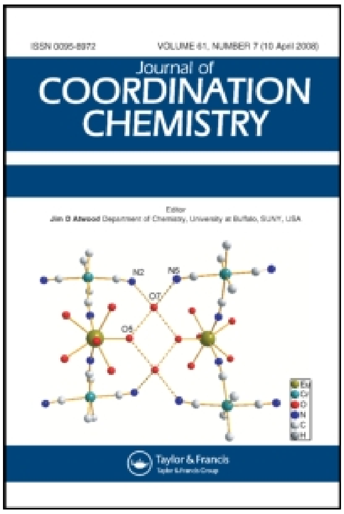

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

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To cite this Article Morzyk, Barbara , Michalska, Danuta and Wojciechowski, Walter(1995) 'INTERACTION OF METAL IONS WITH 3,3-DIMETHYLGLUTARIMIDE', Journal of Coordination Chemistry, 34: 2, 179 — 185
To link to this Article: DOI: 10.1080/00958979508055397
URL: http://dx.doi.org/10.1080/00958979508055397

J. Coord. Chem., 1995, Vol 34, pp. 179–185
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INTERACTION OF METAL IONS WITH 3,3-DIMETHYLGLUTARIMIDE

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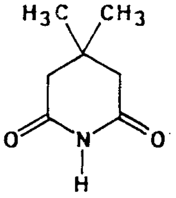
(Received August 5, 1994)

Interaction of the biologically active ligand 3,3-dimethylglutarimide with a series of metal ions has been investigated by a potentiometric method. Acid dissociation constants of the ligand (L) and stability constants for the formation of 1:1 (metal to ligand) complexes with Cu(II), Ni(II), Zn(II), Hg(II), Be(II) and Ag(I) have been determined in aqueous solution at 25.0°C and 0.1 M (KNO_3) ionic strength. It has been shown that silver(I) and mercury(II) ions form two types of complexes, ML and ML_2 in a stepwise manner. It suggested that in the ML_2 complex (where M = Ag, Hg), a linear N-M-N bond is formed through the two deprotonated nitrogen atoms of glutarimide rings.

KEYWORDS: 3,3-dimethylglutarimide, *N*-heterocycles, metal complexes, stability constants

INTRODUCTION

Substituted glutarimide compounds have been reported to possess different CNS (central nervous system) activity ranging from anticonvulsive (antagonist)[1] to convulsive and analeptics (agonist).[2] Some of the studies have attempted to correlate the mode of CNS activity of glutarimides with the site of substitution in the ring and the type of substituent.[3,4] 3,3-dimethylglutarimide shows analeptic action in mice.[2] The biological activity of glutarimides has been investigated in a great number of papers; however little is known about interaction of these molecules with metal ions in solution.[5] It has been suggested[6] that metal ions contribute to the hallucinogenic effect of certain drugs and their role in neuronal functions is significant.



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In view of the pharmacological activity of glutarimides it seemed to be important to study their interaction with metal ions. Therefore, in this work, the interaction of 3,3-dimethylglutarimide (β, β-dimethylglutarimide) with Cu(II), Ni(II), Co(II), Zn(II), Hg(II), Be(II) and Ag(I), as studied by a potentiometric method, is reported.

EXPERIMENTAL

Materials

3,3-Dimethylglutarimide was purchased from the Aldrich Chemical Co. Metal salts were of reagent grade purity. The initial 0.1 M solutions of Cu(II), Ni(II), Co(II), Zn(II), Hg(II), Be(II) and Ag(I) ions were prepared and concentrations determined by complexometric titrations with EDTA or by other analytical methods.[7,8] The aqueous solution of the ligand (0.10 M) was freshly prepared before each titration. Carbonate-free sodium hydroxide (0.1 M) was standardized by titration with potassium hydrogen phthalate.

Measurements

The experimental method consisted of the potentiometric titration of 3,3-dimethylglutarimide with standard sodium hydroxide solution in the absence and presence of the metal ion being investigated. An OP-211 model pH meter (Radelkis, Budapest) with combination glass electrode was used for the pH-metric measurements. The electrode system was calibrated by means of titration of HCl solutions of known titre with solutions of NaOH according to ref. 9. The accuracy of the measured pH was ±0.01. Titrations of the investigated systems were performed at 25.0 ± 0.1°C and the ionic strength was maintained constant at 0.1 M (KNO_3). The metal ion concentration was varied from 2.50 to 10.0 mM and the ligand concentration from 5.0 to 10.0 mM. All metal to ligand molar ratios were tested by at least three titrations.

Calculations

The acid dissociation of neutral 3,3-dimethylglutarimide is related to the usual equilibrium dissociation

$$HL \rightleftharpoons L^- + H^+$$

by the equation

$$K_a = [H^+](aT_L + [H^+] - [OH^-])/\ \{T_L - (aT_L + [H^+] - [OH^-])\}$$

where a = moles of base added per mole of ligand and T_L = total ligand concentration.

The concentration of the bound ligand was determined directly from the shifts in the pH titration curves using the Calvin and Melchior method.[10] The degree of formation $\bar{n}$ and pL (L = free ligand concentration) were computed as in ref. 11 and our previous work.[12a] Non-linear regression analysis has been used to obtain the formation curves and the stability constants of the metal-ligand complexes. Only those data which had been measured in homogeneous solution without precipitation were used in calculations. Computations were performed on a 486 PC.

RESULTS AND DISCUSSION

The acid dissociation constant of DMeGlu at 25°C and 0.1 M (KNO_3) ionic strength has been calculated according to the above equation and is given in Table 1. Potentiometric titration curves of free 3,3-dimethylglutarimide (DMeGlu) and those of DMeGlu in the presence of Hg(II) and Ag(I) ions (1:2 metal to ligand mol ratio) are presented in Figure 1. Similar titration curves were obtained for different metal to ligand mol ratios, indicating formation of mononuclear complexes.

In the systems containing Cu(II), Ni(II), Zn(II), Co(II) and Be(II) the titrations could not be completed because of separation of a solid phase before the second inflection point was reached. Therefore, formation of the 1:1 complexes was assumed in these systems and calculations were performed before the precipitation point. Computed formation curves for the complexes of DMeGlu with all the metal ions studied are shown in Figure 2.

Calculated stability constants of the complexes are given in Table 1. Distribution diagrams demonstrating the influence of pH on the concentration of the ML and ML_2 species are illustrated for Hg(II) in Figure 3.

3,3-Dimethylglutarimide has one ionizable proton at the imido nitrogen atom and the corresponding pK_a is 10.64 at 25°C and 0.1 M (KNO_3) ionic strength. It is of interest to compare the effect of substitution of the glutarimide ring on its basicity. It is known that substitution with CH_3 at position 5 in thymine makes it more basic than uracil. This is indicated by a larger pK_a value and higher stabilities of the metal complexes formed as compared to those of uracil.[11] The pK_a value of unsubstituted glutarimide has been determined potentiometrically in previous studies,[12b] and is 10.07 (at 25°C and μ = 0.1 M in KNO_3).

Thus, substitution with methyl groups at the β position in glutarimide increases the basicity of the NH imido group in the ring (ΔpK_a = 0.57). It is noted that the pK_a values of thymine and uracil also differ by about 0.5 (9.70 and 9.16 for T and U, respectively).[11]

It is known that relatively "soft" metal ions such as Ag(I) and Hg(II), which have a higher affinity for N than for O atoms, are able to replace the proton at N(3) of 1-methyluracil, uridine and thymidine in neutral or even low pH solutions.[13]

Table 1 Acid dissociation constant of 3,3-dimethylglutarimide (DMeGlu) and stability constants of 1:1 and 1:2 (metal to DMeGlu) complexes in aqueous solution at 25.0 ± 0.1°C, $\mu = 0.1$ M (KNO_3)

pK_a	Metal	$\log K^{M}_{ML_2}$	$\log K^{ML}_{ML_2}$	$\Delta\log K^*$
10.64	Cu(II)	6.91 ± 0.03		
	Ni(II)	4.20 ± 0.01		
	Co(II)	4.40 ± 0.01		
	Zn(II)	5.52 ± 0.01		
	Be(II)	7.86 ± 0.02		
	Hg(II)	8.61 ± 0.02	7.00 ± 0.02	-1.61
	Ag(I)	4.82 ± 0.02	3.57 ± 0.02	-1.25

*$\Delta\log K = (\log K^{ML}_{ML_2} - \log K^{M}_{ML})$.

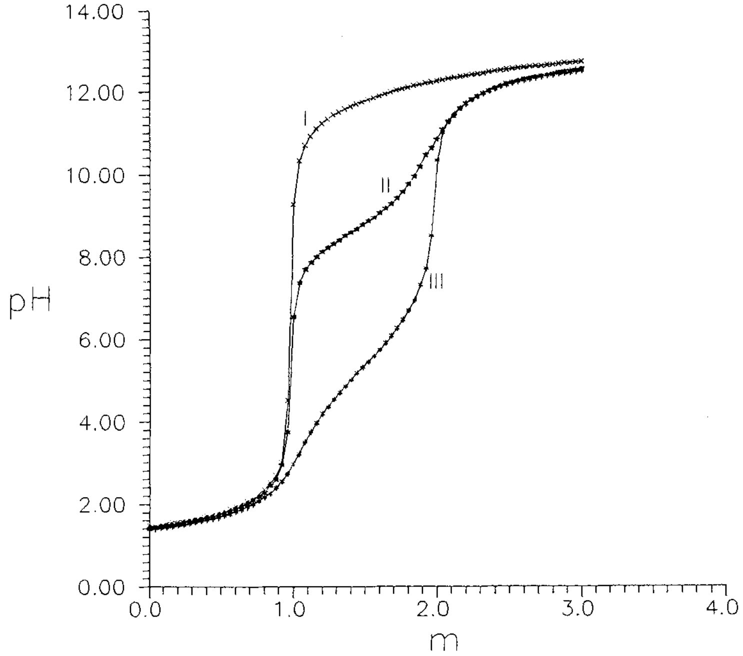

Figure 1 Potentiometric titration curves of 3,3-dimethylglutarimide (DMeGlu) in the absence and presence of metal ions in aqueous solution. The concentration of the ligand and metal ions are 5.0 mM and 2.5 mM, respectively; I = free DMeGlu; II = DMeGlu and Ag(I); III = DMeGlu and Hg(II), m = mole of base added per one mole of metal ion. For free ligand titration "m" corresponds to "a" on the abscissae axis.

Therefore, it is very likely that 3,3-dimethylglutarimide, which has structural and electronic features similar to these nucleic acid bases,[14] may undergo deprotonation at the imido nitrogen during reaction with the above metal ions.

The potentiometric titration curves for DMGlu in the presence of Hg(II) and Ag(I) are illustrated in Figure 1. It is clearly seen from the shift in the titration curves that these metal ions displace proton from the ligand. Since the only site of proton ionization is the imido group of 3,3-dimethylglutarimide, it may be concluded that the ligand binds with metal ions through the deprotonated nitrogen atom of the ring. Titration curves obtained for various ligand to metal mol ratios are very similar. This implies that only mononuclear species are formed in solution. Two inflexions are observed in the curves, suggesting stepwise complex formation of 1:1 (ML) and 1:2 (ML_2) species. It should be emphasized that a very similar effect (two inflexions on the titration curves) has been found in potentiometric studies of uracil or thymine with Hg(II) and Be(II)[11] as well as of urindine (Urd) with Ag(I).[15]

The calculated stability constants of the metal complexes with 3,3-dimethylglutarimide are presented in Table 1. Stability constants of the Cu(II), Ni(II), Co(II) and Zn(II) complexes are somewhat higher than those of the corresponding complexes of uracil and thymine (determined at the same temperature and ionic strength).[16,17] For example, the value of log K^{M}_{ML} for Cu(II) complex

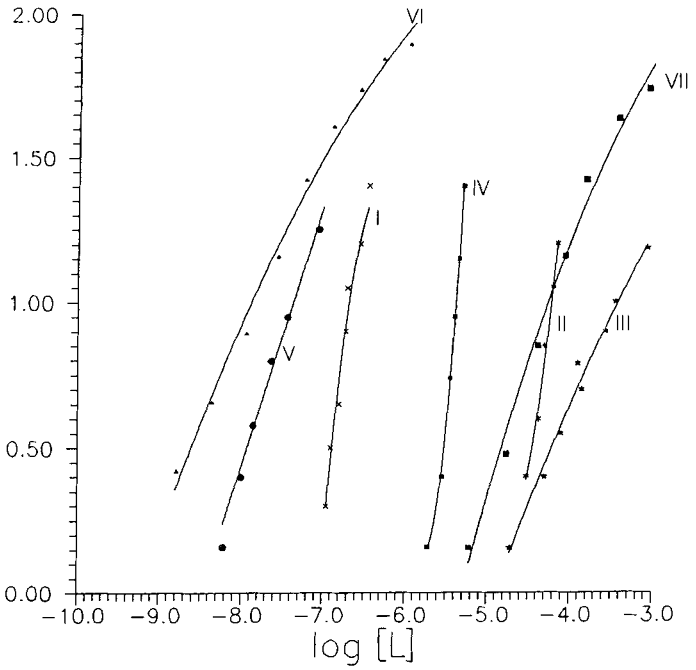

Figure 2 Formation curves of the 3,3-dimethylglutarimide complexes with metal ions: I = Cu(II); II = Co(II); III = Ni(II); IV = Zn(II); V = Be(II); VI = Hg(II); VII = Ag(I).

with DMeGlu is 6.91, whereas the corresponding values for Cu(II)-thymine, Cu(II)-uracil and Cu(II)-uridine are 5.80,[17] 5.60[17] and 4.03,[16] respectively. Decreasing stabilities of the Cu(II) complexes follow the order of decreasing basicity of the ligands, DMeGlu > T > U > Urd.

It is interesting to note that the stability constants of the Hg(II) complexes with DMeGlu (log K_1 = 8.61 and log K_2 = 7.00) are very similar to the corresponding stability constants of Hg(II) complexes with thymine, 8.11 and 6.93, respectively,[11] (measured at the same temperature and ionic strength). It appears from the distribution diagram shown in Figure 3, that Hg(DMeGlu) is the prevailing form in the pH range 4.5–5.7, whereas $Hg(DMeGlu)_2$ species dominates for pH > 5.7 (charges are omitted for simplicity).

Distribution curves for the Ag(I)-DMeGlu system have revealed that in neutral solution the silver ion is able to replace proton from the imido group of the ligand and forms Ag(DMeGlu). This complex dominates at pH = 7-9, whereas at higher pH values (> 9.0) $Ag(DMeGlu)_2$ becomes increasingly important. These data are in agreement with those reported for silver complexes with uracil derivatives.[13] It has been shown by potentiometric titration that silver binds especially strongly to uridine (Urd)[15] and polyuridilic acid (polyU)[18] and the nature of interaction is dependent upon the pH. For instance, at low values of pH (<6.0) the stable structure, AgL (where L = polyU or Urd) is formed by displacement of the N3 proton of the base. At higher pH values (> 8.0) a 1:2 (AgL_2) complex dominates. It has been concluded[15,18] that in the AgL_2 species the silver ion is linearly

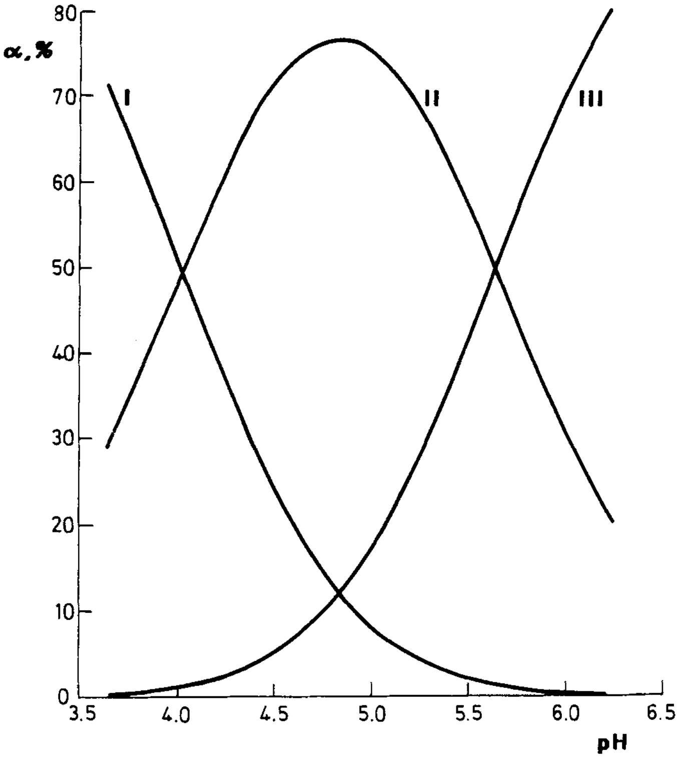

Figure 3 Influence of pH on concentration of Hg-DMeGlu species I = Hg(II); II = HgL^+; III = HgL_2.

coordinated to two uracil groups through the deprotonated N(3) atoms. Furthermore, it should be noted that in the $Hg(l\text{-}MeT)_2$ complex the Hg(II) ion is also linearly coordinated to two nitrogen atoms of two deprotonated thymine molecules, as indicated by X-ray crystal structure analysis.[19]

Since stabilities of the silver(I) and mercury(II) complexes with 3,3-dimethylglutarimide in solution are similar to those of the corresponding complexes of uracil and thymine and their derivatives, it is anticipated that a similar mode of binding may occur in these species. Therefore, it is suggested that in the $M(DMeGlu)_2$ complexes (where M = Ag, Hg) a linear N-M-N bond is formed between two deprotonated nitrogen atoms of glutarimide molecules.

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