Journal of Inorganic Biochemistry 194 (2019) 26–33

Contents lists available at ScienceDirect

Journal of Inorganic Biochemistry

journal homepage: www.elsevier.com/locate/jinorgbio

Complex formation equilibria of polyamine ligands with copper(II) and zinc(II)

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ARTICLE INFO

Keywords:
Potentiometry
UV–visible spectrophotometry
Protonation constant
Complex formation constant
Crystal structures

ABSTRACT

A comprehensive study of the protonation equilibria of a series of polyamine ligands along with their complex formation equilibria with Cu^{2+} and Zn^{2+} is reported in this work. The primary aim of this study has been the achievement of homogeneous thermodynamic data on these ligands, in order to evaluate their influence on the homeostatic equilibria of essential metal ions (Cu^{2+} and Zn^{2+}) in biological fluids. These polyamines are largely used as linkers in the building of chelating agents for iron overload. Potentiometric and spectrophotometric techniques were used for the characterization of protonation and complex formation constants. In addition, the characterization of the formed complexes is discussed together with selected solid-state crystal structures, remarking the influence of the length of the chain and of the linear or tetradentate tripod nature of the polyamine ligands on the stability of the complexes.

1. Introduction

For a long time now, our research group has been involved in the study of chelating ligands for the treatment of the toxic effects of iron overload [1–4]. The stability of the complexes with iron and the selectivity are among the major requisites of an iron chelator. The stability is the true necessary property so that iron, bonded to endogenous ligands in the living organism, could be completely transformed into excretable species. In addition to the numerical value of the stability constants, other factors, such as the stoichiometry of the complex and proton competition, contribute to the binding efficiency of the ligand. Among the methods used for quantifying the effectiveness of a ligand, reviewed by Bazzicalupi et al. [5], we utilize the pM parameter [6], defined as -log[M_f] at [M_T] = 1 μM and [L_T] = 10 μM at pH 7.4, where [M_f] is the concentration of free metal ion and [M_T] and [L_T] are the total concentrations of metal and ligand respectively. The higher the stability of the formed complexes the less metal ion remains free in solution, determining a higher pM value. The stability requisites largely depend on the hard/soft nature of the metal ion, and of the coordinating groups [7–9].

Moreover, a chelating agent must possess high enough selectivity to remove iron without any interference by the essential metal ions in biological fluids. Selectivity depends on the thermodynamic stability of the complexes formed with iron in comparison with the stability of those formed with the essential metal ions. Even if the ligand is selective for iron, a completely different aspect has to be remarked [10]. When the ligand exceeds the stoichiometric amount required to chelate iron, the amount of chelated essential metal ions can reach non-negligible values, according to the essential metal ion/ligand concentration ratios. This leads to a potentially dangerous effect of chelation therapy, i.e. the depletion of essential metal ions.

In this context, we synthesized, starting from the natural iron chelator kojic acid (KA) (Fig. 1 A), a number of chelating agents containing two KA units joined through variable linkers, always attached in position 6 (Fig. 1 B. As main features, these molecules have low toxicity and versatility for metal complex formation. All these ligands were fully structurally characterized both in solid state and in solution for their acid-base properties and complex formation abilities toward iron and aluminium metal ions [11], as well as toward the essential metal ions copper and zinc to give evidence of any disturbance of their homeostatic equilibria [12,13]. Recently, we proposed a different approach in the synthesis of KA derivatives, joining the KA units through simple polyamines by reacting them with the OH groups in position 2 (Fig. 1 C) [14]. Similar complexes were also synthesized joining two salicylamide

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https://doi.org/10.1016/j.jinorgbio.2019.02.006
Received 15 September 2018; Received in revised form 8 February 2019; Accepted 9 February 2019
Available online 18 February 2019
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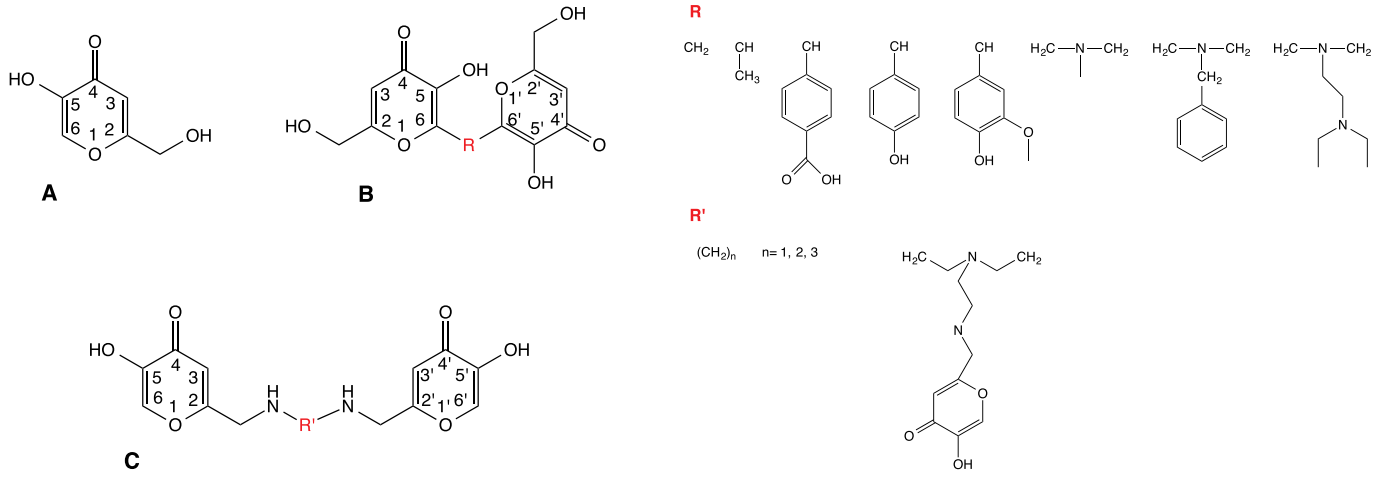


Fig. 1. Chemical structure of A) kojic acid (KA), B) KA derivatives joined in position 6, and C) KA derivatives joined in position 2.

groups [15].

These ligands form stable complexes with the trivalent metal ions, through the oxygen donor atoms, while the linker nitrogen atoms are strongly involved in the coordination process of divalent metal ions. In order to assess the contribution of the nitrogen atoms, we planned a study of protonation and metal complexation of the series of polyamines reported in Table 1, most of which constitute the linkers joining the KA units, to have reliable information on the coordination processes of these polyamines. In fact, even though these amines have been largely considered in literature, the data reported are mostly related to single cases, and in a large part the protonation constants are not reported together with the complex formation constants. The speciation studies necessary to give a clear picture of the behavior of a chelator in a biological fluid requires instead a homogeneous set of protonation and complex stability constants. Furthermore, the comparison of the effects of different polyamines as linkers requires a systematic study on a set of polyamines of variable length, substituents and linear or tripodal nature. In this work, we will present the study of the acid-base properties of these amines, the Cu^{2+} and Zn^{2+} complexation and the speciation model in aqueous solution in NaCl ionic medium (I = 0.1 M). Actually, this salt constitutes the major inorganic constituent of natural and biological fluids, specifically of blood plasma. This investigation involved two complementary analytical techniques that is UV–Vis spectrophotometry and potentiometry. Moreover, the obtained thermodynamic results are discussed considering some relevant structural literature data of the copper and zinc complexes.

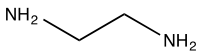
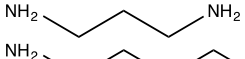
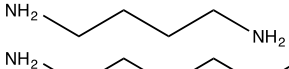
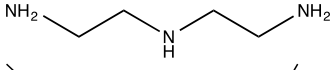
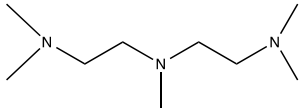
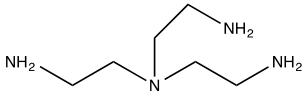
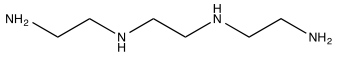
A further aspect of this study has to be considered: the use of chelating agents unable to satisfy all coordination sites of metal atoms has broad chemical and/or biological interest for the synthesis of polynuclear networks or to obtain mixed-ligand metal complexes. Both kinds of compounds could feature suitable structural, electronic and magnetic properties. In mixed-ligand complexes, there are structural evidences that the incoming of secondary ligands can modulate the conformation of the primary (chelating) ligand [16]. These studies offer many expanding possibilities, as the use of other metal ions or chelating agents [17,18].

2. Experimental

2.1. Reagents

Ethylenediamine dihydrochloride (en) (98%), 1,3-diaminopropane dihydrochloride (dpa) (98%), 1,4-diaminobutane dihydrochloride (dba) (≥ 99.0%), diethylenetriamine (dien) (99%), pentamethyldiethylenetriamine (pmdt) (99%), triethylenetetramine dihydrochloride (trien) (98%), NaOH, NaCl and $CuCl_2$ were purchased from Aldrich, HCl from Fluka, ZnO from Carlo Erba and tris(2-aminoethyl) amine (tren) (96%) was an Acros product. The purity of all the reagents

Table 1
IUPAC name, acronym and structural formula of the seven amines object of this study.

IUPAC name	Acronym	Formula	MW	Structure
1,2-Diaminoethane or ethylenediamine	en	$C_2H_8N_2$	60.10	
1,3-Diaminopropane	dpa	$C_3H_{10}N_2$	74.13	
1,4-Diaminobutane	dba	$C_4H_{12}N_2$	88.15	
1,4,7-Triazaheptane	dien	$C_4H_{13}N_3$	103.17	
N,N,N′,N′,N″,N″-Pentamethyldiethylentriamine	pmdt	$C_9H_{23}N_3$	173.30	
2,2′,2″-Triaminotriethylamine	tren	$C_6H_{18}N_4$	146.24	
1,4,7,10-Tetraazadecane	trien	$C_6H_{18}N_4$	146.24	

was checked by NMR. All the reagents were used without further purification. A previously described method for preparing carbonate-free NaOH 0.1 M solution was used [19].

Dien and pmdt solutions were prepared by adding three equivalents of HCl, tren solution by adding four equivalents of HCl, and trien dihydrochloride solution was acidified with two equivalents of HCl. Cu^{2+} solution was prepared by dissolving the required amount of $CuCl_2$ and adding HCl in a stoichiometric amount to prevent copper hydrolysis. Zn^{2+} solution was prepared by dissolving the required amount of ZnO in a water solution to which three stoichiometric amounts of HCl were added. The solutions of Cu^{2+} and Zn^{2+} were standardized by volumetric EDTA titrations.

2.2. Spectrophotometric-potentiometric measurements

Protonation and complex-formation equilibrium studies were carried out using the same conditions described in a previous paper [20]. Solutions (20 mL at working ligand concentration 1.5×10^{-3} M) were titrated with 0.1 M NaOH at 25.0 °C, and 0.1 M NaCl ionic strength. The electrode was daily calibrated for hydrogen ion concentration by titrating HCl with NaOH in the above experimental conditions and the results were analyzed with Gran procedure [21]. Complex formation studies were conducted at constant ligand concentration, 1.5×10^{-3} M, and at variable metal/ligand molar ratios (1:1, 1:2 and 1:3). All the measurements were conducted in triplicate. The reversibility of the complex formation with pH was checked by a back titration with HCl 0.1 M. Combined potentiometric-spectrophotometric measurements were performed for the study of Cu^{2+} complex formation equilibria, while only potentiometric data were collected for the study of Zn^{2+} complexes. Spectra of Cu^{2+} complexes were recorded in the 200–400 nm spectral range using a 0.2 cm path length optical probe (Fig. 2S).

3. Results and discussion

3.1. Protonation equilibria of the pure ligands

Protonation equilibria of the pure ligands were studied by potentiometry at 25 °C and 0.1 M NaCl ionic strength. The titration curves (log $[H^+]$ vs $[OH^-]/[L]$) for the seven ligands are reported in Fig. 2, and some representative cases in Fig. 1S.

The obtained data were processed with Hyperquad program [22] and the results are reported in Table 2. The mean values of the protonation constants found in the IUPAC Database [23] at the same temperature and ionic strength are reported for comparison in Table 1S [24]; the outliers exceeding two standard deviations were not taken into account. As a general remark, the results in Table 2 well agree with the mean literature values, in the limits of both experimental errors and scattering of literature values. Log K_3 of pmdt shows a sensible difference. It has to be remarked that this value, as well as the log K_4 of tren, have to be considered with caution, since the potentiometric titrations started from pH 3. At so acidic pH values, in which potentiometry is not applicable, the lack of spectral variations connected to these protonation steps prevented the use of UV–vis spectrophotometry.

The speciation plots related to the protonation of the seven ligands are reported in Fig. 3.

Both protonation constants log K_1 and log K_2 of the three linear diamines en, dpa and dba increase with the length of the chain (Table 2 and Fig. 4). When three and four CH_2 groups separate the nitrogen atoms, dpa and dba respectively, the values of log K_1 are quite similar to those of the linear monoamines, methylamine, ethylamine, propyl amine and butyl amine (10.51, 10.43, 10.45 and 10.46 according to Shoukry [25,26] and 10.64, 10.66, 10.62 and 10.66, according to Hancock [27]), i.e. the second NH_2 has no influence. However, in en, where two CH_2 separate the two amino groups, the second NH_2 induces a decrease of about 0.8 units in log K_1.

The protonation constants of the second amino group differ more than theoretically expected for two equivalent sites, log K_1 - log K_2 = log 4 = 0.602, for which the ratio of the stepwise protonation constants is 4, governed only by the statistical laws. In fact, the high inductive effect of NH_3^+ on the second protonation constant induces a decrease of log K_2 of about 1 unit in dba (four CH_2 groups), about 2 units in dpa (three CH_2 groups), and about 3 units in en (two CH_2 groups).

Based on the trend of protonation constants of the linear diamines, it is possible to rationalize the log K values of the remaining ligands. In dien, the first external NH_2 group is protonated with log K_1 9.84, equal to that of en in the error limits, i.e. the influence of the –NH- group is similar to that of NH_2 in en at the same distance, being the second NH_2 ineffective for the distance. The second protonation with log K_2 9.02 takes place on the remaining NH_2 group. This decrease depends for about 73% on statistical effects and for the remaining 27% on the charge of first NH_3^+ group. The log K_3 of the third protonation, on the –NH- group, experiences the synergic effect of both the two NH_3^+ groups, leading to log K_3 4.30. The methylated pmdt ligand presents an analogous trend, though the values are further decreased by the inductive effect of the CH_3 groups (log K_1 = 9.27, log K_2 = 8.42, log K_3 = 2.67).

Tren presents a slight increase of the first two protonation constants with respect to the analogous ones of dien due to the effect of the ternary nitrogen atom, different from that of –NH- group. The two charged NH_3^+ groups affect the third protonation on the remaining NH_2 group, leading to a log K_3 8.41. The fourth protonation on the ternary nitrogen group drops to log K_4 2.16 due to the symmetrical proximity of three positively charged nitrogen atoms.

Statistical effects related to the protonation of two equivalent groups were evoked to account for the difference 0.68 between log K_1 and log K_2 in trien [28]. This outcome is indicative of the fact that the positive charge due to the first protonation does not modify the basicity of the nitrogen atom implied in the second protonation, suggesting that the two involved nitrogen atoms are far apart, and supporting the hypothesis that the first two protonations take place on the external nitrogen atoms. Consequently, the two further protonations (log K_3 and log K_4) are related to the inner nitrogen atoms, and the repulsion of vicinal protonated nitrogen atoms explains the further decreases (log K_3 = 6.68 and log K_4 = 3.28) [28].

3.2. Complex formation equilibria with copper and zinc

The complex formation equilibria of the seven polyamines with Cu^{2+} were studied by a joined potentiometric-spectrophotometric procedure [20], while those with Zn^{2+} were studied only potentiometrically. The potentiometric titration curves of the amines in presence of the two metal ions are shown in Fig. 2, and some representative cases in Fig. 1S. The potentiometric data, analyzed with the Hyperquad program [22], allowed obtaining the complexation model and the related complex formation constants reported in Table 3.

Table 3 also reports the pCu and pZn values in order to compare all the ligands that differ in the complexation model, in denticity and in the basicity of coordinating groups. The pM values are used to express the strength of the interaction between the ligand and the metal ions. Selected literature values from the IUPAC Database [23] are reported in Table 2S for comparison [29–62]. The speciation plots of copper and zinc complexes, calculated on the basis of stability constants in Tables 2 and 3, are reported in Fig. 5 at 1:3 metal-ligand ratio, and ligand concentration 3×10^{-3} M.

3.2.1. Copper complexes

The appearance in the UV–visible spectra of two bands accompanies the formation of copper-ligand complexes. The first band is found in the UV region, in the range 250–290 nm with an absorptivity between 3000 and 4500 $M^{-1}\,cm^{-1}$, used in spectrophotometric determination

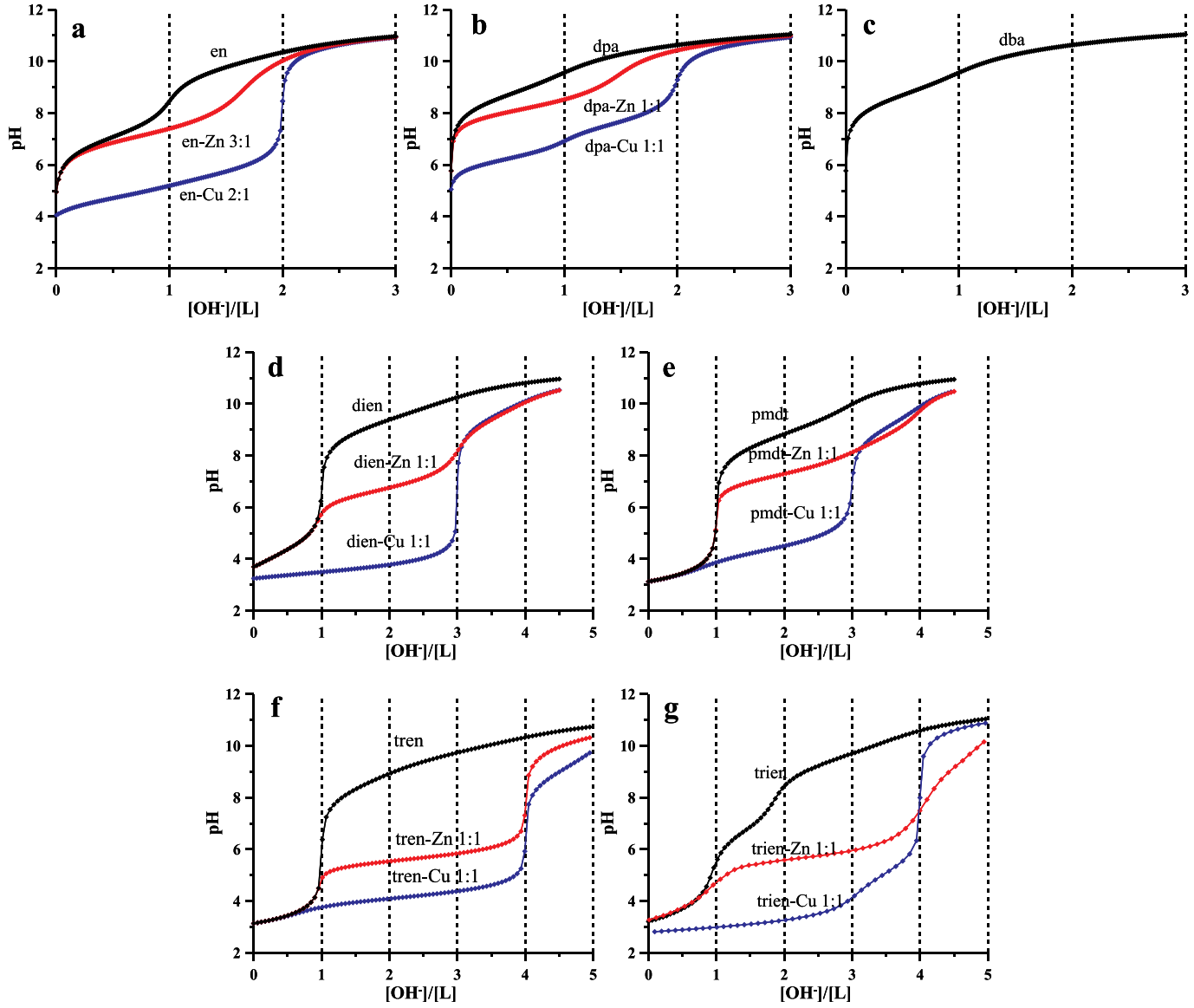


Fig. 2. Potentiometric titrations of the pure ligands (black), of the Cu-Ligand systems (blue) and of the Zn-Ligand systems (red). a) en, b) dpa, c) dba, d dien, e) pmdt, f) tren, g) trien. The ligand concentration was always 0.0015 M, and the used ligand metal ratios are reported on the figures. In the case of dba, no metal complex was formed, and precipitation of metal hydroxides occurred.

Table 2
Protonation constants (log K) of the seven ligands at 25 °C and 0.1 M NaCl ionic strength.

Compound	log K_1	log K_2	log K_3	log K_4
en	9.81(4)	7.08(3)	–	–
dpa	10.61(3)	8.72(2)	–	–
dba	10.85(4)	9.70(2)	–	–
dien	9.84(1)	9.02(3)	4.30(4)	–
pmdt	9.27(3)	8.42(2)	2.67(1)	–
tren	10.08(2)	9.55(1)	8.41(2)	2.16(4)
trien	9.79(2)	9.11(3)	6.68(1)	3.28(3)

(Fig. 1S), and a second of a low intensity in the visible region, in the range 550–650 nm and an absorptivity between 60 and 80 M^{-1} cm^{-1}.

Starting from the simplest linear diamines, en forms with Cu^{2+} strong $[Cu(en)]^{2+}$ and $[Cu(en)_2]^{2+}$ complexes, characterized by a pCu value 9.9. At mM concentration, the formation of the first $[Cu(en)]^{2+}$ complex reaches its maximum at pH about 5, and the second complex $[Cu(en)_2]^{2+}$ is almost completely formed at pH = 7 (Fig. 5). Some representative solid state structures of the 1:2 Cu^{2+}-en complexes are reported in Table 3S. The literature availability of the solid-state structures of the predominant found complexes will support our solution findings. It will allow us to discuss the principal structural features of the complexes carrying out some confident useful observations.

For example, in the crystal of the $[Cu(en)_2H_2O]^{2+}$ cation (CCDC Ref. Code RUZROV), copper forms two five-membered chelating rings, adopting a square pyramidal geometry with four N coordinating atoms from the two en ligands (Cu-N: 1.979–2.013 Å) and one O atom (Cu-O: 2.396 Å) from a distal water molecule (Table 3S 1) [63].

Cu^{2+} forms with dpa complexes similar to those reported with en, but of lower stability. $[Cu(dpa)]^{2+}$ is formed at pH just before 7 and $[Cu(dpa)_2]^{2+}$ is completely formed at pH = 9 (Fig. 5). The pCu value with dpa is 6.4, i.e. 3.5 units lower than that with en. This depends both on the lower complex formation constants of dpa with copper (Table 3) that accounts for about 40% and on the much higher protonation constants (Table 2) that favor the proton competition toward the basic nitrogen atoms for about 60%. In the solid state, copper forms with dpa a 1:2 $[Cu(dap)_2(H_2O)]^{2+}$ complex cation with two six-membered

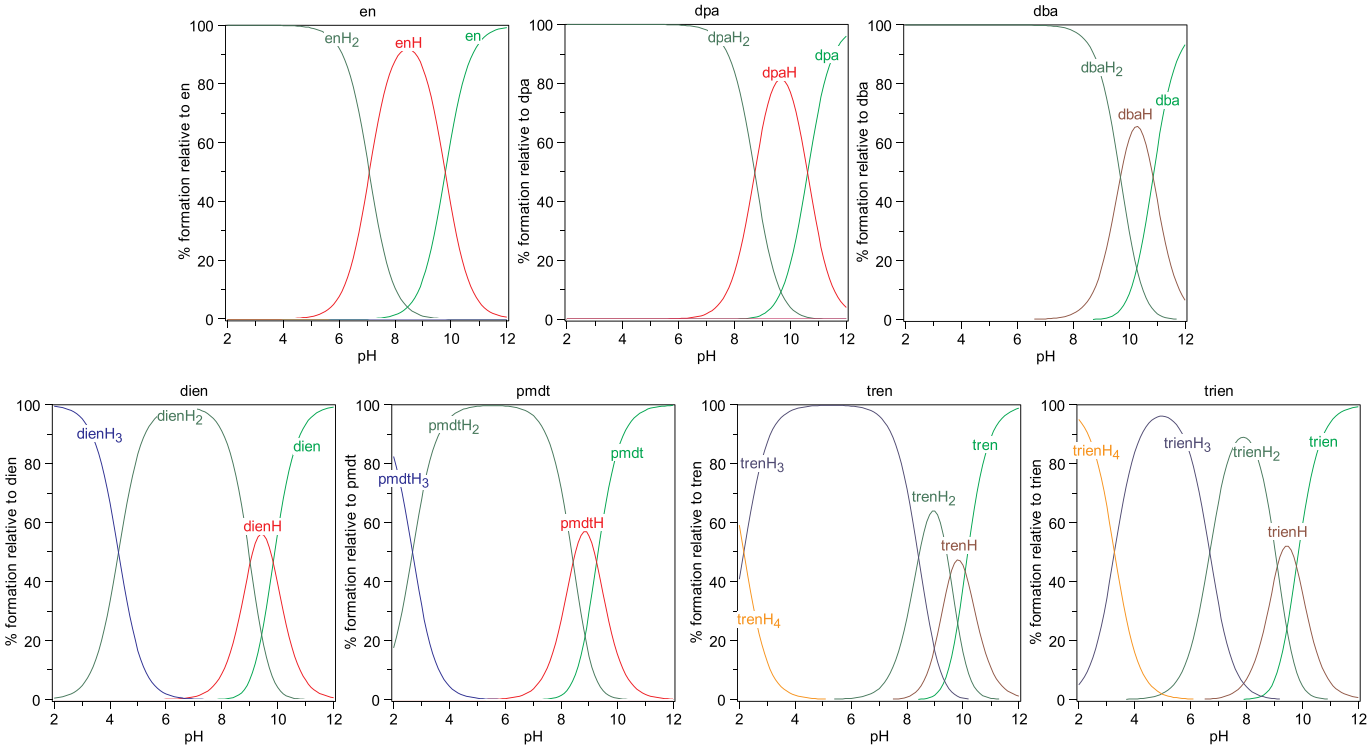


Fig. 3. Speciation plots relative to the protonation of the pure ligands.

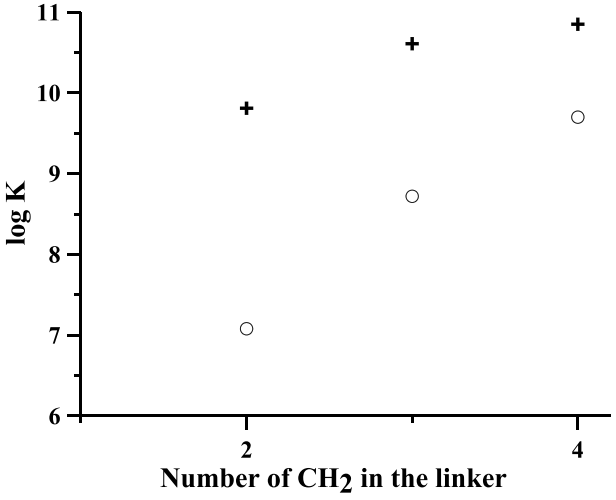


Fig. 4. Trend of protonation constants (log K_1 (+), log K_2 (o)) of the three linear diamines vs the number of CH_2 groups in the connecting chain.

chelating rings (CCDC Ref. Code IWEVEM) (Table 3S 3). Despite this fact, this cation resembles that of the previously reported Cu-en complex since it is a five coordinated square pyramid with four N atoms from two dpa ligands [Cu-N: 2.002–2.026 A] and one oxygen from a coordinated water molecule [Cu-O: 2.593 A]. The Cu—O weak interaction is remarked by the evident Jahn-Teller distortion of the Cu^{2+} cation that leads to the elongation of the Cu—O distance [64].

The length of the chain in dba prevents the formation of stable seven-membered chelating ring complexes with copper ions. In this context, the work of Gasowska et al. [65], which reports on copper-dba complexes, must be taken with caution, being the appearance of the titration curve only determined by the formation of copper hydroxides. Our potentiometric and spectrophotometric measurements on the dba—Cu^{2+} system did not give evidence of complex formation.

Table 3
Complex formation (log β) constants with Cu^{2+} (upper table) and Zn^{2+} (lower table), determined at 25 °C and 0.1 M ionic strength[a].

Model	en	dpa	dien	pmdt	tren	trien[b]
Cu^{2+}						
MLH	–	–	–	–	–	23.4(1)
ML	10.48(2)	9.80(4)	16.15(4)	12.04(2)	18.83(1)	20.3(1)
MLH_{-1}	–	–	6.47(6)	2.94(3)	9.80(3)	–
ML_2	19.43(3)	17.20(5)	22.23(8)	–	–	–
pCu	**9.9**	**6.4**	**12.7**	**10.1**	**13.9**	**17.1**
Zn^{2+}						
MLH	–	–	–	–	–	18.06(6)
ML	5.75(2)	6.00(5)	8.90(2)	6.35(5)	14.40(2)	12.24(3)
MLH_{-1}	–	–	−0.51(3)	−2.35(6)	4.09(3)	2.90(6)
ML_2	10.66(3)	–	13.85(6)	–	–	–
ML_3	13.61(3)	–	–	–	–	–
pZn	**6.0**	**6.0**	**6.1**	**6.0**	**9.5**	**9.2**

[a] No complex formed between Cu^{2+} and Zn^{2+}, and dba.
[b] Data from reference [28].

Recently, in an attempt to prepare solid-state complexes between a salicylamide derivative containing dba in the linker and Cu^{2+}, we obtained a crystal of the "complex" between copper and dba [15], which structure is shown in Fig. 6. An alternating organic/inorganic layered structure consisting of discrete square planar $[CuCl_4]^{2-}$ and $[C_4H_{14}N_2]^{2+}$ units, is contacted through a combination of electrostatic and N-H···Cl hydrogen bonds (2.36 Å, 159.8°). There is close packing within the inorganic layers that brings adjacent Cu-Cl-Cu distances just below Van der Waals distance, and the copper center adopts a pseudo octahedral geometry with a Jahn-Teller distortion, similar to many Cu^{2+} compounds.

Going to the more complex ligands, dien forms with Cu^{2+} a 1:1 complex CuL, completely formed at pH > 4, which further stabilizes at pH > 8 giving a CuL_2 complex and a hydroxo complex CuLOH. A pCu 12.7 is reached with this ligand, mainly due to the CuL complex. In the solid-state the [Cu Br dien]Br crystal was studied. The geometry around

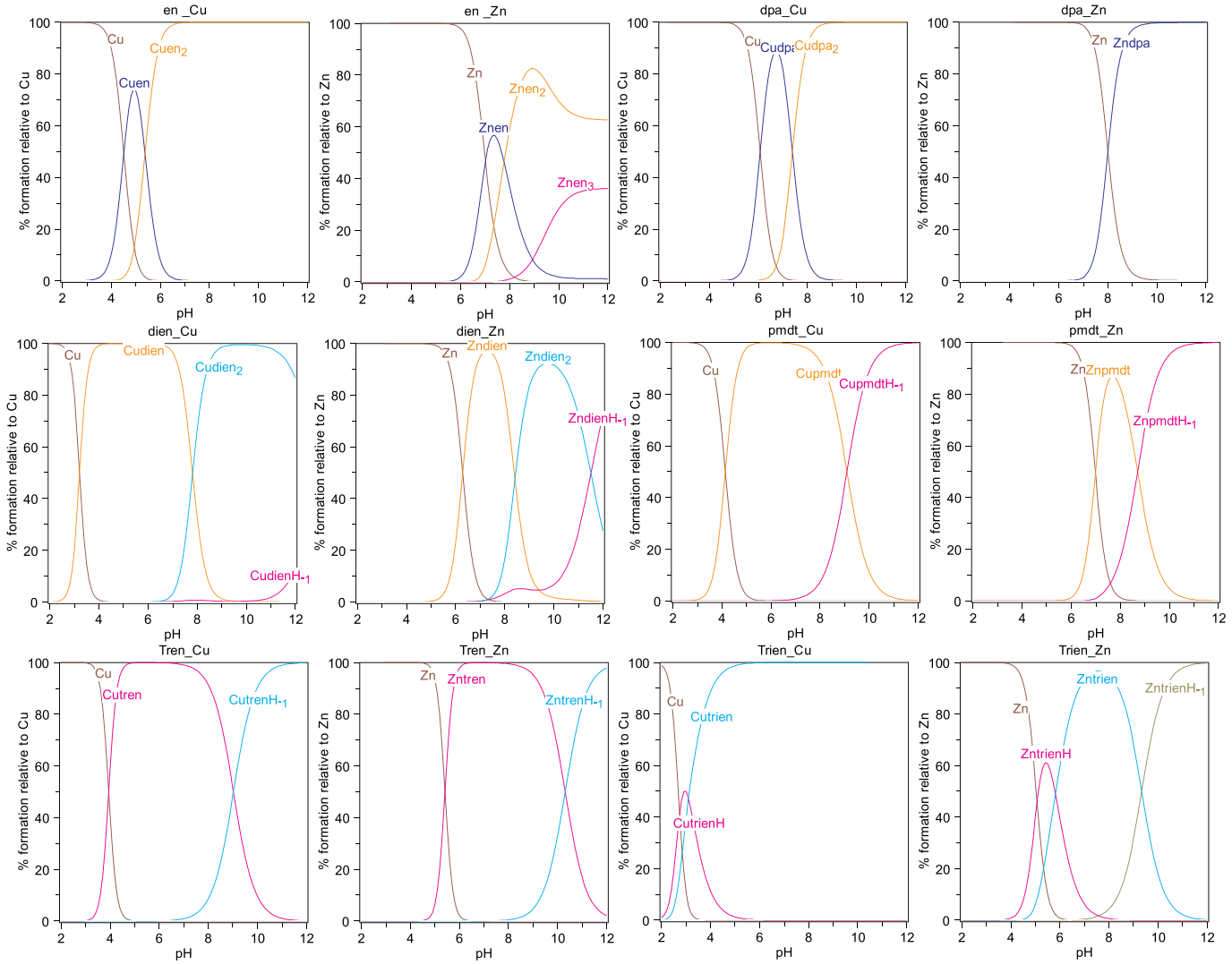


Fig. 5. Speciation plots for copper and zinc complex formation. These plots were calculated using the protonation and stability constants in Tables 2–3. Ligand concentration 3×10^{-3} M and a 1:3 metal: L ratios were used for metal complex formation calculations.

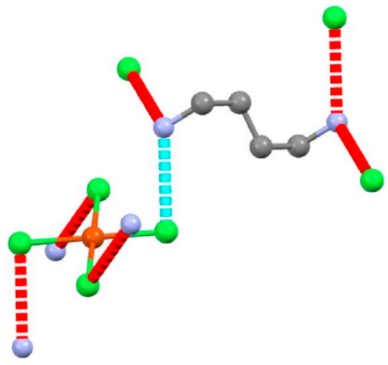


Fig. 6. View of the interaction between the $[CuCl_4]^{2-}$ and dba units within the crystal structure of the complex (Cu-orange; Cl-green; N- blue; C-grey). H-bonds depicted as cyan dotted lines while intermolecular contacts depicted as red dotted lines.

the Cu atom is best described as square planar with Br and three N donor atoms in the plane, forming two adjacent five-membered rings (CCDC Ref. Code TAGMIX [66]). The distances N-Cu^{2+} and the angles N-Cu-N are similar to those of en. The greater stability of the complexes depends on entropic factors related to the proximity of chelating groups. Recently, it was reported the X-ray crystallographic characterization of $[CuL_2]I_2$ (Table 3S 5, CCDC Ref. Code VAMTEL), which reveals a distorted octahedral Cu^{2+} center coordinated by six amine groups of two dien ligands with Cu—N distances in the range 2.009 Å to 2.454 Å. These distances are longer than the comparable Cu—N bond distances in the mono-ligated complexes (1.986 Å to 2.034 Å) [67,68] (Table 3S 5). In pmdt, structurally similar to dien, the presence of the five CH_3 groups alters both the protonation constants (the first two 0.5 units lower than those of dien, and the third 1.5 unit) and more drastically the complex formation constants. The formation of CuL_2 complexes is hindered by steric constraints. The CuL complex is stable in the pH range 5–8, then transforms in the CuLOH hydroxo complex. The pCu drops to 10.1, respect to the value 12.7 with dien. In the solid state, a CuL complex was examined (CCDC Ref. Code ETAMCW [69]). The copper atom is coordinated by the three nitrogen atoms of the ligand, a chloride ion and one oxygen atom from a perchlorate group. The coordination is approximately square pyramidal, with the copper atom displaced 0.168 Å from the plane defined by Cl and the three N atoms as the four atoms describing the base of the square pyramid. The apex of the pyramid is occupied by one O atom of the perchlorate group. The distances are [Cu-N: 2.038–2.066 A], [Cu-O: 2.681 A], [Cu-Cl: 2.226 A]. Further structures are reported with copper coordinated by two chloride ions (CCDC Ref. Code FIHWOJ [70]), (CCDC Ref. Code

TAWFOM [71]) or two bromide ions (CCDC Ref. Code OCULUT [72]) presenting fundamentally analogous results.

In tren, a stable CuL complex is entirely formed in the pH window 5–8, which transforms at pH > 8 in the hydroxo CuLOH complex. The additional NH_2 group, with respect to dien, determines a pCu 13.9, with an increase of 1.2 units. In the solid-state structure presented by Laskowski et al. (Table 3S 9), a five membered complex is formed, with copper coordinated by the three NH_2 groups, and the apical nitrogen atom while a chlorine atom occupies the fifth position. (CCDC Ref. Code CTRENB [73]).

The last considered ligand trien forms, starting at pH < 3, a copper complex CuLH coordinated by three nitrogen atoms, which reaches its maximum concentration at pH 3.2, and then transforms in the tetra-coordinated CuL complex completely formed at pH > 5, reaching the extremely high pCu 17.1. This depends on the perfect square planar complex CuL, whose structure was determined in the solid state (CCDC Ref. Code PAJSEY [74]) (Table 3S 11).

3.2.2. Zinc complexes

Similarly to copper, also Zn^{2+} forms in solution $[Zn(en)]^{2+}$ and $[Zn(en)_2]^{2+}$ complexes, of lower stability than those of copper, and also a $[Zn(en)_3]^{2+}$complex. $[Zn(en)]^{2+}$ complex reaches its maximum at pH about 7, $[Zn(en)_2]^{2+}$at pH 9, and at pH > 10 $[Zn(en)_2]^{2+}$ and $[Zn(en)_3]^{2+}$complexes coexist in a about 60/40 ratio. The pZn (6.01) is extremely low, about four units lower than that of copper (9.9). $[Zn(en)_3]^{2+}$ complexes were also obtained and studied in the solid-state (Table 3S 2). The complex reported with CCDC Ref. Code AXTAF contains a discrete $[Zn(en)_3]^{2+}$ cation and iodide anions: the Zn^{2+} ion, six-coordinated by three en molecules, adopts an octahedral geometry, with the length of zinc-nitrogen bonds varying from 2.169 to 2.215 Å [75].

Dpa forms with Zn^{2+} only a 1:1 complex with a stability constant similar to that of the analogous complex with en; at any rate the proton competition determines the formation of this complex only at pH values > 7. The value of pZn is extremely low (6.01). No structure of dap complexes with zinc is reported in literature.

As described for copper complexes, the length of the chain in dba prevents the formation of stable seven ring complexes with zinc ions. No solid-state structure is available.

In the case of dien, Zn^{2+} forms complexes of similar stoichiometry of those formed by Cu^{2+}, but of lower stability, as remarked by the speciation plot in Fig. 5. The pZn is 6.1. In the solid state the structure of a $[Zn(dien)_2]^{2+}$ complex was presented by Lu et al. [76]. In this complex, Zn^{2+} ion is coordinated by two tridentate dien ligands to form octahedral complex cations, with Zn − N bond lengths (2.114–2.294 Å) (CCDC Ref. Code ZOJNOD).

Analogously to what observed with copper, the pmdt ligand does not form1:2 complexes. The $[Zn(pmdt)]^{2+}$ complex reaches its maximum formation at pH 8, and then transforms in the hydroxo complex $[Zn(pmdt)OH]^{+}$. Also in this case pZn is extremely low.

A $[Zn(pmdt)]^{2+}$ complex involving a tetrasulfide group was studied in the solid state, in which a high tension exists between the two sides of pmdt (Zn-N: 2.176–2.312 A, Zn-S: 2.355–2.439 A) (CCDC Ref. Code VAFMAQ [77]).

Zn^{2+} forms together with tren complexes of exceptional stability in solution. For instance, the $[Zn(tren)]^{2+}$ complex is already completely formed at pH 6, and is stable till pH 9, where it transforms into the hydroxo $[Zn(tren)OH]^{+}$ complex. The pZn to 9.5 (3.5 units higher than the corresponding value with dien) is decisively remarkable. These results in solution are supported and explained by the structural results. Tren forms with Zn^{2+} a complex similar to that observed with Cu^{2+} in which the zinc atom (CCDC Ref. Code AZZNPB) is penta-coordinated to one chlorine atom and four nitrogen atoms in a trigonal bipyramidal configuration [78]. The short length of the Zn-nitrogen bonds in this compound, lower than those of all the other zinc complexes, explains the high stability of this complex. It should be noted that Zn^{2+}, according to its $3d^{10}$ configuration, does not have any preferential coordination geometry, therefore it is the tetradentate tripodal polyamine tren which induces the stable trigonal bipyramidal configuration in this compound unlike the latter linear polyamines.

Trien behaves with Zn^{2+} in a similar way to that with Cu^{2+}, being the formation of complexes translated at higher pH values in the speciation plot (Fig. 5). A further hydroxo complex ZnLOH is formed at pH > 9. Also in this case high pZn values are reached but lower than that with tren.

The structure of a zinc complex characterized by an iodine atom in the 5th position was presented by Marongiu et al. (CCDC Ref. Code ZNETAM [79]). The coordination around the central zinc atom is square pyramidal with the zinc atom 0.71 Å above the plane of the four nitrogen atoms of the ligand molecule. The values of coordination bond lengths, Zn-N(prim) 2.13 Å, Zn-N(*sec*) 2.19 Å, Zn—I 2.59 Å fall all in the range expected for covalent Zn—N bonds. This square pyramidal coordination around the central zinc atom with the zinc atom above the plane of the four nitrogen atoms does not allow reaching the maximum thermodynamic stability, as in the case of tren.

4. Concluding remarks

The results presented herein involve the study of complex formation between a set of polyamine ligands via solution techniques and solid state, allowing some conclusive remark.

- In the three linear diamines the strength of the complexes decreases with the length of the chain, passing from en to dpa, and falls down with dba, which lacks of any capacity of forming copper and zinc complexes.
- The increase of the number of nitrogen atoms spaced by two methylene groups (en, dien, trien) gives a progressive increase of the stability constants.
- The ratio between copper and zinc complex formation constants is almost constant (about 1.7) for all the ligands, as can be inferred by the low dispersion of points around the regression line log β_{Zn} vs log β_{Cu} reported in Fig. 7.
- In this regression line, the point relative to the only non-linear studied polyamine, tren, is a remarkable outlier. Even if tren forms a strong complex with copper (pCu 13.9), this ligand forms a complex of unique strength with zinc, and the ratio log β_{1Cu}/log β_{1Zn} drops to 1.3. This is due to the arrangement of tren that allows zinc to reach a particularly stable trigonal bipyramidal configuration, pointed out by the small distances between the zinc ion and the coordinating nitrogen atoms from the NH_2 groups.

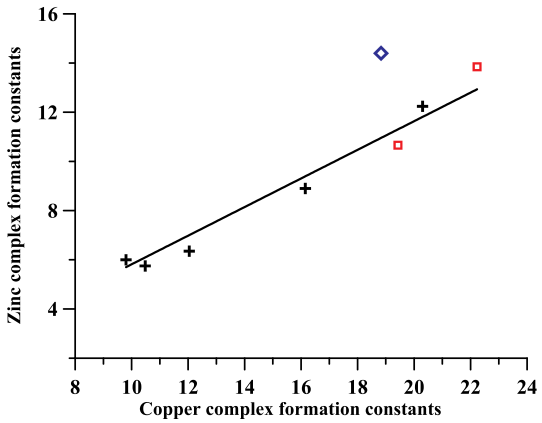


Fig. 7. Log β relative to the formation of zinc complexes vs log β of copper complexes. Log β_1 are reported with the symbol (+), log β_2 for en and dien with (□) and log β_1 for tren with (◇). Tren was excluded in the calculation of the regression line through the origin.

- The results here presented have been useful to explain the behaviour of the ligands presented in Fig. 1 toward Cu^{2+} and Zn^{2+}. In particular, they support and explain the extremely high value of pZn of the ligand with three KA units connected by tren [80].

Acknowledgements

VMN acknowledges the financial support by MIUR-PRIN 2015 - 2015MP34H3.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2019.02.006.

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