recent years there has been much study on a quantitative basis of the formation, dissociation, and stability of metal-biguanide complexes; those of bivalent metals like copper and nickel have received particular attention in this respect. The isolation of a series of unibiguanide and bis(biguanide) complexes of copper(II), and of bis(biguanide) and tris(biguanide) complexes of cobalt(III) and chromium(III), demonstrates that in these cases the complex formation occurs stepwise through successive stages, in agreement with Bjerrum's theory (13). In the case of nickel(II) and palladium(II) biguanide complexes, however, only their bis(biguanide) compounds could be prepared. A physicochemical study of the mechanism of formation and decomposition of many of the metal-biguanide complexes has made it possible to define precisely the conditions and range of existence of these complexes inclusive of any of their intermediate products and to determine the instability constant of each. Two experimental methods have been mainly employed for this purpose:

(1) The measurement of the pH of solutions in which the decomposition or formation of metal-biguanide complexes occurs and of the dissociation constants of the protonated biguanide ligand concerned (34, 36, 157).

(2) Spectrophotometric measurement of the optical density of the colored complex in solution in which its formation or decomposition occurs, together with a knowledge of the dissociation constants of the protonated ligands concerned (109, 114, 167).

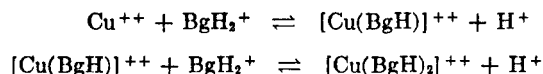
The formation and decomposition of metal-biguanide complexes have been discussed on a statistical basis in the light of Bjerrum's theory (13) as occurring generally in a reversible manner through consecutive inter-

mediate stages except in the case of nickel and palladium (34, 36, 109, 114).

A detailed study of the formation and decomposition of some copper(II) and nickel(II) complexes of different biguanides by the pH/potentiometric method has led to the conclusion that the copper(II) biguanide complexes are formed or decomposed in aqueous solution in two successive steps, involving an intermediate stage of unibiguanide complexes, while the nickel(II) biguanide complexes, as well as the copper(II) and nickel(II) dibiguanide complexes, suffer complete dissociation in a single step and are also formed in a single step from their components. In the case of copper the successive instability constants for the unibiguanide and bis(biguanide) complexes are distinguished by the symbols k_1 and k_2 ; the overall constant K is given by the product $k_1 \cdot k_2$ (34, 105).

The spectrophotometric method has also led to more or less similar values for the instability constants of many of these copper(II) and nickel(II) biguanide complexes (109, 114, 167). Table 23 gives these values in a collected form.

The stepwise and reversible formation of copper(II) biguanide complexes is represented as follows (34), where BgH = a molecule of any biguanide.



From table 23 the following order of stability for the 4-covalent copper(II) and nickel(II) complexes of different biguanides can be deduced: copper ethylenedibiguanide > copper biguanide > copper methylbiguanide \approx copper ethylbiguanide \approx copper (2-hydroxyethyl)biguanide \approx copper (3-hydroxypropyl)biguanide \approx copper (2-methoxyethyl)biguanide \approx copper (3-methoxypropyl)biguanide \approx copper phenylbiguanide > copper dimethylbiguanide > copper *m*-phenylenedibiguanide \approx copper diethylbiguanide.

There is only a slight variation in the order for nickel complexes: nickel ethylenedibiguanide > nickel biguanide > nickel (2-hydroxyethyl)biguanide \approx nickel (3-hydroxypropyl)biguanide > nickel methylbiguanide \approx nickel ethylbiguanide \approx nickel (2-methoxyethyl)biguanide \approx nickel (3-methoxypropyl)biguanide \approx nickel phenylbiguanide > nickel dimethylbiguanide.

In all cases the nickel complexes are much less stable than the corresponding copper complexes; the overall value of the instability constant for the nickel complex of any particular biguanide is generally 10^4 to 10^5 times greater than that of the corresponding copper complex (i.e., the pK value is 4–5 units less).

From a consideration of the K_a values (table 1) of the different biguanides, the instability constant values of whose copper(II) and nickel(II) complexes are listed in table 23, they can be arranged in the following order of their basic strength: ethylenedibiguanide > bi-

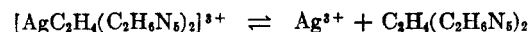
guanide \approx methylbiguanide \approx ethylbiguanide \approx (2-hydroxyethyl)biguanide \approx (3-hydroxypropyl)biguanide \approx (2-methoxyethyl)biguanide \approx (3-methoxypropyl)biguanide \approx dimethylbiguanide \approx diethylbiguanide \approx *m*-phenylenedibiguanide > phenylbiguanide.

No strict correlation between the basic strength of the ligands and the stability of their metal complexes could, however, be made (14, 16, 19, 20, 21, 35, 114).

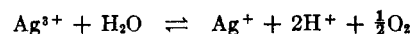
A comparison of the overall pK values of 4-covalent copper(II) and nickel(II) complexes of biguanides and dibiguanides with those of other ligands, as given below, shows that biguanides and dibiguanides behave as the most powerful coördinating agents of all these ligands.

Ligand	pK (Copper Complex)	pK (Nickel Complex)
Salicylaldehyde and its derivatives.....	8–14.4 (20, 87)	9.2 (87)
Acetylacetone and its derivatives.....	12–17.4 (20)	12.4 (87)
Ammonia.....	12.6 (1)	7.8 (1)
Ethylenediamine.....	19.6 (21)	13.8 (21)
Tetramines.....	18.8–20.4 (1, 156a)	14–14.6 (1, 156a)
Biguanides.....	14.3–18.5	10.4–13.5
Dibiguanides.....	14.4–21.0	17.1 (for ethylenedibiguanide)

The stability of the silver(III) ethylenedibiguanide nitrate in 2 *N* potassium nitrate solution has been determined from the equilibrium constant of the reaction between the complex salt and hydrogen ion (nitric acid), using the acid dissociation constants of the ethylenedibiguanide base. The equilibrium constant was derived from the pH and Ag^{3+} -ion concentration of the equilibrated solution. The latter was obtained from a measurement of the redox potential of the equilibrated solutions in the presence of Ag^+ ion. It has been found that the silver(III) ethylenedibiguanide complex, like the corresponding copper(II) and nickel(II) complexes, dissociates in a single stage. The value of the instability constant of the complex ion for the reaction:



was also corrected for any decomposition of the trivalent silver ion in aqueous solution. The decomposition of the latter in solution is believed to proceed as follows:



The corrected value for the instability constant of the complex nitrate is given by $pK = 52.16$ at $\mu = 2$ *M* potassium nitrate and 32°C. (157), as against 21.66 of the copper(II) ethylenedibiguanide complex (34).

From determinations of the equilibrium constants of the decomposition reactions of cobalt(III) tris(biguanide) and cobalt(III) tris(phenylbiguanide) complexes with acids and of the concentration of Co^{3+} ions in solution by the potentiometric method the instability

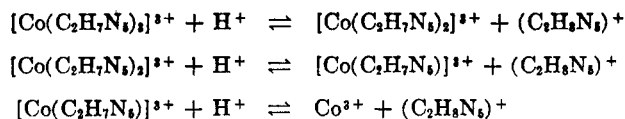
TABLE 23

Instability constants of copper(II) and nickel(II) biguanide complexes
 Values by both potentiometric and spectrophotometric methods are given wherever available
 Temperature = 32°C.; μ = ionic strength

Ligand	Instability Constants		References
	Copper complex	Nickel complex	
Biguanide.....	$k_1 = 7.87 \times 10^{-11}$ $k_2 = 5.76 \times 10^{-9}$ $K = 4.54 \times 10^{-19}$	$K = 3.31 \times 10^{-14}$	(34)
	$k_1 = 4.95 \times 10^{-11}$ $k_2 = 6.01 \times 10^{-9}$ $K = 2.98 \times 10^{-19}$ $\epsilon_1 = 36.0$ (660 m μ); pH = 4.25 $\epsilon_2 = 38.5$ (520 m μ); pH > 7.0 $\mu = 0.5 M$ KCl	$K = 3.24 \times 10^{-14}$ $\epsilon = 50.0$ (460 m μ) $\mu = 0.5 M$ KCl pH = 8	(109, 114)
<i>N</i> ¹ -Methylbiguanide.....	$k_1 = 3.0 \times 10^{-10}$ $k_2 = 2.36 \times 10^{-9}$ $K = 7.08 \times 10^{-19}$	$K = 1.66 \times 10^{-18}$	(34)
	$k_1 = 2.8 \times 10^{-10}$ $k_2 = 2.66 \times 10^{-9}$ $K = 7.45 \times 10^{-19}$ $\epsilon_1 = 36.0$ (660 m μ); pH = 4.85 $\epsilon_2 = 40.0$ (520 m μ); pH > 7.0 $\mu = 0.5 M$ KCl	$K = 0.65 \times 10^{-18}$ $\epsilon = 55.0$ (465 m μ) $\mu = 0.5 M$ KCl pH = 8.6	(109, 114)
<i>N</i> ¹ -Ethylbiguanide.....	$k_1 = 3.68 \times 10^{-10}$ $k_2 = 2.70 \times 10^{-9}$ $K = 1.02 \times 10^{-17}$	$K = 1.66 \times 10^{-18}$	(34)
<i>N</i> ¹ -Phenylbiguanide.....	$k_1 = 8.52 \times 10^{-10}$ $k_2 = 2.05 \times 10^{-9}$ $K = 1.77 \times 10^{-17}$	$K = 5.25 \times 10^{-18}$	(34)
	$k_1 = 5.83 \times 10^{-10}$ $k_2 = 4.76 \times 10^{-9}$ $K = 2.77 \times 10^{-17}$ $\epsilon_1 = 42.16$ (650 m μ); pH = 4.85 $\epsilon_2 = 65.5$ (550 m μ); pH > 7.0 $\mu = 0.5 M$ KCl	$K = 9.12 \times 10^{-18}$ $\epsilon = 65.0$ (460 m μ) $\mu = 0.5 M$ KCl pH = 7.8	(109, 114)
<i>N</i> ¹ , <i>N</i> ¹ -Dimethylbiguanide.....	$k_1 = 3.2 \times 10^{-9}$ $k_2 = 8.5 \times 10^{-9}$ $K = 2.72 \times 10^{-16}$	$K = 4.27 \times 10^{-11}$	(34)
<i>N</i> ¹ , <i>N</i> ¹ -Diethylbiguanide.....	$k_1 = 1.04 \times 10^{-9}$ $k_2 = 4.68 \times 10^{-7}$ $K = 4.9 \times 10^{-16}$		(34)
<i>N</i> ¹ -(2-Hydroxyethyl)biguanide.....	$k_1 = 1.1 \times 10^{-10}$ $k_2 = 1.13 \times 10^{-7}$ $K = 1.24 \times 10^{-17}$ $\epsilon_1 = 47.39$ (640 m μ); pH = 4.75 $\epsilon_2 = 46.88$ (540 m μ); pH = 8.0 $\mu = 0.2 M$ KCl	$K = 2.97 \times 10^{-16}$ $\epsilon = 51.0$ (460 m μ) pH = 8.0 $\mu = 0.2 M$ KCl	(167)
<i>N</i> ¹ -(3-Hydroxypropyl)biguanide.....	$k_1 = 2.70 \times 10^{-10}$ $k_2 = 0.38 \times 10^{-7}$ $K = 1.03 \times 10^{-17}$ $\epsilon_1 = 34.67$ (650 m μ); pH = 4.75 $\epsilon_2 = 45.10$ (525 m μ); pH = 7.5 $\mu = 0.2 M$ KCl	$K = 4.76 \times 10^{-16}$ $\epsilon = 48.71$ (470 m μ) pH = 8.0 $\mu = 0.2 M$ KCl	(167)
<i>N</i> ¹ -(2-Methoxyethyl)biguanide.....	$k_1 = 1.70 \times 10^{-10}$ $k_2 = 0.32 \times 10^{-7}$ $K = 0.56 \times 10^{-17}$ $\epsilon_1 = 43.35$ (640 m μ); pH = 4.8 $\epsilon_2 = 47.30$ (525 m μ); pH = 7.5 $\mu = 0.2 M$ KCl	$K = 10.04 \times 10^{-16}$ $\epsilon = 66.69$ (460 m μ) pH = 8.25 $\mu = 0.2 M$ KCl	(167)
<i>N</i> ¹ -(3-Methoxypropyl)biguanide.....	$k_1 = 3.02 \times 10^{-10}$ $k_2 = 0.39 \times 10^{-7}$ $K = 1.17 \times 10^{-17}$ $\epsilon_1 = 37.80$ (645 m μ); pH = 5.0 $\epsilon_2 = 47.88$ (525 m μ); pH = 7.5 $\mu = 0.2 M$ KCl	$K = 1.77 \times 10^{-16}$ $\epsilon = 64.21$ (465 m μ) pH = 8.25 $\mu = 0.2 M$ KCl	(167)
<i>N</i> ¹ , <i>N</i> ¹ -Ethylenedibiguanide.....	$K = 2.2 \times 10^{-19}$ $K = 2.14 \times 10^{-22}$ $\epsilon = 50.5$ (520 m μ); pH = 4.0 $\mu = 0.25 M$ KCl	$K = 7.08 \times 10^{-16}$ $K = 3.61 \times 10^{-16}$ $\epsilon = 54.0$ (470 m μ) pH = 5.5 $\mu = 0.25 M$ KCl	(34) (109, 114)
<i>N</i> ¹ , <i>N</i> ¹ -(<i>m</i> -Phenylene)dibiguanide.....	$K = 3.63 \times 10^{-16}$		(34)

Complex	k_1	k_2	k_3	K
Co(III) tris(biguanide).....	8.55×10^{-29}	2.46×10^{-13}	2.31×10^{-13}	4.85×10^{-55}
Co(III) tris(phenylbiguanide).....	5.80×10^{-29}	5.76×10^{-14}	2.34×10^{-13}	7.80×10^{-55}

constants of these complexes have been calculated (36). In accordance with Bjerrum's view (13) the 6-covalent cobalt(III) tris(biguanide) complexes have been shown to decompose in three consecutive stages:



The instability constants, k_1 , k_2 , and k_3 , for each stage (unibiguanide to tris(biguanide)), as well as the overall constant $K = k_1 \cdot k_2 \cdot k_3$ at 33°C., are given above (36). The K value for hexamminecobalt (III), however, is only of the order of 10^{-34} (81).

The stability of chromium(III) biguanide and of chromium(III) phenylbiguanide complexes has been investigated in a similar manner from a study of their decomposition with acids (8). The successive instability constants, k_2 and k_3 , only have been determined in these cases at 32°C. (8).

Complex	k_2	k_3
Cr(III) tris(biguanide).....	1.77×10^{-14}	1.27×10^{-8}
Cr(III) tris(phenylbiguanide).....	1.11×10^{-12}	1.56×10^{-8}

A comparison of the instability constants of cobalt(III) and chromium(III) biguanide complexes shows that the cobalt(III) complexes are more stable than their chromium analogs, and that the stability decreases with the number of biguanide molecules in the complex. In solution both the bis(biguanide) and the unibiguanide complexes presumably combine with the necessary number of water molecules for the saturation of the coordination number of the central metal atom in an octahedral configuration.

VI. METAL COMPLEXES OF GUANYLUREAS

A. COPPER(II) GUANYLUREAS

The formation of rose-red copper(II) guanylurea by the action of sodium hydroxide upon a solution containing copper(II) sulfate and a guanylurea salt was first observed as early as in 1862 by Haag (69). The reaction was regarded as a test for guanylurea. A similar observation was also made by Baumann (10, 11).

The composition of the rose-red copper(II) guanylurea is given as $\text{Cu}(\text{C}_2\text{H}_6\text{ON}_4)_2 \cdot 2\text{H}_2\text{O}$ (40, 74). By analogy with the copper biguanide base it is best represented as $[\text{Cu}(\text{C}_2\text{H}_6\text{ON}_4)_2](\text{OH})_2$.

The use of guanylurea was suggested for the detection of copper in a manner similar to that for nickel (63).

By treating the base with different acid solutions

under specified conditions Dubský and Strnad (40) have prepared a number of complex copper(II) guanylurea salts as noted below:

Salt	Properties
$\text{CuR}_2 \cdot 4\text{HCl}$	Transparent, light blue
$\text{CuR}_2 \cdot 4\text{HCl} \cdot 2\text{H}_2\text{O}$	Light blue
$(\text{RH})_2 \cdot \text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	Green
$\text{CuR}_2 \cdot 4\text{HCl} \cdot 2\text{KOH}$	Violet
$(\text{RH})_2 \cdot \text{CuBr}_2 \cdot \text{H}_2\text{O}$	Golden-brown
$(\text{CuR}_2)_2 \cdot 2\text{HBr} \cdot 6\text{H}_2\text{O}$	Violet precipitate
$\text{CuR} \cdot \text{HI}$ (more likely CuRI).....	Difficultly soluble; violet-black
$\text{CuR}_2 \cdot \text{H}_2\text{SO}_4$	Insoluble; violet
$\text{CuR}_2 \cdot 2\text{HNO}_3$	Grayish blue
$\text{CuR}_2 \cdot \text{HNO}_3 \cdot \text{H}_2\text{O}$	Light violet
$\text{CuR}_2 \cdot 4\text{NO}_2 \cdot 2\text{KOH}$	Grayish violet

Most of these compounds can be represented by the general formula $[\text{Cu}(\text{RH})_2]\text{X}_2$ as salts of the complex copper guanylurea base, where $\text{RH} =$ a molecule of guanylurea ($\text{C}_2\text{H}_6\text{ON}_4$) and $\text{X} =$ a univalent anion or an equivalent thereof.

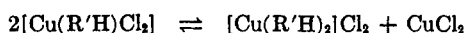
A complex sulfate of composition $[\text{Cu}(\text{RH})_2]\text{SO}_4 \cdot 1.5\text{H}_2\text{O}$ has also been prepared in the form of sparingly soluble, red-violet crystals by treating an ammoniacal solution of copper(II) sulfate with one of guanylurea sulfate (118). The complex sulfate on treatment with barium chloride solution gave red-violet crystals of the corresponding chloride (118).

Copper(II) N^4 -phenylguanylurea base, $[\text{Cu}(\text{C}_6\text{H}_5\text{C}_2\text{H}_4\text{ON}_4)_2]$, has been obtained in the form of a violet crystalline precipitate by the action of an ammoniacal copper(II) sulfate solution on one of N^4 -phenylguanylurea hydrochloride. The chloride of the complex copper base was prepared in the form of light blue crystals by digesting copper(II) hydroxide with a solution of the phenylguanylurea hydrochloride. In a similar manner the light blue crystals of the complex sulfate were obtained from copper(II) hydroxide and phenylguanylurea sulfate (118). The violet color of the complex copper(II) phenylguanylurea (anhydrobase) changes to light blue on formation of its chloride and sulfate. This seems to suggest that in the former the metal-ligand bonds are of the planar covalent type with the formation of an inner-metallic complex, while in the latter they are of ionic character, giving rise to an associated complex of the cuprammine type. A structural study of the base and its salts will be of particular interest in this respect.

The preparation and properties of the complex compounds of copper(II) with a number of N^1 -alkylguanylureas have recently been described by Dutta and Rây (46). It has been found that in addition to the copper(II) bis(alkylguanylurea) complexes, all of which are rose-red in color, in a few cases copper(II) unialkylguanylurea complexes of a deep blue color can also be obtained. This denotes a close analogy with copper(II)

biguanide complexes. Copper(II) bis(alkylguanylurea) complexes are much more stable than the copper(II) bis(guanylurea) and bis(*N*⁴-phenylguanylurea) complexes. Solutions of the complex copper(II) bis(alkylguanylurea) bases in water or alcohol can be boiled without any change, while those of the copper(II) bis(guanylurea) or bis(*N*⁴-phenylguanylurea) complexes decompose with separation of copper(II) hydroxide under the same conditions (46).

The copper(II) unialkylguanylurea complexes are formed at pH 4.0. In aqueous solution they undergo transformation to the rose-red bis(alkylguanylurea) complexes (46).



The solubility of the copper(II) bis(alkylguanylurea) salts in water decreases with the increase in the chain length of the substituent alkyl groups, whereas it increases in alcohol (46).

The complex copper(II) bis(alkylguanylurea) acetates were obtained by heating on the water bath a mixture of copper(II) acetate, dicyandiamide, and an alcohol containing the appropriate alkyl group. On cooling the mixture the acetate separated in red-violet shining crystals. Other salts were prepared from the complex acetate by the usual methods. The complex bases were obtained by the addition of alkali to the aqueous or alcoholic solution of the complex acetates or chlorides (46).

Copper(II) unimethylguanylurea and uniethylguanylurea compounds were prepared by the addition of 3 *N* hydrochloric acid to an aqueous solution of their corresponding bis complexes until the color of the solution changed from red-violet to deep blue (pH 3.8–4.0). On concentration and cooling the deep blue crystals of the complex dichlorocopper(II) unialkylguanylurea separated out (46).

The composition and properties of the copper(II) alkylguanylurea complexes that have been described up to now are summarized in table 24.

Copper(II) bis[*N*¹-(2-hydroxyethyl)guanylurea] sulfate, $[\text{Cu}(\text{C}_2\text{H}_4\text{OHC}_2\text{H}_5\text{ON}_4)_2]\text{SO}_4 \cdot 2\text{H}_2\text{O}$, was prepared by heating a mixture of dicyandiamide, copper(II) acetate, and ethylene glycol on the water bath at 50°C.; the mixture was filtered and the filtrate was then cooled after mixing with a concentrated solution of ammonium sulfate. The salt separated as a rose-colored precipitate (46).

All hydrated salts lose their water at 110°C., and the carbonates lose both carbon dioxide and water at 120°C.

All complex copper compounds of guanylurea and its substituted derivatives are decomposed by acids.

Magnetic susceptibilities of a number of these complex compounds of copper(II) have been measured; their moment values have been found to lie between 1.62

TABLE 24

The known copper(II) alkylguanylurea complexes
R'H = a molecule of the substituted guanylurea

Ligand	Complex ^(a)	Reference
<i>N</i> ¹ -Methylguanylurea... $\text{CH}_3\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl, Br, I, SCN, NO ₂ , NO ₃ , ClO ₄ , CH ₃ COO (2.5), $\frac{1}{2}\text{CO}_3$ (3), $\frac{1}{2}\text{C}_2\text{O}_4$ (3.5), $\frac{1}{2}\text{SO}_4$ (3.5), $\frac{1}{2}\text{S}_2\text{O}_8$, $\frac{1}{2}\text{HPO}_4$ (5.5) Δ_∞ (35°C.) for the chloride = 121.4 mhos $[\text{Cu}(\text{R}'\text{H})\text{Cl}_2]$, dichlorocopper methyl- guanylurea	(46)
<i>N</i> ¹ -Ethylguanylurea.... $\text{C}_2\text{H}_5\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (1.5), Br (2), I, SCN, NO ₂ , NO ₃ (1), ClO ₄ , CH ₃ COO (4.5), $\frac{1}{2}\text{CO}_3$ (5), $\frac{1}{2}\text{C}_2\text{O}_4$ (3.5), $\frac{1}{2}\text{SO}_4$ (3), $\frac{1}{2}\text{S}_2\text{O}_8$ (1), $\frac{1}{2}\text{CrO}_4$ (2) Δ_∞ (35°C.) for the chloride = 129.2 mhos $[\text{Cu}(\text{R}'\text{H})\text{Cl}_2]$, dichlorocopper ethyl- guanylurea	(46)
<i>N</i> ¹ -Isopropylguanylurea. $\text{C}_3\text{H}_7\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (2), Br (1.5), I (2), NO ₂ , CH ₃ COO (3.5), $\frac{1}{2}\text{CO}_3$ (4), $\frac{1}{2}\text{SO}_4$ (1)	(46)
<i>N</i> ¹ -(<i>n</i> -Butyl)guanylurea. $\text{C}_4\text{H}_9\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (2), Br (2), SCN (1), NO ₂ , NO ₃ (1), ClO ₄ (0.5), CH ₃ COO (1.5), $\frac{1}{2}\text{SO}_4$ (1.5), $\frac{1}{2}\text{S}_2\text{O}_8$ (1), $\frac{1}{2}\text{HPO}_4$ (2)	(46)
<i>N</i> ¹ -Isobutylguanylurea.. $\text{C}_4\text{H}_9\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (2), Br (1.5), SCN (1), NO ₂ (2), ClO ₄ , CH ₃ COO (2), $\frac{1}{2}\text{SO}_4$	(46)
<i>N</i> ¹ -Isopentylguanylurea... $\text{C}_5\text{H}_{11}\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (2), Br, SCN (2), NO ₂ (2), ClO ₄ , CH ₃ COO (1), $\frac{1}{2}\text{SO}_4$ (0.5)	(46)
<i>N</i> ¹ -(<i>n</i> -Hexyl)guanylurea. $\text{C}_6\text{H}_{13}\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (0.5), Br (1), NO ₂ (2), ClO ₄ , CH ₃ COO (1.5), $\frac{1}{2}\text{SO}_4$ (0.5), $\frac{1}{2}\text{S}_2\text{O}_8$ (0.5)	(46)
<i>N</i> ¹ -Benzylguanylurea.... $\text{C}_6\text{H}_5\text{CH}_2\text{C}_2\text{H}_5\text{ON}_4$	$[\text{Cu}(\text{R}'\text{H})_2]$, $[\text{Cu}(\text{R}'\text{H})_2]\text{X}_2$ X = Cl (3), Br, SCN, CH ₃ COO (1), $\frac{1}{2}\text{SO}_4$ (3)	(46)

^(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

and 1.86 Bohr magnetons, in agreement with the theoretically expected value for the presence of one unpaired electron in the molecule (47, 118).

B. NICKEL(II) GUANYLUREAS

As with biguanides, nickel(II) combines with two molecules of guanylurea and substituted guanylureas to form yellow complexes of the inner-metallic type.

The formation of a dense yellow crystalline precipitate of nickel(II) guanylurea, $[\text{Ni}(\text{C}_2\text{H}_5\text{ON}_4)_2] \cdot 2\text{H}_2\text{O}$, by the addition of a solution of any nickel(II) salt to one of guanylurea in dilute alkali, was suggested as a delicate test for nickel by Grossmann and Schück (61, 64). Methods were also developed for the gravimetric estimation of nickel and its separation from other metals (59, 62, 65, 66). A volumetric method for the determination of nickel based upon the titration of the nickel(II) guanylurea precipitate with potassium cyanide solution, using silver iodide as indicator, has also been suggested (60). A method for the acidimetric titration of nickel after precipitation with guanylurea has likewise been worked out (38, 52).

The nickel(II) guanylurea, like the corresponding

copper(II) compound, is best represented as a base, $[\text{Ni}(\text{C}_2\text{H}_5\text{ON}_4)_2](\text{OH})_2$ (118).

Dubský and Strnad (40) have described the preparation of some nickel(II) guanylurea salts under strictly specified conditions. Their compositions are represented thus:

- (A) $[\text{Ni}(\text{R})_2] \cdot 4\text{HCl} \cdot 2\text{H}_2\text{O}$ (yellow-green)
- (B) $[\text{NiCl}_4]\text{H}_2 \cdot 2\text{RH} \cdot \text{H}_2\text{O}$; also with $2\text{H}_2\text{O}$ (yellow)
- (C) $[\text{Ni}(\text{R})_2] \cdot 2\text{HNO}_3 \cdot 2\text{H}_2\text{O}$ (orange-yellow)

Compound A, however, may be better represented as a double salt like $\text{NiCl}_2 \cdot 2\text{RH}_2\text{Cl} \cdot 2\text{H}_2\text{O}$, while compound C may be regarded as a true complex salt, $[\text{Ni}(\text{RH})_2](\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ or $[\text{Ni}(\text{RH})_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$, with planar or octahedral configuration, respectively. But the orange-yellow color of the nitrate gives rise to a strong presumption in behalf of the square planar configuration of its molecule with d_{sp^2} hybrid bonds.

Nickel(II) N^4 -phenylguanylurea, $[\text{Ni}(\text{C}_6\text{H}_5\text{C}_2\text{H}_5\text{ON}_4)_2] \cdot \text{H}_2\text{O}$, has been prepared in the form of sparingly soluble, orange-yellow crystals by the reaction between N^4 -phenylguanylurea hydrochloride and nickel(II) sulfate in ammoniacal solution. It is decomposed by warm alkali with separation of nickel(II) hydroxide, and is, therefore, much less stable than nickel(II) guanylurea. The chloride and sulfate of the nickel(II) phenylguanylurea complex have been obtained in the form of green crystals by digesting nickel(II) hydroxide with concentrated solutions of the phenylguanylurea hydrochloride and sulfate, respectively (118).

A large number of nickel(II) complexes with many different N^1 -alkylguanylureas, resembling those of copper(II), have recently been described (47). All are orange-yellow in color and are more stable than the nickel(II) complexes of guanylurea and N^4 -phenylguanylurea. The aqueous or alcoholic solution of the complex nickel(II) N^1 -alkylguanylurea compounds can be boiled without decomposition. They are not decomposed even by warm dilute alkali solutions. The complex nickel(II) guanylurea base is, on the other hand, known to decompose with separation of nickel(II) hydroxide, when its aqueous suspension is heated to boiling. As in the case of the copper(II) alkylguanylurea complexes, the solubility of the nickel(II) complexes in water decreases with increase in the chain length of the substituent in the guanylurea molecule, whereas the solubility in alcohol increases (47).

The complex nickel(II) alkylguanylurea bases have been obtained as bright yellow, crystalline precipitates by the addition of an excess of sodium hydroxide solution to one containing a mixture of nickel(II) sulfate and the alkylguanylurea sulfate concerned. By treating the complex bases with 2 *N* hydrochloric acid or by digesting them with concentrated ammonium chloride solution on the water bath, their chlorides were pre-

pared. The other salts of the complex bases were obtained from the chlorides by the action of appropriate alkali metal salts in aqueous or aqueous alcoholic solution (47).

The composition and properties of the nickel(II) alkylguanylurea complexes that have been prepared are listed in table 25.

TABLE 25

The known nickel(II) alkylguanylurea complexes
 R'H = a molecule of a substituted guanylurea

Ligand	Complex ^(a)	Reference
N^1 -Methylguanylurea... $\text{CH}_3\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}')_2], [\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{Cl}, \text{NO}_3, \frac{1}{2}\text{SO}_4$ (3), $\frac{1}{2}\text{S}_2\text{O}_8$ (2.5) Λ_∞ (35°C.) for the chloride = 125.5 mhos	(47)
N^1 -Ethylguanylurea... $\text{C}_2\text{H}_5\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}')_2], [\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{Cl}$ (2), Br (1), I, ClO_4 , $\frac{1}{2}\text{SO}_4$ (7) Λ_∞ (35°C.) for the chloride = 123.9 mhos	(47)
N^1 -Isopropylguanylurea... $\text{C}_3\text{H}_7\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}')_2], [\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{Cl}$ (2.5), $\frac{1}{2}\text{SO}_4$ (1)	(47)
N^1 -(<i>n</i> -Butyl)guanylurea... $\text{C}_4\text{H}_9\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}')_2], [\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{Cl}$ (0.5), NO_3 , $\frac{1}{2}\text{SO}_4$ (4)	(47)
N^1 -Isobutylguanylurea... $\text{C}_4\text{H}_9\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}')_2], [\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{Cl}$ (2), $\frac{1}{2}\text{SO}_4$ (0.5)	(47)
N^1 -Isoamylguanylurea... $\text{C}_5\text{H}_{11}\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}')_2], [\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{Cl}$ (2), Br, I, NO_3 (1.5), $\frac{1}{2}\text{SO}_4$ (0.5)	(47)
N^1 -(<i>n</i> -Hexyl)guanylurea... $\text{C}_6\text{H}_{13}\text{C}_2\text{H}_4\text{ON}_4$	$[\text{Ni}(\text{R}'\text{H})_2]\text{X}_2$ $\text{X} = \text{OH}, \text{Cl}, \frac{1}{2}\text{SO}_4$	(47)

(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals. The hydrated salts lose water at 110°C.

All the nickel(II) complexes of guanylurea and substituted guanylureas are decomposed by acids. With a few exceptions they are orange-yellow or yellow in color. Measurement of the magnetic properties of many of these yellow or orange-yellow compounds shows that they are diamagnetic, while the nickel(II) N^4 -phenylguanylurea chloride and sulfate, which form light green crystals, are paramagnetic with moment values of 2.84 and 2.64 Bohr magnetons, respectively (93, 118, 120). These values are in close agreement with that of the free nickel(II) ion with two unpaired electrons. These two light green nickel(II) compounds may, therefore, be viewed as ionic or outer-level complexes. The yellow or orange-yellow nickel(II) complexes, being diamagnetic, should consequently be regarded as having square planar structure with d_{sp^2} hybrid bonds (92, 93).

C. PALLADIUM(II) GUANYLUREAS

Palladium(II) combines with guanylurea and substituted guanylureas to form complexes which resemble the corresponding nickel(II) complexes in composition and properties. The palladium(II) complexes are comparatively more stable and less soluble than their nickel analogs, as is the case with their biguanide complexes. The palladium(II) guanylureas form light yellow crystals and are diamagnetic like its biguanide

complexes. Their methods of preparation resemble those of their biguanide complexes or of the corresponding nickel(II) complexes (48, 48a).

Table 26 gives a list of the palladium(II) guanylureas that have been described in the literature.

TABLE 26

The known palladium(II) guanylurea complexes
RH = a molecule of guanylurea; R'H = a molecule of a substituted guanylurea

Ligand	Complex ^(a)	References
Guanylurea..... C ₂ H ₅ ON ₄	[Pd(RH) ₂]X ₂ X = OH, Cl (0.5)	(67, 118)
N ⁴ -Phenylguanylurea.... C ₆ H ₅ C ₂ H ₅ ON ₄	[Pd(R') ₂], [Pd(R'H) ₂]X ₂ X = OH (1), Cl R'H ₂ [PdCl ₂]	(118)
N ¹ -Methylguanylurea... CH ₃ C ₂ H ₅ ON ₄	[Pd(R'H) ₂]X ₂ X = Cl (2), I (2), SCN (1), NO ₂ (2.5), $\frac{1}{2}$ SO ₄ (2), $\frac{1}{2}$ Pd(SCN) ₂ (ruby-red) Λ_{∞} (32°C.) for the chloride = 85.6 mhos	(48, 48a)
N ¹ -Ethylguanylurea.... C ₂ H ₅ C ₂ H ₅ ON ₄	[Pd(R') ₂], [Pd(R'H) ₂]X ₂ X = Cl (2.5), I (2), SCN (1), $\frac{1}{2}$ SO ₄ (3), $\frac{1}{2}$ Pd(SCN) ₂ (ruby-red) Λ_{∞} (32°C.) for the chloride = 112.4 mhos	(48, 48a)
N ¹ -(n-Butyl)guanylurea.. C ₄ H ₉ C ₂ H ₅ ON ₄	[Pd(R') ₂]·0.5H ₂ O, [Pd(R'H) ₂]X ₂ X = Cl (2), $\frac{1}{2}$ SO ₄ (2)	(48, 48a)
N ¹ -Isobutylguanylurea.. C ₄ H ₉ C ₂ H ₅ ON ₄	[Pd(R') ₂]	(48, 48a)
N ¹ -Isoamylguanylurea... C ₅ H ₁₁ C ₂ H ₅ ON ₄	[Pd(R') ₂]	(48, 48a)
N ¹ -(n-Hexyl)guanylurea.. C ₆ H ₁₃ C ₂ H ₅ ON ₄	[Pd(R') ₂]·0.5H ₂ O	(48, 48a)

^(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals. All the hydrated salts lose their water at 110°C.

The palladium(II) N¹-methyl(or ethyl)guanylurea thiocyanate, on treatment with dilute acids, is transformed into the insoluble, beautiful, ruby-red palladium(II) bis(methyl(or ethyl)guanylurea) thiocyanatopalladite with elimination of some alkylguanylurea (48a). In this they resemble the corresponding palladium(II) biguanide complexes (107).

D. COBALT(III) GUANYLUREAS

Tripositive cobalt has been found to combine with guanylurea and substituted guanylureas to form complexes which resemble the corresponding biguanide complexes of the element in color, solubility, and magnetic properties (diamagnetic). Curiously enough, however, while the cobalt(III) alkylbiguanide complexes are comparatively less stable than those formed by the simple unsubstituted biguanide, the order of stability in the case of the guanylurea complexes seems to have been reversed. The cobalt(III) N¹-alkylguanylurea complexes are more readily obtained and give rise to a series of much more stable salts.

Only one compound of the simple guanylurea, cobalt(III) tris(guanylurea), Co(C₂H₅ON₄)₃, and one of N⁴-phenylguanylurea, Co(C₆H₅C₂H₅ON₄)₃·1.5H₂O, have been described. The former is obtained in the form of

sparingly soluble, scarlet crystals by heating on the water bath a solution of hexamminecobalt(III) chloride with a strongly alkaline solution of guanylurea sulfate in calculated proportions. The latter, prepared in a similar manner, forms red crystals soluble in water. Both the compounds are decomposed by acids and strong alkalis (118).

Several fairly stable cobalt(III) complexes with various N¹-alkylguanylureas have recently been described. They have been prepared by oxidizing with hydrogen peroxide a mixture in aqueous alkaline solution of a cobalt(II) salt and the alkylguanylurea concerned. The cobalt(III) tris(alkylguanylurea) bases form rose-red crystals. From the bases, the chlorides and sulfates have been prepared by neutralization with the appropriate dilute acids (48, 48a). Table 27 gives a list of the compounds studied.

TABLE 27

The known cobalt(III) alkylguanylurea complexes
R'H = a molecule of an alkylguanylurea

Ligand	Complex ^(a)	Reference
N ¹ -Methylguanylurea... CH ₃ C ₂ H ₅ ON ₄	[Co(R'H) ₃]X ₃ X = OH (3), Cl (4.5), $\frac{1}{2}$ SO ₄ (4)	(48, 48a)
N ¹ -Ethylguanylurea.... C ₂ H ₅ C ₂ H ₅ ON ₄	[Co(R') ₃]·0.5H ₂ O, [Co(R'H) ₃]X ₃ X = Cl (5), $\frac{1}{2}$ SO ₄ (5)	(48, 48a)
N ¹ -(n-Butyl)guanylurea.. C ₄ H ₉ C ₂ H ₅ ON ₄	[Co(R') ₃], [Co(R'H) ₃](SO ₄) ₂ ·3H ₂ O	(48, 48a)
N ¹ -Isobutylguanylurea.. C ₄ H ₉ C ₂ H ₅ ON ₄	[Co(R') ₃]·H ₂ O, [Co(R'H) ₃]X ₃ X = Cl (1.5), $\frac{1}{2}$ SO ₄ (6.5)	(48, 48a)
N ¹ -Isoamylguanylurea... C ₅ H ₁₁ C ₂ H ₅ ON ₄	[Co(R') ₃]·0.5H ₂ O	(48, 48a)
N ¹ -(n-Hexyl)guanylurea.. C ₆ H ₁₃ C ₂ H ₅ ON ₄	[Co(R') ₃]·2H ₂ O, [Co(R'H) ₃](SO ₄) ₂ ·12H ₂ O	(48, 48a)

^(a) The figure in parentheses after an anion denotes the number of water molecules in the crystals.

The action of potassium cyanide solution on cobalt(III) tris(methylguanylurea) and cobalt(III) tris(ethylguanylurea) chloride or sulfate has led to the preparation of dicyanocobalt(III) bis[methyl(or ethyl)guanylurea] in the form of the yellow anhydrobase, [Co(R'H)(R')(CN)₂], where R'H = a molecule of methyl(or ethyl)guanylurea (48, 48a). These are sparingly soluble in water and resemble the corresponding dicyanocobalt(III) bis(biguanide) complexes (161).

E. CHROMIUM(III) GUANYLUREAS

Only a few chromium(III) alkylguanylurea complexes have been described (48, 48a).

Chromium(III) tris(N¹-methylguanylurea) sulfate, [Cr(CH₃C₂H₅ON₄)₃](SO₄)₂·9H₂O, was obtained as insoluble, orange-red crystals when the dark, rose-red solution formed by the addition of a solution of chrome alum to an alkaline solution of methylguanylurea sulfate was neutralized with dilute sulfuric acid (48, 48a).

In a similar manner complex chromium(III) bases of butylguanyl-, isobutylguanyl-, and isoamylguanylurea have been obtained as insoluble, rose-red pre-

precipitates by the action of a solution of chrome alum on an alkaline solution of the individual alkylguanyliurea sulfate. These are soluble in alcohol and have the composition $[\text{Cr}(\text{C}_4\text{H}_9\text{C}_2\text{H}_4\text{ON}_4)_3] \cdot \text{H}_2\text{O}$, $[\text{Cr}(\text{C}_4\text{H}_9\text{C}_2\text{H}_4\text{ON}_4)_3]$, and $[\text{Cr}(\text{C}_6\text{H}_{11}\text{C}_2\text{H}_4\text{ON}_4)_3] \cdot 2\text{H}_2\text{O}$, respectively (48, 48a).

The chromium(III) alkylguanyliurea complexes are similar to, but less stable than, the corresponding cobalt(III) complexes.

F. ZINC GUANYLUREAS

Zinc methylguanyliurea, $[\text{Zn}(\text{CH}_3\text{C}_2\text{H}_4\text{ON}_4)_2] \cdot 0.5\text{H}_2\text{O}$, and zinc ethylguanyliurea, $[\text{Zn}(\text{C}_2\text{H}_5\text{C}_2\text{H}_4\text{ON}_4)_2] \cdot 0.5\text{H}_2\text{O}$, were obtained in the form of white crystals by the action of sodium zincate on methyl(or ethyl)guanyliurea sulfate in aqueous solution. They resemble the corresponding biguanide complexes and are slowly hydrolyzed by water in the cold, but more rapidly on heating, with separation of zinc hydroxide. They can, however, be recrystallized from hot alkali solution containing a small quantity of the chelating ligand (115).

VII. METAL COMPLEXES OF GUANYLTHIOUREA

The metal complexes of guanylthiourea have been studied only to a very limited extent. But these differ in some cases from those of guanyliurea, though the two ligands resemble each other closely in composition and properties. This seems to indicate the presence of metal-sulfur bonds in the molecules of metal complexes of guanylthiourea (see Section III, B).

(a) With guanylthiourea copper(II) forms only one type of complex in which only one molecule of the ligand is bound per metal atom.

Diaquocopper(II) uniguanylthiourea base, $[\text{Cu}(\text{H}_2\text{O})_2(\text{C}_2\text{H}_6\text{SN}_4)]\text{OH}$, is obtained in the form of insoluble brown crystals when a cold solution of copper(II) sulfate is added to a strongly ammoniacal solution of guanylthiourea (126). In the absence of ammonia the sulfate of the complex base, containing 4 H_2O , is precipitated (126). Both the complex base and its sulfate are decomposed by warm dilute hydrochloric acid with separation of copper(II) sulfide (126). The compounds show a magnetic moment value of approximately 1.5 Bohr magnetons (126), which seems to suggest the development of antiferromagnetism or metal-metal bonding in the crystal.

(b) Nickel(II) bis(guanylthiourea), $[\text{Ni}(\text{C}_2\text{H}_6\text{SN}_4)_2] \cdot 1.5\text{H}_2\text{O}$, separates as an insoluble, orange precipitate when a solution of nickel(II) sulfate is added to one of guanylthiourea which has been rendered strongly alkaline with sodium hydroxide (126). The substance is diamagnetic like all orange-yellow nickel(II) complexes and has, therefore, a square planar configuration with d_{sp^2} hybrid bonds. At 100°C . it loses water, forming an anhydrobase, and is readily decomposed by warm dilute

acids though unaffected even by boiling alkalis (126).

(c) Poddar and Rây (97) have described a cobalt(II) bis(guanylthiourea), $[\text{Co}(\text{C}_2\text{H}_6\text{SN}_4)_2](\text{OH})_2 \cdot \text{H}_2\text{O}$, which is formed as a brown crystalline precipitate when a solution of cobalt(II) chloride, ammonium chloride, and guanylthiourea is treated in the cold with a dilute solution of potassium hydroxide until the mixture becomes almost neutral. The compound is decomposed by warm alkalis with the formation of cobalt(II) sulfide; it is also decomposed by acids, and changes color, probably owing to decomposition, on exposure to air for a long time (97). It gives a value for the magnetic moment of 1.8 Bohr magnetons (97), corresponding to the presence of one unpaired electron in the molecule, in perfect agreement with the theoretically expected value for a square planar cobalt(II) complex with d_{sp^2} hybrid bonds. At 105°C . the substance loses three molecules of water and is converted to the anhydrobase, $\text{Co}(\text{C}_2\text{H}_6\text{SN}_4)_2$ (97).

(d) Palladium(II) bis(guanylthiourea) base, $[\text{Pd}(\text{C}_2\text{H}_6\text{SN}_4)_2](\text{OH})_2 \cdot \text{H}_2\text{O}$, was obtained as an insoluble, cream-colored powder when a solution of palladium(II) chloride and guanylthiourea in dilute hydrochloric acid was treated with one of sodium acetate and sodium hydroxide (97). The compound is decomposed by dilute acids with formation of palladium(II) chloride; boiling dilute alkali solutions decompose it with separation of palladium(II) sulfide (97).

When an ammoniacal solution of palladium(II) chloride was added to one of guanylthiourea, chocolate-colored, silky needles of diamminepalladium(II) guanylthiourea chloride, $[\text{Pd}(\text{NH}_3)_2(\text{C}_2\text{H}_6\text{SN}_4)]\text{Cl} \cdot \text{H}_2\text{O}$, gradually separated out (97). The compound is slightly soluble in water and alcohol on warming, but is decomposed by acids and alkalis (97). From a consideration of the color of the complexes and of their decomposition with formation of palladium(II) sulfide in boiling alkalis the authors (97) assumed the occurrence of a palladium-sulfur bond in their molecules. There is, however, no direct evidence for this assumption, since the formation of palladium(II) sulfide by the action of boiling alkalis might be attributed to the decomposition of the ligand itself. The decomposition of the palladium(II) bis(guanylthiourea) base by acids with formation of palladium(II) chloride cannot, on the other hand, be accounted for on this basis. But in all other respects the palladium(II) complexes behave like those of nickel(II) (97).

(e) When a solution of hexamminecobalt(III) chloride was warmed with guanylthiourea in potassium hydroxide solution until the color of the solution turned red and was then kept, after filtration, in the cold overnight, chocolate-brown crystals of the cobalt(III) tris(guanylthiourea) base, $[\text{Co}(\text{C}_2\text{H}_6\text{SN}_4)_3](\text{OH})_3$, separated (97). The compound is insoluble in water and alcohol, but is decomposed by alkalis with formation

of cobalt sulfide (97). It loses three molecules of water at 105°C., giving the anhydrobase, $\text{Co}(\text{C}_2\text{H}_5\text{SN}_4)_3$ (97).

When, in place of caustic potassium hydroxide, sodium acetate was used in the above preparation, deep red, shining crystals of diamminecobalt(III) bis(guanylthiourea) base, $[\text{Co}(\text{NH}_3)_2(\text{C}_2\text{H}_5\text{SN}_4)_2] \cdot 2\text{H}_2\text{O}$, were obtained (97). The compound is slightly soluble in hot water and is decomposed by alkalis (97). It combines with acids to form salts, of which the chloride is highly soluble and the sulfate almost insoluble in water (97).

Both the cobalt(III) tris(guanylthiourea) and the diamminecobalt(III) bis(guanylthiourea) bases are diamagnetic like all cobalt(III) complexes (97).

(f) With an excess of mercuric chloride in aqueous solution guanylthiourea gives a white precipitate having the composition $\text{C}_2\text{H}_4\text{SN}_4 \cdot 2\text{HgCl} \cdot \text{HgCl}_2 \cdot 4\text{H}_2\text{O}$ (97). It is decomposed slowly by hot water and rapidly by alkali solution with formation of black mercury(II) sulfide (97). To a certain extent the compound resembles the infusible white precipitate and indicates the presence of two reactive amino groups in a molecule of guanylthiourea.

VIII. STABILITY OF METAL-GUANYLUREA COMPLEXES

Though the metal complexes of simple unsubstituted guanylurea and of N^4 -phenylguanylurea are much less stable than those of biguanide and phenylbiguanide, the metal complexes of N^1 -alkylguanyl ureas are more or less stable than those of alkylbiguanides. This has been verified quantitatively in the case of copper(II) and nickel(II) complexes of guanylurea, N^1 -methylguanylurea, and N^1 -ethylguanylurea (44).

An acid solution of a copper(II) salt containing an excess of guanylurea or an alkylguanylurea hydrochloride on gradual treatment with a solution of an alkali turns progressively blue. The intensity of the blue color reaches its maximum value for the wavelength 650–660 $m\mu$ (absorptivity maximum) at pH 6.5–6.75 for guanylurea and at pH 4.5 for methylguanylurea and

ethylguanylurea. With increasing pH the blue color changes slowly to red-violet with a maximum intensity at or above pH 7 for methylguanylurea and ethylguanylurea, and above pH 7.5 for guanylurea having the wavelength of maximum absorptivity at 530–540 $m\mu$ (44). The composition of the blue complex in solution in the case of alkylguanylureas was determined by Job's method from the spectrophotometric measurement of its optical density (44, 73, 184). This gave a metal-ligand ratio of 1:1, indicating the formation of a uniguanylurea complex corresponding to the copper(II) uniguanylurea complexes with almost the same wavelength for absorptivity maximum. This led to the preparation of unimethylguanylurea and uniethylguanylurea complexes of copper(II) (see Section VI, A). The red-violet color at higher pH corresponds to the formation of copper(II) bis(guanylurea) complexes with practically the same wavelength for absorptivity maximum as that for copper(II) bis(biguanide) complexes. The copper(II) guanylurea complexes are thus shown to be formed in two successive stages like the copper(II) biguanide complexes (44). The values of the instability constant of copper(II) guanylurea and copper(II) alkylguanylurea complexes have been determined from a study of their formation reactions by measuring the optical density of the colored solutions and the dissociation constants of the protonated ligands (44). The values obtained are collected in table 28.

A similar study has shown that the nickel(II) complexes of methylguanylurea and ethylguanylurea, like the nickel(II) biguanide complexes, are formed in a single stage to give only the bis(alkylguanylurea) complexes with their absorptivity maximum at 440–450 $m\mu$ and optimum pH above 7.4, as against 460–470 $m\mu$ and pH above 7.9 for the corresponding nickel(II) biguanide complexes (44, 109). The values of their instability constants, thus determined (44), are included in table 28.

The values of the instability constants of copper(II)

TABLE 28
Instability constants of copper(II) and nickel(II) alkylguanylureas (44)
 $\mu = 0.1 M$ potassium chloride; temperature = 32°C.

Complex	pH (optimum)	Optimum Wavelength	ϵ	Instability Constant
		$m\mu$		
Copper guanylurea				
Uni complex.....	6.5–6.75	660	38.3	$k_1 = 7.86 \times 10^{-5}$
Bis complex.....	7.5	540	38.3	$k_2 = 7.76 \times 10^{-4}$
				K (overall) = $k_1 k_2 = 6.1 \times 10^{-9}$
Copper N^1 -methylguanylurea				
Uni complex.....	4.5	660	32.4	$k_1 = 1.5 \times 10^{-5}$
Bis complex.....	7.0	540	43.4	$k_2 = 6.8 \times 10^{-5}$
				K (overall) = 1.02×10^{-10}
Copper N^1 -ethylguanylurea				
Uni complex.....	4.5	660	32.2	$k_1 = 2.1 \times 10^{-10}$
Bis complex.....	7.0	540	43.5	$k_2 = 2.37 \times 10^{-5}$
				K (overall) = 5.0×10^{-16}
Nickel N^1 -methylguanylurea.....	7.4	440	55.2	$K = 5.5 \times 10^{-11}$
Nickel N^1 -ethylguanylurea.....	7.4	440	47.0	$K = 1.55 \times 10^{-12}$

and nickel(II) guanylurea complexes show that the substitution by alkyl groups at the N^1 -position of the ligand considerably increases the stability of their copper and nickel complexes, making them comparable to, though somewhat less stable than, those of their corresponding biguanide complexes. The values of table 28 give the following order of stability for the guanylurea complexes of copper(II) and nickel(II):

Copper N^1 -ethylguanylurea > copper N^1 -methylguanylurea >>
copper guanylurea

Nickel N^1 -ethylguanylurea > nickel N^1 -methylguanylurea

Copper guanylureas > nickel guanylureas

The value of the stability constant of the copper(II) biguanide (unsubstituted) complex, on the other hand, is much greater than that of the copper(II) guanylurea (unsubstituted), their pK values differing by about 11 units (K_{Cu} for biguanide = 4.5×10^{-19} ; K_{Cu} for guanylurea = 6.1×10^{-8}). For a comprehensive generalization in this respect further work on the copper(II) and nickel(II) complexes, involving a larger variety of substituted guanylureas, is needed.

A quantitative study on the stability of guanylurea complexes of other metals, as also of the metal complexes of guanylthiourea, is, however, lacking.

In this connection it might be worth noting that dithiobiuret, $H_2NCSNHCSNH_2$, the disulfur analog of biuret and biguanide, though closely related to guanylthiourea, fails to form any stable complex with metals (7a). It is acidic and very sparingly soluble in water and acids. In alkaline solutions it behaves as a powerful reducing agent with separation of sulfur from decomposition.

An attempt has been made in this review to present a more or less complete, up-to-date account of the work on the metal complexes of biguanides and guanylureas with an indication of the scope for further study in the subject relating to its preparative, structural, and kinetic aspects. The disposition and nature of the metal-ligand bond in the complexes have been discussed and the need for an x-ray examination of the structure of these complexes has been stressed. Biguanides in general have been found to constitute a group of very remarkable chelating agents combining with quite a large number of elements of the transition series to give rise to coordination complexes of extraordinary stability, often of intense color and with capacity to stabilize the higher valence state of the central metal atom.

The reviewer wishes to acknowledge gratefully the assistance of Dr. N. R. Sengupta in the collection and verification of references, and of Dr. D. Bandyopadhyay (Banerjea) in revising the manuscript with helpful comments and suggestions, calculated to eliminate many ambiguities and errors.

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