Pergamon

PII: S0277-5387(97)00076-4

Polyhedron Vol. 16, No. 19, pp. 3261–3266, 1997
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0277-5387/97 $17.00+0.00

The non-formation of macrocyclic tetraamides by coordinated ligand reactions

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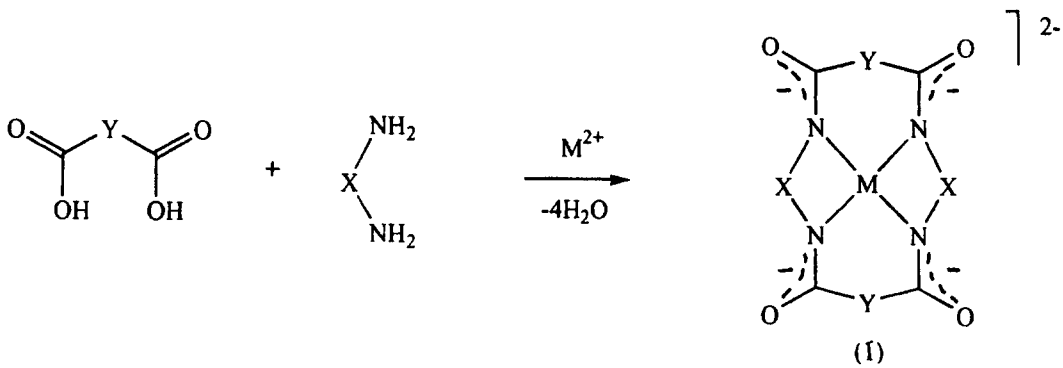
(Received 13 January 1997; accepted 13 February 1997)

Abstract—A recent paper has described the synthesis of macrocyclic tetraamide complexes by the reaction of a diamine (ethylenediamine or propylenediamine) with malonic, succinic or glutaric acids in methanol solution in the presence of a metal(II) salt at room temperature. We present evidence that macrocycle formation does not occur under these conditions and only mixed-ligand complexes are formed. The blue crystalline complex obtained with malonic acid, 1,3-diaminopropane and copper(II) chloride is shown by X-ray crystallography to be $[Cu(mal)(pn)Cl_2]^{2-}\,pnH_2^{2+}$ (mal = malonate; pn = 1,3-diaminopropane). The structure comprises discrete $[Cu(mal)(pn)Cl_2]^{2-}$ anions and pnH_2^{2+} cations. Within the anionic complex the geometry at each copper(II) is tetragonal with two long axial bonds to the chloride ligands, Cu—Cl(1) = 2.862(2) and Cu—Cl(2) = 3.042(2) Å. The malonato ring has a boat conformation with Cu—O = 1.966(3) Å and the 1,3-diaminopropane ring a chair conformation with Cu—N = 1.993(4) Å. A crystallographic mirror plane bisects the two rings through the copper and chloride ligands. © 1997 Elsevier Science Ltd

Keywords: crystallography; macrocyclic tetraamide; copper complex; metal template.

A recent paper [1] has described the synthesis of a series of divalent copper(II), nickel(II) and zinc(II) complexes of 14- to 20-membered tetraamide macrocycles as shown in Scheme 1. The general method of synthesis involved reaction of the metal(II) salt of the diamine (ethylenediamine or propylenediamine) with malonic, succinic or glutaric acids in methanol solution at room temperature for 7 h. Mixing an aliphatic amine with a carboxylic acid at room temperature results in the formation of a salt. To convert this salt to an amide requires



Scheme 1.

$$RCOOH + R'NH_2 \longrightarrow RCOO^-NH_3^+R' \longrightarrow RCONHR' + H_2O$$

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temperatures which are normally too high for the survival of the amide. The formation of an amide is normally carried out after conversion of the carboxyl component to a more reactive acyl derivative which can react with the amino component under mild conditions. Suitable reactive acyl derivatives with good leaving groups are esters, acid chlorides and acyl azides. For example, the ligand dioxocyclam (2) is prepared by the reaction of 1,9-diamino-3,7-diazanonane (2,3,2-tet) with diethyl malonate under high dilution conditions in ethanol [2], Scheme 2.

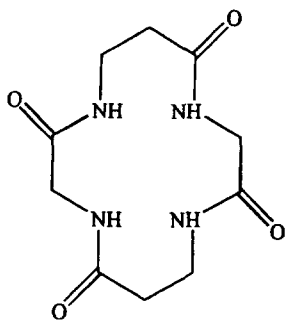
For the reasons outlined above we were doubtful if amide formation to give macrocycles such as (1) had taken place under the mild conditions described by Shakir *et al.* [1]. In the presence of metal ions it appeared that the most likely products would be mixed-ligand complexes of the diamine and the dicarboxylic acid. We present evidence that this is indeed the case. A number of macrocyclic tetra-amides have been described in the literature. Rybka and Margerum [3] have discussed the chemistry of the ligand **3**, which was prepared by the conventional methods employed in peptide synthesis.

An American group [4] has described a general method for the synthesis of macrocyclic tetraamide ligands by aminolysis of the thiazolidine-2-thione amides of dicarboxylic acids with diamines. Macrocyclic tetramides such as (4) can be prepared in high yield by this route. Attempts to develop ligands which are capable of stabilizing high oxidation states of metal ions has led to the design of non-innocent ligands [5]. The structures of chromium(V) oxo complexes with the two tetra-amide ligands (5) and (6) have been determined. Both structures were found to contain non-planar amide groups and in (5) all four amide groups are non-planar.

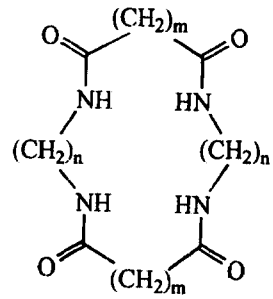
EXPERIMENTAL

The reaction between propylenediamine and malonic acid in the presence of copper(II) chloride in methanol solution was carried out as previously described [1]. The pale blue complex obtained did not give the analytical data expected for the macrocyclic structure. Found: C, 31.0; H, 4.7; N, 8.45. Calc. for $C_{12}H_{20}N_4O_4CuCl_2$: C, 34.1; H, 4.8; N, 13.4%. The complex had λ_{max} 650 nm in aqueous solution.

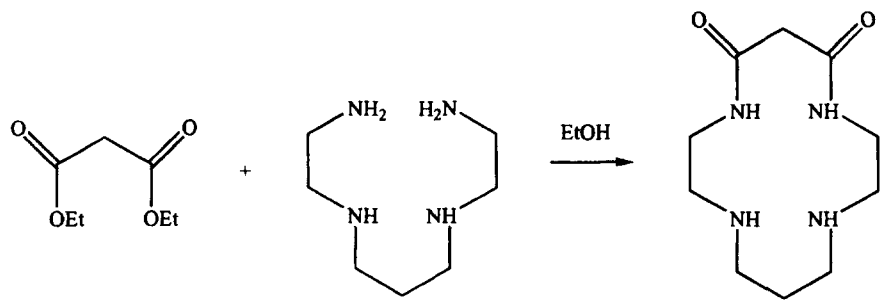
The copper complex was studied by ion exchange methods using a Sephadex C-25 cation exchange column. The complex was sorbed on the column and a green complex eluted with water. A blue band remained on the column and was eluted with 2.0 mol dm^{-2} NaCl. The UV–vis spectrum of the green complex had λ_{max} 854 nm and was very similar to that of $[Cu(mal)_2]^{2-}$. The cationic blue complex had λ_{max} 578



(3)

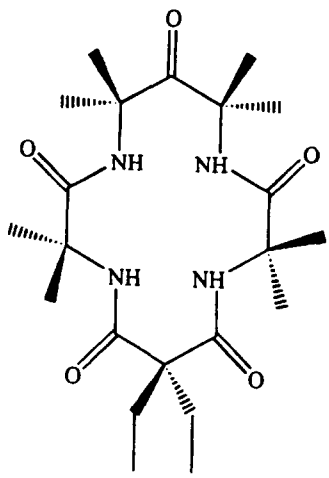


(4)

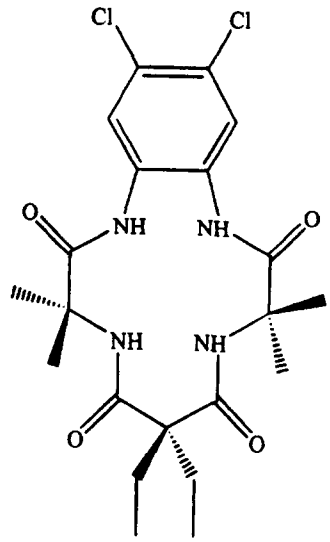


(2)

Scheme 2.



(5)



(6)

nm identical to that of $[Cu(pn)_2]^{2+}$. The spectrum of the prepared complex in aqueous solution has λ_{max} 650 nm, which is very comparable to that of a 1 : 1 mixture of $[Cu(mal)_2]^{2-}$ and $[Cu(pn)_2]^{2+}$.

In a further experiment the complex was sorbed on a Sephadex C-25 cation exchange column and eluted with dilute HCl (pH 3.5). A blue complex was eluted and on standing blue needles deposited. The IR spectrum of this complex indicated the presence of a protonated amine function and gave a positive test for chloride with silver nitrate. The complex can be formulated $[Cu(pn)(mal)Cl_2]^{2-}[pnH_2]^{2+}$. Found: C, 27.7; H, 6.3; N, 14.4. Calc. for $C_9H_{24}N_4O_4CuCl_2$: C, 27.95; H, 6.3; N, 14.5%. The complex had λ_{max} 624 nm in aqueous solution. Potentiometric titration of the complex with sodium hydroxide solution gave a well defined end point and a value for the equivalent weight of 196.35, which corresponds to a molecular weight of 392.7 if there are two titratable protons (theory = 386.7).

Physical measurements

UV–vis spectra were determined with a Phillips 8720 spectrophotometer using aqueous solutions. IR spectra were obtained using KBr discs on a Perkin–Elmer 1710 Fourier-transform IR spectrophotometer.

Crystal structure determination of $[Cu(pn)(mal)Cl_2][pnH_2]$

A blue needle crystal grown from aqueous solution of approximate dimensions $0.10 \times 0.15 \times 0.35$ mm mounted on a glass fibre was used in the X-ray analysis.

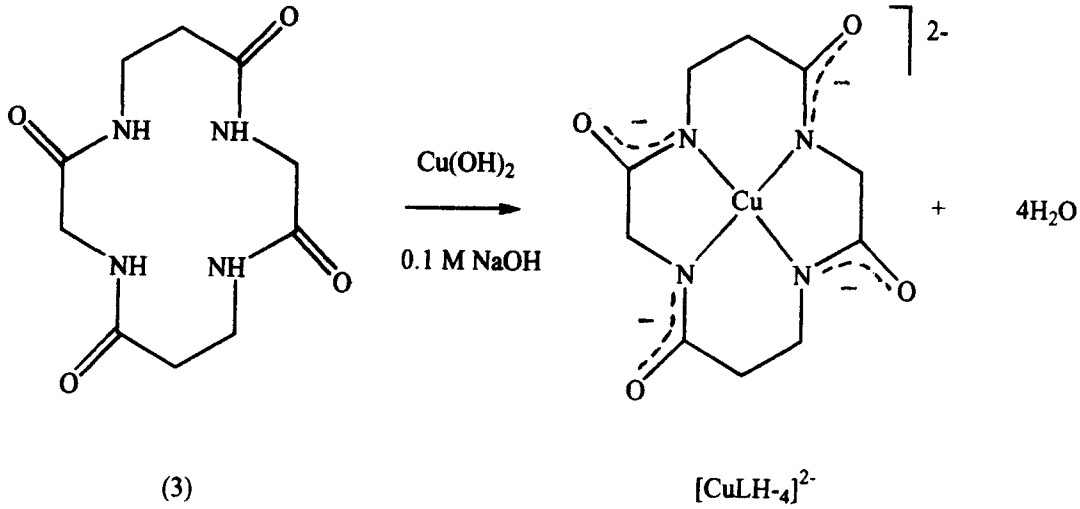
Crystallographic data. $C_9H_{24}N_4O_4CuCl_2$, M = 386.77, orthorhombic, space group *Pnma* (no. 62), $a = 9.080(4)$, $b = 9.406(5)$, $c = 18.403(4)$ Å, $V = 1571(1)$ Å^3, $Z = 4$, $D_{calc} = 1.634$ g cm^{-3}, $F(000) = 804$, λ(Mo-K_α) = 0.71069 Å and $\mu = 17.46$ cm^{-1}.

Data for structure determination were collected at room temperature with a Rigaku AFC7S automatic diffractometer with graphite monochromated Mo-K_α radiation. The ω–2θ scan technique was used. A total of 1265 reflections were measured, of which 847 with $I > 3\sigma(I)$ were used in the structure refinement. Lorentz and polarization corrections were applied.

The structure was solved by direct methods [6] and expanded using Fourier techniques [7]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final R and R_w values were 0.035 and 0.032, respectively. The maximum and minimum peaks in the final difference map were 0.51 and −0.58 e Å^{-3}, respectively. All calculations were carried out using the teXsan [8] crystallographic software package of the Molecular Structure Corporation.

RESULTS AND DISCUSSION

Mixing ethanolic solutions of $[Cu(pn)_2]^{2+}$ and $[Cu(mal)_2]^{2-}$ gives an immediate precipitate of a complex, which is probably $[Cu(pn)_2][Cu(mal)_2]$ or a mixed-ligand complex of the type [Cu(pn)(mal)]. This complex has an IR spectrum identical to that of the complex prepared by Shakir *et al.* [1]. The complex does not have the properties of a cyclic amide derivative. Rybka and Margerum [3] have shown that the tetraamide ligand *cyclo*-β-alanyglycyl-β-alanyglycyl (3 = L) reacts as a slurry with $Cu(OH)_2$ in 0.1 mol dm^{-3} sodium hydroxide in 10–15 min to give the com-



(3) $[CuLH_{-4}]^{2-}$

Scheme 3.

plex $[CuLH_{-4}]^{2-}$, in which four amide groups are deprotonated, Scheme 3.

The visible spectrum of $[CuLH_{-4}]^{2-}$ is characterized by a single band at 488 nm ($\varepsilon = 54$ dm^3 mol^{-1} cm^{-1}). The position and intensity of this band is independent of pH from pH 8.2 to 14.0, indicating that all four amide groups are deprotonated at pH 8.2 and that the complex is fully formed. The room-temperature ESR spectrum supports this structure. The number of lines due to nitrogen hyperfine coupling shows that there are four equivalent nitrogen donors in plane.

The position of the copper(II) *d–d* transition in complexes of this type can be estimated by the rules developed by Billo [9]. The *d–d* band for a copper(II) complex with four deprotonated amide donors is predicted to occur at *ca* 520 nm and this value is close to that observed in the copper complex of *N*-formyltriglycine. The lower absorption maximum of 488 nm observed with (4) has been attributed to the presence of the macrocyclic ligand, which leads to a somewhat stronger ligand field. Thus, the available spectroscopic data indicates that the copper(II) complex of a macrocyclic tetraamide ligand should give rise to a *d–d* band in the region of 500 nm, due to the strong ligand field exerted by the depronated amide nitrogen donors. The copper(II) complex prepared by Shakir's procedure gives a band in basic solution at *ca* 620 nm and thus a macrocyclic tetraamide is not formed under the conditions described.

Analytical and chromatographic results also indicate that a macrocyclic tetraamide is not produced in the reaction and only simple complexes of the type $[Cu(pn)_2][Cu(mal)_2]$ or mixed-ligand complexes [Cu(pn)(mal)] are formed by the procedure described. Experiments using other metal ions such as zinc(II) and nickel(II) gave similar results and we conclude that macrocyclic tetraamides cannot be prepared by the procedure described by Shakir *et al.* [1]. These conclusions are confirmed by the crystal structure described below.

Crystal structure of $[Cu(mal)(pn)Cl_2]^{2-}pnH_2^{2+}$

The crystal structure of the complex and the atomic numbering scheme is shown in Fig. 1. Selected bond lengths and angles are summarized in Table 1. The $[Cu(mal)(pn)Cl_2]^{2-}$ anion is six-coordinate with an $N_2O_2Cl_2$ donor set. The anion lies on a mirror plane passing through Cu(1), Cl(1), Cl(2), C(4) and C(6). The copper(II) is coordinated by the two nitrogen donors of the donor set. The copper(II) is coordinated by the two nitrogen donors of 1,3-diaminopropane [Cu—N = 1.993(4) Å] and the two carboxylate donors of the malonato ligand [Cu—O = 1.966(3) Å]. The fifth and sixth coordination sites about the tetragonal copper are occupied by chloride ions, Cu—Cl(1) 2.862(2) and Cu—Cl(2) 3.042(2) Å. The 1,3-diaminopropane and the malonate form six-membered chelate rings which have different conformations. The diamine ring has a chair conformation and the malonate ring a boat conformation. A similar arrangement has been observed in the complex [Cu(pn)(mal)] [10]. The Cu—O bond distances in a range of malonate complexes are summarized in Table 2. These values fall in the range 1.909–1.994 Å and are dependent on the nature of the other ligand in the mixed-ligand complex. The counter cation in the complex is pnH_2^{2+}, which shows no unusual features.

The crystallographic results confirm that a tetraamide ligand is not produced in these reactions and that only mixed-ligand complexes are formed.

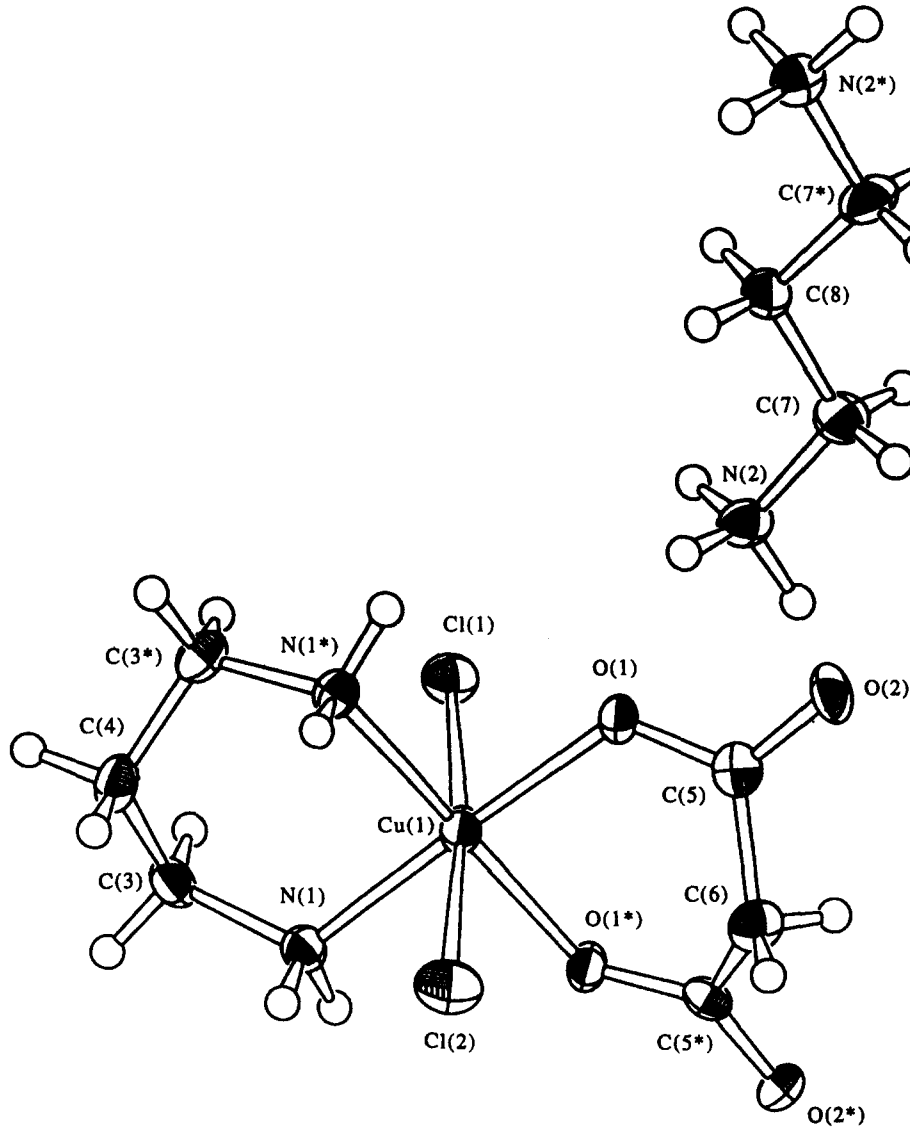


Fig. 1. ORTEP view of the crystal structure of $[Cu(pn)(mal)Cl_2][pnH_2]$ with the atomic numbering scheme.

Table 1. Molecular geometry dimensions (distances in Å, angles in °)

Cu(1)—Cl(1)	2.862(2)	N(1)—C(3)	1.475(6)
Cu(1)—Cl(2)	3.042(2)	N(2)—C(7)	1.483(6)
Cu(1)—O(1)	1.966(3)	C(3)—C(4)	1.509(7)
Cu(1)—N(1)	1.993(4)	C(5)—C(6)	1.509(6)
O(1)—C(5)	1.281(6)	C(7)—C(8)	1.500(6)
O(2)—C(5)	1.237(6)		

Cl(1)—Cu(1)—Cl(2)	175.47(7)	Cu(1)—O(1)—C(5)	124.9(4)
Cl(1)—Cu(1)—O(1)	90.0(1)	Cu(1)—N(1)—C(3)	118.8(3)
Cl(1)—Cu(1)—N(1)	93.1(1)	N(1)—C(3)—C(4)	111.1(5)
Cl(2)—Cu(1)—O(1)	93.2(1)	C(3)—C(4)—C(3)	114.7(6)
Cl(2)—Cu(1)—N(1)	83.8(1)	O(1)—C(5)—O(2)	121.6(5)
O(1)—Cu(1)—O(1)	89.8(2)	O(1)—C(5)—C(6)	117.7(5)
O(1)—Cu(1)—N(1)	176.7(2)	O(2)—C(5)—C(6)	120.7(5)
O(1)—Cu(1)—N(1)	89.0(1)	C(5)—C(6)—C(5)	116.5(6)
O(1)—Cu(1)—N(1)	176.7(2)	N(2)—C(7)—C(8)	112.4(4)
N(1)—Cu(1)—N(1)	92.0(2)	C(7)—C(8)—C(7)	109.9(6)

Table 2. Cu—O distances (Å) in copper(II) malonate complexes

$[Cu^{II}(NH_2CH_2CH_2NHMe)(mal)] \cdot H_2O$	1.956(6)	1.940(6)	Ref. 11
$[Cu^{II}(NH_2CH_2CH_2CH_2NH_2)(mal)]$	1.994(7)	1.988(7)	Ref. 12
$[Cu^{II}(Me_2C(NH_2)CH_2NHPr^i)(mal)(H_2O)] \cdot H_2O$	1.952(6)	1.924(6)	Ref. 13
$[Cu^{II}(EtNHCH_2CH_2NHEt)(mal)(H_2O)] \cdot H_2O$	1.950(3)	1.950(4)	Ref. 14
$[Cu^{II}(phen)(mal)(H_2O)] \cdot 1.5H_2O$	1.909(3)	1.919(3)	Ref. 15
$[Cu^{II}(mal)(pn)Cl_2]^{2-}pnH_2^{2+}$	1.966(3)	1.966(3)	This work

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