High Thermodynamic Stability and Extraordinary Kinetic Inertness of Copper(II) Complexes with 1,4,8,11-Tetraazacyclotetradecane-1,8-bis(methylphosphonic acid): Example of a Rare Isomerism between Kinetically Inert Penta- and Hexacoordinated Copper(II) Complexes

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Abstract: In an aqueous solution at room temperature, 1,4,8,11-tetraazacyclotetradecane-1,8-bis(methylphosphonic acid) (H_4L^1) and Cu^{II} form a pentacoordinated (pc) complex, pc-$[Cu(L^1)]^{2-}$, exhibiting conformation **I**[*] of the cyclam ring. At high temperature, the complex isomerises to a hexacoordinated isomer, *trans*-O,O-$[Cu(L^1)]^{2-}$, with a *trans*-**III**[*] conformation of the cyclam ring. In pc-$[Cu(L^1)]^{2-}$, four ring nitrogen atoms and one phosphonate oxygen atom are arranged around Cu^{II} in a structure that is half-way between a trigonal bipyramid and a tetragonal pyramid, with one phosphonic acid group uncoordinated. In the *trans*-O,O-$[Cu(L^1)]^{2-}$ isomer, the nitrogen atoms form a plane and the phosphonic acid groups are in a mutually *trans* configuration. A structurally very similar ligand, 4-methyl-1,4,8,11-tetraazacyclotetradecane-1,8-bis(methylphosphonic acid) (H_4L^2), forms an analogous pentacoordinated complex, pc-$[Cu(L^2)]^{2-}$, at room temperature. However, the complex does not isomerise to the octahedral complex analogous to *trans*-O,O-$[Cu(L^1)]^{2-}$. Because of the high thermodynamic stability of pc-$[Cu(L^1)]^{2-}$, ($\log\beta = 25.40(4)$, 25 °C, $I = 0.1$ mol dm^{-3} KNO_3) and the formation of protonated species, Cu^{II} is fully complexed in acidic solution ($-\log[H^+] \approx 3$). Acid-assisted decomplexation of both of the isomers of $[Cu(H_2L^1)]$ takes place only after protonation of both uncoordinated oxygen atoms of each phosphonate moiety and at least one nitrogen atom of the cycle. The exceptional kinetic inertness of both isomers is illustrated by their half-lives $\tau_{1/2} = 19.7$ min for pc-$[Cu(H_2L^1)]$ and $\tau_{1/2}$ about seven months for *trans*-O,O-$[Cu(H_2L^1)]$ for decomplexation in 5 M $HClO_4$ at 25 °C. The mechanism of formation of pc-$[Cu(L^1)]^{2-}$ is similar to those observed for other macrocyclic complexes.

Keywords: cyclam derivatives · kinetics · macrocyclic ligands · phosphonate ligands · stability constants

Introduction

Polyazamacrocycles with coordinating pendant arms form very stable complexes with a wide range of metal ions. The ligands encapsulate metal ions in the macrocyclic cavity and the complexes often exhibit both thermodynamic and kinetic stability.[1] Convenient properties of the complexes have been explored for use in such applications as contrast agents in magnetic resonance imaging[2] or for the labelling of biological substances with metal radioisotopes for diagnostic and therapeutic purposes.[3] For the latter of these uses, a metal ion is coordinated by a suitable bifunctional ligand, ensuring, as a result of strong metal binding, no deposition of harmful radioisotopes in the body, while also allowing conjugation of the complex to a biomolecule by means of another reactive group. Biomolecules such as small peptides,[4] monoclonal antibodies or their fragments,[5] and biotin[6] can be labelled through a reactive group placed on the macrocycle rim or on a carbon atom of a pendant arm, as well as directly through an acetate pendant group with the formation of an amide functionality.[4, 7]

Of a number of metal ions, Cu^{II} has attracted the greatest interest because of the occurrence of several copper isotopes convenient for use in nuclear medicine; ^{64}Cu or ^{67}Cu are mostly used. Both of these isotopes (half-life 12.8 h; β^+ 655 keV; β^- 573 keV; γ 511 keV and half-life 62 h; β^- 577, 484, and 395 keV; γ 93 and 185 keV, respectively) can be used

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[*] For classification of the cyclam ring conformation in complexes, see B. Bosnich, C. K. Poon, M. Tobe, *Inorg. Chem.* **1965**, *4*, 1102.

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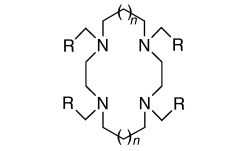
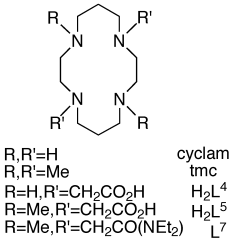
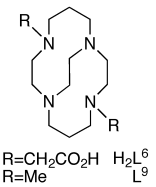


in diagnosis and radioimmunotherapy.[3] Several copper(II)-containing bioconjugates have passed some clinical trials.[3a, 8] The metal chelating units in the bioconjugates are mostly derivatives of H_4dota and H_4teta. Therefore, Cu^{II} complexes of the two ligands and their derivatives have been thoroughly investigated.[9–16]

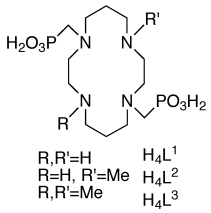
To find ligands with different properties, investigation of macrocycles containing methylphosphonic ($-CH_2-PO_3H_2$) or methylphosphinic ($-CH_2-P(R)O_2H$) groups started several years ago.[17–20] Variation of the R group in the phosphinic acid derivatives leads to a change in the ion selectivity[19, 20] and other properties of the macrocyclic compounds.[21] Transition-metal ion complexes of phosphorus acid analogues of H_4dota and H_4teta were sparingly investigated with the exception of H_8dotp and H_8tetp.[22–24] It was found that these two ligands contain two very basic ring nitrogen atoms[22, 23] and are somewhat selective toward large metal ions.[17c] We studied the influence of the methyl(phenyl)phosphinic acid pendant arms on the ability of the 12- and 14-membered tetraazacycles to complex transtion-metal[25, 26] and lanthanide ions.[27] Our investigation of Cu^{II} complexes of the ligands shows their high thermodynamic stability, the reasonable kinetic inertness of [Cu(H_2dotp^{Ph})], and the kinetic lability of [Cu(H_2tetp^{Ph})] in acid-assisted decomplexation.[26] A comparison of complexation properties of macrocycles with acetic and phosphorus acid pendant arms has been reviewed recently.[28]

To design hexadentate ligands suitable for the first-row transtion-metal ions, 1,8-diacetic derivatives of cyclam, H_2L^4 and H_2L^5, were synthesized.[29, 30] The ligands form the expected octahedral complexes with metal ions; however, the acetate ligand containing secondary amine groups (H_2L^4) is not stable in aqueous solution, owing to the easy formation of tricyclic lactam.[29, 31] The cyclam modified with two acetate pendant arms in positions 1 and 4 was prepared by template synthesis on Co^{III}.[32] Other examples of such hexadentate ligands are 1,11- and 1,8-bis(2-pyridylmethyl) cyclam derivatives.[33] For these ligands, a pentacoordinated copper(II) complex with the cyclam ring conformation of **I** and octahedral *cis*-**V** nickel(II) complexes were obtained. Bucher et al.[34a,b] recently investigated several 1,8-bis(*N*,*N*-dimethylcarbamoyl)methyl and other 1,8-disubstituted cyclam derivatives and isolated complexes with **I** and *trans*-**III** conformations of the cyclam ring. Sterically constrained hexadentate ligands with acetate pendants also exclude the possibility of inner lactam formation.[35] Several other hexadentate ligands containing acetate,[36] acetamide,[34c, 37] or hydroxyalkyl[36c, 38] pendant arms in the 1,8-positions on the C-substituted cyclam ring were studied. A majority of the complexes contain a cyclam ring in the *trans*-**III** conformation. A fully encapsulated Cu^{II} ion is present in a complex with an ethylene cross-bridged cyclam derivative containing two acetate (H_2L^6) or acetamide pendant arms.[39] The structures of the ligands impose the formation of complexes with the *cis*-**V** ligand conformation.[39, 40] The complexes exhibit very high stability both in vitro and in vivo, however the rate of complexation is very slow.[40]





We decided to synthesize[41] 1,8-bis(phosphonic acid) derivatives of cyclam in order to overcome the unwanted formation of lactam rings mentioned above. The ligands, like other aminoalkylphosphonic acid derivatives, are highly basic.[41] Therefore, high values of stability constants and high kinetic inertness, resulting from coordination of all donor atoms of the ligands, are expected. As the cyclam skeleton is very suitable for copper(II), we present here our results obtained on copper(II) complexes of 1,4,8,11-tetraazacyclotetradecane-1,8-bis(methylphosphonic acid) (H_4L^1) and two similar ligands H_4L^2 and H_4L^3. They can be considered as model compounds for the more complex ligands that could possibly be used in nuclear medicine. Our studies on cobalt(III)[42] and nickel(II)[43] complexes of this class of ligands have been published.



Results and Discussion

Synthesis and crystal structures: At room temperature, the H_4L^1 ligand forms a blue complex with Cu^{II}, which is easily crystallised in a diprotonated form. The complex is pentacoordinated and the denotation "pc" will be used for this arrangement throughout the text in order to distinguish it from the high-temperature octahedral form. The crystal structure of the complex was determined for the 5.5 hydrate but the bulk was analysed as a lower hydrate; the crystals slowly lose some water of hydration. Selected bond lengths and angles are listed in Table 1. The molecular structure of the complex is shown in Figure 1 together with the atom-numbering scheme. The unit cell contains two independent molecules of the complex with only slightly different bonding parameters. The nitrogen atoms of the ring do not form a plane and the bonding parameters point to a highly distorted environment of Cu^{II}. For pentacoordinated complex species, the coordination sphere can be considered as a square pyramid or trigonal bipyramid. We used published criteria to determine the coordination geometry.[44] The first[44a] is based on a comparison of basal angles of the polyhedron giving a parameter of $\tau = 0$ for an ideal tetragonal pyramid and $\tau = 1$ for an ideal trigonal bipyramid. Our complex gives $\tau = 0.492$ and $\tau = 0.504$ for the two independent molecules. The other method[44b] compares the dihedral angles of

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Table 1. Bond lengths [Å] and bond angles [°] of pc-$[Cu(H_2L^1)]\cdot 5.5H_2O$ (molecule A), *trans*-O,O-$[Cu(H_2L^1)]\cdot 2H_2O$, and pc-$[Cu(H_2L^2)]\cdot 3H_2O$.

pc-$[Cu(H_2L^1)]\cdot 5.5H_2O$		*trans*-O,O-$[Cu(H_2L^1)]\cdot 2H_2O$		pc-$[Cu(H_2L^2)]\cdot 3H_2O$	
bond lengths					
Cu1–N1	2.077(2)	Cu1–O1	2.369(1)	Cu1–N1	2.107(2)
Cu1–N4	2.016(2)	Cu1–N1	2.084(2)	Cu1–N4	2.060(2)
Cu1–N8	2.068(2)	Cu1–N4	2.010(2)	Cu1–N8	2.101(2)
Cu1–N11	2.005(2)			Cu1–N11	2.037(2)
Cu1–O11	2.218(2)			Cu1–O11	2.227(2)
angle					
N1-Cu1-O11	83.66(7)	O1-Cu1-N1	86.34(6)	N1-Cu1-O11	84.18(7)
N4-Cu1-N1	86.46(8)	O1-Cu1-N4	91.80(6)	N4-Cu1-N1	86.49(9)
N4-Cu1-N8	93.84(8)	O1-Cu1-N1[a]	93.66(6)	N4-Cu1-N8	94.99(9)
N4-Cu1-O11	104.72(8)	O1-Cu1-N4[a]	88.20(6)	N4-Cu1-O11	106.29(8)
N8-Cu1-N1	178.44(7)	O1-Cu1-O1[a]	180	N8-Cu1-N1	178.45(9)
N8-Cu1-O11	94.78(7)	N1-Cu1-N4	86.79(7)	N8-Cu1-O11	95.82(8)
N11-Cu1-N1	93.20(8)	N1-Cu1-N4[a]	93.21(7)	N11-Cu1-N1	92.79(9)
N11-Cu1-N4	148.91(8)	N1-Cu1-N1[a]	180	N11-Cu1-N4	150.57(9)
N11-Cu1-N8	87.34(7)	N4-Cu1-N4[a]	180	N11-Cu1-N8	85.7(1)
N11-Cu1-O11	106.14(8)			N11-Cu1-O11	102.89(8)

[a] Symmetry-derived atoms.

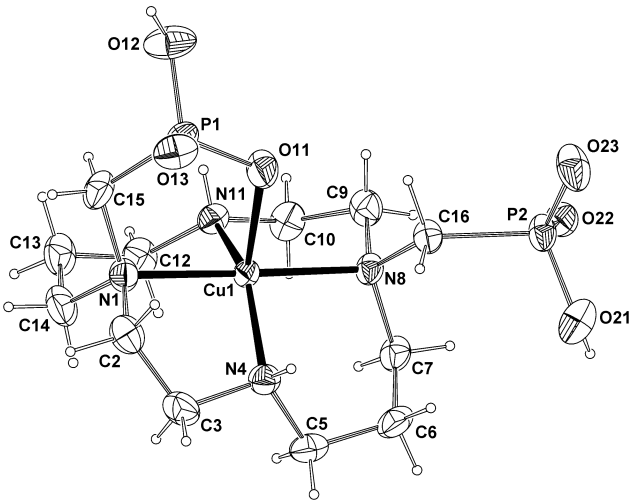

Figure 1. Molecular structure of pc-$[Cu(H_2L^1)]$ (molecule A).

normalized coordination polyhedrons. By analysis using this approach, we can consider the coordination sphere to be slightly closer to a trigonal-bipyramidal arrangement. Therefore, two opposite secondary amine nitrogen atoms and the oxygen atom of one phosphonate group can be considered to be in the equatorial plane and two nitrogen atoms bearing pendant moieties are coordinated in the axial positions. The Cu–N lengths in the equatorial plane are shorter (Cu1–N4 2.016(2) Å and Cu1–N11 2.005(2) Å) than those in the axial positions (Cu1–N1 2.077(2) Å and Cu1–N8 2.068(2) Å). The orientation of the substituents at the nitrogen atoms of the ring indicates conformation **I**. One phosphonic acid group is not coordinated.

One proton is bound to each phosphonate group. The molecules of the complex are connected by short intermolecular hydrogen bonds (range of donor – acceptor distances 2.51 – 2.60 Å) between oxygen atoms of the pendant arms. In addition, the crystal structure is stabilised by a three-dimensional network of other intermolecular hydrogen bonds between phosphonate groups, hydrate water molecules, and secondary nitrogen atoms. No intramolecular hydrogen bonds similar to those found in structures of octahedral *cis*-O,O cobalt(III)[42] or nickel(II)[43] complexes of H_4L^1 were found.

Comparing the geometry of the coordination sphere of pc-$[Cu(H_2L^1)]\cdot 5.5H_2O$ with other *N*,*N*′,*N*″,*N*‴-tetrasubstituted derivatives of the cyclam, we can see that conformation **I** of the cyclam ring is common for Cu^{II} complexes. In contrast to our complex, nitrogen atoms mostly form a plane below the copper atom and the donor atom of a pendant arm is usually coordinated in the apical position of a square pyramid.[45] However, this arrangement is rather unusual for disubstituted cyclam derivatives,[1a, 45] though a structure almost identical to pc-$[Cu(H_2L^1)]$ was recently observed in $[Cu(L^7)]^{2+}$.[34b] A comparison of bond lengths and angles shows identical values except for that of the Cu–O bond, which is slightly longer in the phosphonic acid derivative (2.218(2) Å for Cu1–O11 and 2.146 Å for Cu–O(C)) because of the bulky phosphorus atom. A similarly distorted structure was found for a Cu^{II} complex of the cyclam derivative bearing 1,11-bis(2-pyridylmethyl) pendant arms; only one pyridine group was coordinated as well.[33a] Conformation **I** is also present in Cu^{II} complexes of the *N*-monoacetate derivative of cyclam with several methyl groups on its rim.[36c] However, in the *N*-monoacetate complex, the coordination around copper(II) is much closer to a square pyramid with the acetate in the axial position.

Heating of an aqueous solution of pc-$[Cu(H_2L^1)]$ leads to isomerization to a violet thermodynamic product, *trans*-O,O-$[Cu(H_2L^1)]$. The reaction takes place with a reasonable rate only at temperatures above 80 °C; the low-temperature isomer is stable at room temperature (only a very weak spot of the *trans* isomer was observed by TLC after an aqueous solution of pc-$[Cu(H_2L^1)]$ was left standing at room temperature for six months). Such isomerism is very unusual in copper(II) chemistry and, to the best of our knowledge, has only been observed for a few macrocyclic ligands: L^7,[34b] *N*,*N*′,*N*″,*N*‴-tetramethylcyclam (tmc),[46a, 47] and the Curtis macrocycle.[48] Guilard et al.[34b, 46a] prepared *trans* complexes of L^7 and tmc by the dropwise addition of a $Cu(BF_4)_2$ solution to a hot, basic, aqueous solution of the ligands. Meyerstein et al.[47] induced the isomerization of $[Cu(tmc)]^{2+}$ (tmc in conformation **I**) by reduction to a Cu^{I} complex, which is conformationally labile, and forms the *trans* isomer after re-oxidation. Direct isomerisation of complexes with nitrogen substituted cyclam-like ligands, as found for pc-$[Cu(H_2L^1)]$ giving *trans*-O,O-$[Cu(H_2L^1)]$, has not previously been observed.

The *trans*-O,O-$[Cu(L^1)]^{2-}$ complex crystallized in a diprotonated form. Selected bond parameters are listed in Table 1. The molecular structure of *trans*-O,O-$[Cu(H_2L^1)]$ with the atom-numbering scheme is shown in Figure 2. The molecule is centrosymmetric with copper(II) in an axially-elongated octahedral arrangement. Four nitrogen atoms are equatorially coordinated and lie in a plane, while the oxygen atoms of the phosphonate groups are *trans* to each other. The Jahn – Teller

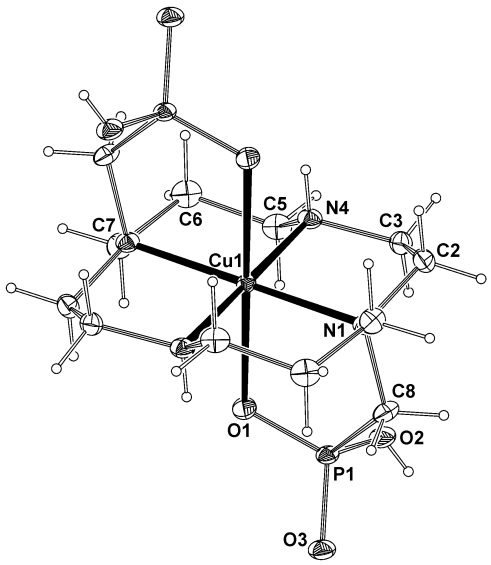

Figure 2. Molecular structure of *trans*-O,O-[Cu(H_2L^1)].

distortion of the octahedron along the Cu–O bonds (Cu1–O1 2.369(1) Å) is apparent from a comparison of Cu–N and Cu–O lengths; the Cu1–N4 (2.010(2) Å) bonds are distinctly shorter than those of tertiary nitrogen atoms (Cu1–N1 2.084(2) Å) (Table 1). Cyclam is in the most common *trans*-**III** conformation.[45] Each phosphonate group binds one proton, and two phosphonate moieties of neighbouring complex molecules form a pair of intermolecular hydrogen bonds O2–H2···O3′ and O2′–H2′···O3 (O2···O3′ distance 2.534(2) Å, angle O2–H2–O3′ 169(1)°), resulting in an eight-membered ring (–P–O–H···O–P–)$_2$. The complex molecules connected through the hydrogen bonds form infinite chains very similar to those found in the structure of *trans*-O,O-[Co(HL^1)]·3H_2O.[42] Very recently, the same (–P–O–H···O–P–)$_2$ rings with almost identical parameters were found in a Cu^{II} complex of the phosphonic acid derivative of 1,10-diaza-18-crown-6.[83] As in the low-temperature isomer, the crystal structure is stabilized by a three-dimensional network of additional hydrogen bonds between water molecules, phosphonate, and secondary amine groups (range of donor-acceptor distances 2.844–3.070 Å).

The structure of the *trans*-O,O-[Cu(H_2L^1)] complex can be compared with Cu^{II} complexes of other cyclam-like ligands with coordinating pendant arms, which have *trans* octahedral arrangements.[10b, 11, 31, 34–38] In all cases except one,[11] the pendant arm donor atoms are located at the axial positions of the octahedron. Equatorial Cu–N bond lengths (Cu1–N4 2.010(2) Å and Cu1–N1 2.084(2) Å) in *trans*-O,O-[Cu(H_2L^1)] are comparable with those from the literature (2.01–2.15 Å), as are those for the Cu–O axial bonds (Cu1–O1 2.369(1) Å and 2.25–2.41 Å, respectively). In the exception mentioned above,[11] the coordination sphere of copper(II) in the complex with 6-(4-nitrobenzyl) H_4teta derivative is also octahedral; however, with the *cis*-N_4O_2 geometry and two acetate groups uncoordinated. In this case, two nitrogen atoms bearing the uncoordinated acetate groups are located in axial positions with elongated Cu–N bonds.

Complexation properties of H_4L^1 with other metal ions were investigated, and cobalt(III)[42] and nickel(II)[43] complexes were prepared and their structures determined. Both of the metal ions form *cis* octahedral isomers *cis*-O,O-[Co(HL^1)] and *cis*-O,O-[Ni(H_2L^1)] with a *cis*-**V** conformation of the cyclam ring after reaction at room temperature. The reaction at about 100 °C gave *trans*-O,O-[Co(HL^1)]. Complex *cis*-O,O-[Ni(H_2L^1)] is converted to the *trans*-O,O-[Ni(H_2L^1)] isomer after we heated it in an acid solution for several hours. The conformation of the azacycle in the *trans* isomers is *trans*-**III** as expected. The isomerisation of the nickel(II) complexes was surprising and similar to those observed for the copper(II) complexes studied here.

To investigate the isomerism of the Cu^{II} complexes with this family of ligands, we also prepared Cu^{II} complexes of H_4L^2 and H_4L^3. The ligands have only a minor structural change substitution of one or two secondary nitrogen atoms with methyl groups. The crystal structure was determined for pc-[Cu(H_2L^2)]·3H_2O. Selected bonding parameters of pc-[Cu(H_2L^2)]·3H_2O are listed in Table 1. The molecular structure is shown in Figure 3. The structural parameters are very similar to those found for pc-[Cu(H_2L^1)]·5.5H_2O. In contrast to pc-[Cu(H_2L^1)], the pc-[Cu(H_2L^2)] and [Cu(H_2L^3)] complexes (see below) do not isomerize to the *trans*-O,O forms under the same or similar conditions. The nitrogen atoms with methyl groups are probably resistant to inversion and the change of conformation of the azacycle can therefore not occur.

Spectral and electrochemical properties: The *trans*-O,O-[Cu(H_2L^1)] isomer has two d–d absorptions typical of tetragonally elongated octahedral Cu^{II} complexes.[49] The

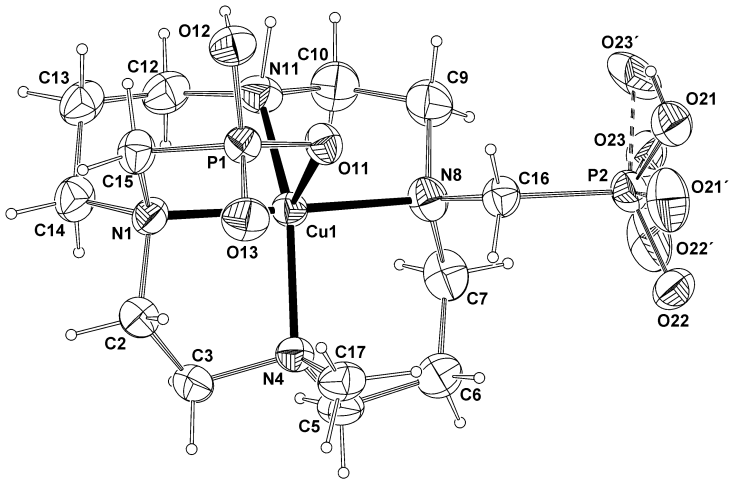

Figure 3. Molecular structure of pc-[Cu(H_2L^2)].

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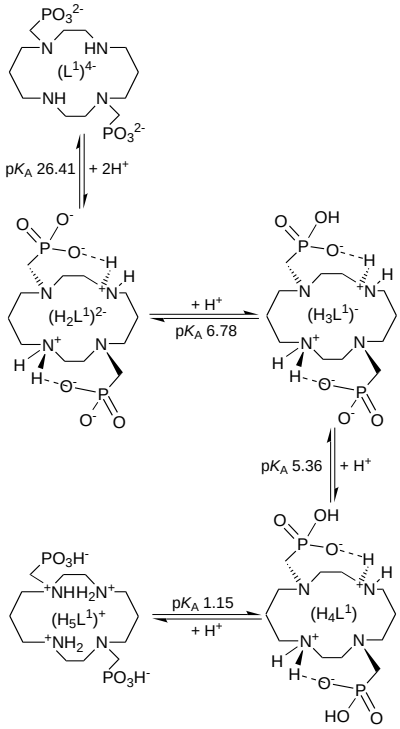
lower-energy absorption occurs at 974 nm ($\varepsilon = 90\ mol^{-1}\,dm^3\,cm^{-1}$) and is assigned to the $d_{z^2} - d_{x^2-y^2}$ transition. The visible absorption occurs at 553 nm ($\varepsilon = 100\ mol^{-1}\,dm^3\,cm^{-1}$) and it is assigned to the d_{xy}, d_{xz}, $d_{yz} - d_{x^2-y^2}$ transition.[49, 50]

The pc-[Cu(H_2L^1)] isomer exhibits a similar spectrum with two absorptions at 970 nm ($\varepsilon = 155\ mol^{-1}\,dm^3\,cm^{-1}$) and 596 nm ($\varepsilon = 300\ mol^{-1}\,dm^3\,cm^{-1}$), as does pc-[Cu($H_2L^2$)] with bands at 967 nm ($\varepsilon = 103\ mol^{-1}\,dm^3\,cm^{-1}$) and 653 nm ($\varepsilon = 217\ mol^{-1}\,dm^3\,cm^{-1}$). In the spectrum of [Cu(H_2L^3)], the visible absorption is shifted to 687 nm ($\varepsilon = 250\ mol^{-1}\,dm^3\,cm^{-1}$). The near infrared absorption found in the spectra indicates coordination in the axial positions and thus, the structures found in the solid state are also assumed to be present in solution. The coordination spheres are stable in the $-\log[H^+]$ region (0.1–8.5), because no changes in the character of the d–d transitions were observed.

The red shift of the visible transitions on going from the *trans*-O,O-[Cu(H_2L^1)] to pc-[Cu(H_2L^1)], pc-[Cu(H_2L^2)], and [Cu(H_2L^3)] corresponds to the decreasing ligand field resulting from a change in the geometry of the coordination sphere and the lower basicity of the tertiary nitrogen atoms in H_4L^3 and H_4L^2 relative to H_4L^1; this is analagous to a series of Cu^{II} complexes with cyclam and tmc.[51] In the UV region, the expected charge-transfer (CT) absorptions were observed. For the *trans*-O,O-[Cu(H_2L^1)] isomer, the absorption at 275 nm ($\varepsilon = 6900\ mol^{-1}\,dm^3\,cm^{-1}$) was unchanged in the $-\log[H^+]$ region that we studied. In the pc-[Cu(H_2L^1)] isomer, the CT transition was split into two bands at 270 and 310–325 nm, and this points to separation of the Cu–O and Cu–N transitions. The intensity of the band at 270 nm increases from $\varepsilon = 5500$ to $7000\ mol^{-1}\,dm^3\,cm^{-1}$ with decreasing $-\log[H^+]$, corresponding to the protonation of one or more phosphonate groups. Similar changes in the UV/Vis spectra with $-\log[H^+]$ change were observed for H_4L^1 complexes with Co^{III} and Ni^{II}.[42, 43]

The pc-[Cu(H_2L^1)] complex is irreversibly reduced in a two-electron step to elemental copper at relatively low potential, $E_p = -0.57$ V (vs. SCE). A similar value was observed for the one-electron step Cu^{II}/Cu^{I} of $[Cu(L^7)]^{2+}$.[34b] Such two-electron reduction might be a consequence of amalgam formation resulting from the use of a mercury electrode. Irreversible reduction of the high-temperature *trans*-O,O-[Cu(H_2L^1)] isomer to elemental copper takes place at $E_p = -0.69$ V (vs. SCE). Above the potential of 0 V, Cu^0 is re-oxidized to Cu^{II} and, during repeated scans on the same drop, a new reduction peak is observed at $E_p = -0.57$ V. It is assigned to the pc-isomer formed from the free ligand and re-oxidized Cu^{II} at the temperature of the CV measurements (Figure S1, Supporting Information). Peak assignment was confirmed by addition of pc-[Cu(H_2L^1)] to the measured solution. This is an additional verification of the fact that the low-temperature pc-isomer is a kinetic product of the reaction between Cu^{II} and H_4L^1. Very similar redox potentials for two-electron reduction were recently observed for $[Cu(tmc)]^{2+}$ complexes the isomer with configuration **I** of the cyclam ring is reduced at a potential of -0.57 V and the *trans*-**III** isomer exhibits a potential of -0.62 V.[47]

Potentiometric studies: Dissociation constants of H_4L^1 and the sites of protonation were determined previously.[41] The first two protonations take place on the secondary amino groups. The deprotonations are almost simultaneous and, therefore, only the sum of $pK_1 + pK_2 = 26.41$ was determined. The subsequent constants $pK_3 = 6.78$ and $pK_4 = 5.36$ correspond to the monoprotonation of the phosphonate groups. The protonation is highly influenced by the presence of strong intramolecular N–H···O hydrogen bonds[41] and, therefore, values of pK_3 and pK_4 are slightly lower then corresponding constants in other macrocyclic phosphonate ligands. The next constant ($pK_5 = 1.15$) was assigned to protonation at the third nitrogen atom of the macrocyclic ring (Scheme 1).



Scheme 1. Protonation scheme of H_4L^1.

Equilibrium data are shown in Tables 2 and 3. Formation of the pentacoordinated complex starts in the acidic region and at $-\log[H^+] \approx 3$ almost all Cu^{II} is complexed (Figure 4) in stable species with protonated phosphonate groups (see the crystal structure). On the basis of comparison of corresponding dissociation constants of the complex (Table 3) and the free ligand (above), we can assign $pK_A = 7.05$ to protonation of the uncoordinated phosphonate (the pK_A value is not decreased by the formation of the hydrogen bond in the free ligand or by coordination in the complex) and $pK_A = 5.10$ to the protonation of the coordinated phosphonate group.

Complex pc-$[Cu(L^1)]^{2-}$ ($\log\beta_{011} = 25.40$) is more thermodynamically stable than most cyclen and cyclam derivatives with coordinating pendant arms (Table 3). Higher stability constants were found for only $[Cu(cyclam)]^{2+}$ and $[Cu(homocyclen)]^{2+}$, in which copper(II) is ideally coordinated in the equatorial plane by four nitrogen atoms. As the ligands

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Table 2. Stability and protonation (dissociation) constants of complexes pc-[Cu(H_2L^1)] and *trans*-O,O-[Cu(H_2L^1)] (25 °C; 0.1 mol dm^{-3} KNO_3 or 0.1 mol dm^{-3} KCl).

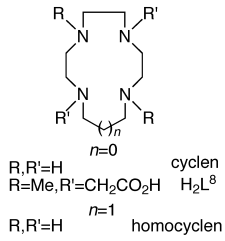
Equilibrium	pc-[Cu(H_2L^1)]				*trans*-O,O-[Cu(H_2L^1)]			
	logβ[a]	pK_A	logβ[b]	pK_A	logβ[c]	pK_A	logβ[b]	pK_A
$Cu^{II}+(L^1)^{4-} \rightleftharpoons [Cu(L^1)]^{2-}$	25.40(4)	–	–	–	26.50(9)	–	–	–
$Cu^{II}+H^+ +(L^1)^{4-} \rightleftharpoons [Cu(HL^1)]^-$	32.45(3)	7.05	–	–	33.03(8)	6.53	–	–
$[Cu(L^1)]^{2-}+H^+ \rightleftharpoons [Cu(HL^1)]^-$	–	–	7.03(5)	7.03	–	–	6.39(1)	6.39
$Cu^{II}+2H^+ +(L^1)^{4-} \rightleftharpoons [Cu(H_2L^1)]$	37.55(2)	5.10	–	–	38.42(4)	5.39	–	–
$[Cu(L^1)]^{2-}+2H^+ \rightleftharpoons [Cu(H_2L^1)]$	–	–	12.18(6)	5.15	–	–	11.66(1)	5.27
$[Cu(L^1)]^{2-}+3H^+ \rightleftharpoons [Cu(H_3L^1)]^+$	–	–	13.70(7)	1.52	–	–	12.87(1)	1.21

[a] logβ calculated from titration of Cu^{II}/H_4L^1 system (0.1 mol dm^{-3} KNO_3). [b] logβ calculated from titration of pc- or *trans*-O,O-[Cu(H_2L^1)] (0.1 mol dm^{-3} KNO_3). [c] logβ calculated from titration of Cu^{II}-H_4L^1 system as described in Experimental Section (high temperature; 0.1 mol dm^{-3} KCl).

Table 3. Comparison of stability constants of Cu^{II} with H_4L^1 and similar ligands.

Ligand	logβ_2 of ligand	logβ ([CuL])	pCu[b]	Ref.
H_4L^1	26.41	25.40 (pc)	8.1	this work
		26.50 (*trans*)	8.6	this work
cyclam	21.7	27.2	11.3	[52]
homocyclen[a]	21.0	29.1	12.7	[52]
cyclen[a]	20.2	24.8	10.9	[52]
H_4teta	20.70	20.49	9.5	[13a]
H_4dota	21.85	22.25	8.9	[13a]
H_3do3a[a]	21.95	26.49	8.4	[12c]
H_8tetp	26.3	26.6	8.9	[22b]
H_8dotp	23.63	25.4	9.0	[22a]
H_4tetp^{Ph}	19.79	17.19	7.3	[26]
H_4dotp^{Ph}	18.81	20.37	9.2	[26]
H_2L^8	21.76	20.85	8.1	[53]

[a] Homocyclen = 1,4,7,10-tetraazacyclotridecane; cyclen = 1,4,7,10-tetraazacyclododecane; H_3do3a = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid. [b] Calculated for $-\log[H^+] = 7.4$ and $c_M = c_L = 0.004$ mol dm^{-3}.



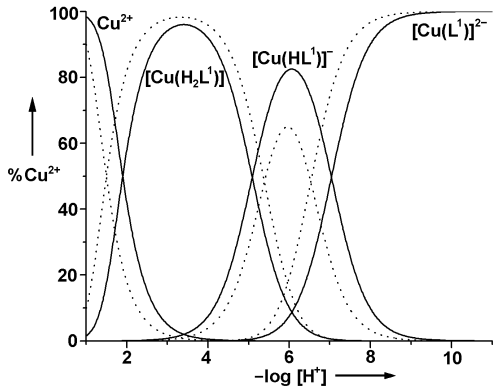


Figure 4. Distribution diagrams for systems with pc-$[Cu(L^1)]^{2-}$ (full line) and *trans*-$[Cu(L^1)]^{2-}$ (dotted line); $c_L = 0.004$ mol dm^{-3}, $c_{Cu} = 0.004$ mol dm^{-3}.

in Table 3 have very different protonation constants, a better means for comparison of the binding affinity of the ligands is the parameter pCu (the negative logarithm of the concentration of free Cu^{II}), calculated for the systems under identical conditions (in this case, $-\log[H^+] = 7.4$ and M:L = 1:1; Table 3). The highest values were found for the unsubstituted macrocycles. The other ligands exhibit similar values within 1.5 orders of magnitude. The relatively low pCu values of the phosphonate ligands are a consequence of the high basicity of the ring nitrogen atoms (logβ_2, Table 3) and, therefore, the high proton affinity of the amines. Comparison[28] of the stability constants of a wide range of Cu^{II} chelates with amine ligands containing acetic or phosphinic/phosphonic acid pendant arms showed that the stability of their Cu^{II} complexes is predominantly governed by the overall basicity of the coordinated nitrogen atoms.

Unfortunately, there is no direct means to determine the thermodynamic stability of the high-temperature *trans*-O,O-$[Cu(L^1)]^{2-}$ isomer. For a reasonable estimation, we used a technique similar to the method used for other Cu^{II}-macrocyclic complexes.[15a] We left solutions in ampoules to establish an equilibrium at 90 °C. No low-temperature isomer was present at the end of equilibration. Then, we measured $-\log[H^+]$ of the solutions in the ampoules at 25 °C and calculated the stability and protonation constants of the *trans* isomer. The acid dissociation constants are reliable (see below) but the value of stability constant (log$\beta = 26.50$) of the fully deprotonated *trans*-O,O-$[Cu(L^1)]^{2-}$ complex is not constant at 25 °C and the real thermodynamic constant would be higher. Protonation constants determined from the titration correspond to protonation of the coordinated phosphonate groups.

Because of the kinetic inertness of both of the complexes, we tried to find values of their third protonation constants, which could be of help in the interpretation of kinetic data (see below). Therefore, we considered the complexes as simple acids and determined their protonation constants. The results are presented in Table 2. The values of the first two constants determined by these acid–base titrations correspond very well to values obtained from titrations of the Cu^{II}-H_4L^1 system for both of the isomers. It confirms that Cu^{II} is fully complexed in the $-\log[H^+]$ regions corresponding to those protonations. In pc-$[Cu(H_3L^1)]^+$, protonation of the

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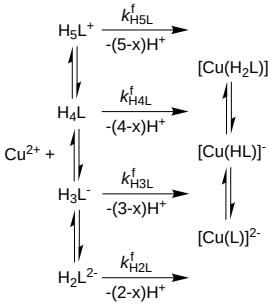
uncoordinated phosphonate group is suggested by the higher value of $pK_3 = 1.52$. However, the third proton must be bound to the oxygen atom of the phosphoryl group (P=O) of the coordinated phosphonate moiety in *trans*-O,O-$[Cu(H_3L^1)]^+$, which leads to $pK_3 = 1.21$. The value is similar to $pK_3 = 1.15$ of *cis*-O,O-$[Ni(H_3L^1)]^+$, in which the P=O group is protonated as well.[43] Protonation of the phosphonate pendant was also observed in *cis*-O,O- and *trans*-O,O-$[Co(H_2L^1)]^+$ ($pK_2 = 1.74$ and 1.87, respectively).[42] Protonation of the phosphoryl P=O bond seems to be possible in such stable complexes without complex decomposition. Similar protonated species are stable even in the solid state and crystal structures have been determined for several differently protonated forms of *cis*-O,O- and *trans*-O,O-$[Ni(H_xL^1)]Cl_{x-2} \cdot y\,H_2O$ ($x = 2-4$).[43]

Formation kinetics of pc-$[Cu(H_2L^1)]$: During the titration experiments we realized that the complexation kinetics at low $-\log[H^+]$ are relatively slow, which permitted us to investigate the formation kinetics using conventional techniques. The experiment was arranged under pseudo-first-order conditions with a ten-fold Cu^{II} excess at $-\log[H^+] = 1-3.1$ (the time course of spectral changes are shown in Figure S2). In this $-\log[H^+]$ region, a mixture of penta- ($(H_5L^1)^+$) and tetraprotonated (H_4L^1) ligand species with a very small amount of the triprotonated ($(H_3L^1)^-$) form are present in solution (Figures 4 and S3). In an additional $-\log[H^+]$ region (3–5) we studied using the stopped-flow technique, the main ligand species is $(H_3L^1)^-$ with a small amount of $(H_2L^1)^{2-}$. All of the protonated species can take part in complexation with Cu^{II} to form the diprotonated complex $[Cu(H_2L^1)]$ (the final complex species in the $-\log[H^+]$ regions studied, see Figures 4 and S3). The processes are characterised by corresponding rate constants k^f_{H2L}, k^f_{H3L}, k^f_{H4L}, and k^f_{H5L} (Scheme 2).



Scheme 2. Complexation of Cu^{II} with H_4L^1.

It was proved that the formation reaction is first order with respect to copper, $k^f_{obs} = k^f_2 \times [Cu^{II}]_t$ (where $[Cu^{II}]_t$ is the total concentration of Cu^{II}). Therefore, the formation of complexes with higher metal-to-ligand ratios can be excluded. This is also supported by a linear dependence $\log k^f_{obs} = n\text{x}\log[Cu^{II}]_t + \log k^f_2$ with slope $n = 1$ (see Supporting Information, Figures S4A and S4B). The second-order rate constants k^f_{HnL} for the protonated ligand species were fitted as a function of acidity (Figure S4C) according to Equation (1), in which β_i are overall protonation constants of the ligand.

Several models were tested with the set of reacting species and the results point to a unique model with three ligand forms as the reacting species according to Scheme 2. The corresponding partial rate constants are $k^f_{H2L} = (1.97 \pm 0.39) \times 10^5\,M^{-1}s^{-1}$, $k^f_{H3L} = (1.38 \pm 0.18) \times 10^3\,M^{-1}s^{-1}$, and $k^f_{H4L} = 0.17 \pm 0.05\,M^{-1}s^{-1}$. From comparison of k^f_{H2L}, k^f_{H3L}, and k^f_{H4L} ($1.97 \times 10^5/1.38 \times 10^3 \approx 140$ and $1380/0.17 \approx 8100$) it is immediately apparent that there are unusually high differences in the reactivities of the protonated forms of the ligand, between two and four orders of magnitude. The high contrast in the reactivity of differently protonated species of macrocyclic ligands is well established for the formation of lanthanide(III) ion complexes with H_4dota;[54] however, the difference is much larger here. It can be explained by taking into consideration the solution structure of the ligand.[41] Species H_4L^1 is protonated on two secondary amine nitrogens and each phosphonate group is monoprotonated. The deprotonated phosphonate oxygen atom is strongly hydrogen bonded to the protonated amine group. Therefore, the H_4L^1 ligand species behaves as a diprotonated moiety incapable of any strong complexation to an external metal ion.[41] After removal of one proton from the phosphonate group, the group becomes sufficiently basic to anchor a metal ion and is able to bring the ion close to the nitrogen atoms, which have a high affinity for Cu^{II}. The effect is amplified in diprotonated species but the difference in the reactivity of $(H_3L^1)^-$ and $(H_2L^1)^{2-}$ species is not so high. In addition, the overall charge of the species also plays a role; the positively charged $(H_5L^1)^+$ form was found to be completely unreactive under the conditions employed, mainly because of electrostatic repulsion between the ligand species and the metal cation. On the other hand, the negative charge on the $(H_3L^1)^-$ species can assist a metal cation in getting into the proximity of the ligand molecule.

Hence, the mechanism of the complexation is the same as that given for M^{II}-H_4dota and M^{II}-H_4teta systems,[55] in which fast formation of a weak complex between M^{II} and the pendant acetate arms is followed by a slow transfer to the macrocyclic cavity. A high dependence of the reactivity of differently protonated ligand species to Cu^{II} was recently observed for cyclam derivatives with additional amine groups on the cycle rim and the reactivity was along similar lines to our suggestions above.[56]

Isomerisation kinetics: To obtain more information about the mechanism of the unusual isomerisation of pc-$[Cu(L^1)]^{2-}$ we examined the kinetics of its conversion to the high-temperature *trans* isomer. We expected that such isomerisation may be base-catalyzed (conjugate-base (CB) mechanism) as was observed in the Ni^{II}-cyclam system[57a–d] and in some other complexes of cyclam-like ligands with Cu^{II}.[48, 58] Surprisingly, increasing the $-\log[H^+]$ (in the range of 9.5–13) with NaOH did not lead to such acceleration of the reaction, which would have allowed us to follow the process spectrophotometrically. However, we found that the reaction is highly promoted in the presence of high concentrations of ammonia. The isomerisation kinetics were measured in the temperature 55–73 °C range at total ammonia concentrations ranging from 2.0 to 11.0 mol dm^{-3}. No reaction was observed in the absence of ammonia under the experimental conditions

$$k^f_2 = \frac{k^f_{H2L} \times \beta_{p,2} \times [H^+]^2 + k^f_{H3L} \times \beta_{p,3} \times [H^+]^3 + k^f_{H4L} \times \beta_{p,4} \times [H^+]^4 + k^f_{H5L} \times \beta_{p,5} \times [H^+]^5}{\sum_{i=2}^{n=5} \beta_{p,i} \times [H^+]^i} \quad (1)$$

we used. The absorbance decreases (Figure S5) at 325 nm (pc-$[Cu(L^1)]^{2-}$ absorption maximum) and increases at 282 nm (*trans*-O,O-$[Cu(L^1)]^{2-}$ absorption maximum) were used for calculations of k_{obs}^{is}; the same values of k_{obs}^{is} were obtained from changes at each of the wavelengths. The isosbestic point at 305 nm indirectly proves the presence of only two absorbing species. Only two species were also found using capillary-zone electrophoresis (CZE) to check the course of the reaction in aqueous solution.[59] The observed pseudo-first order rate constant k_{obs}^{is} is dependent only on the ammonia concentration (Equations (2) and (3), Figure S6). As no

$$k_{obs}^{is} = \frac{k^{is} \times K^{is} \times [NH_3]}{1 + K^{is} \times [NH_3]} \quad (2)$$

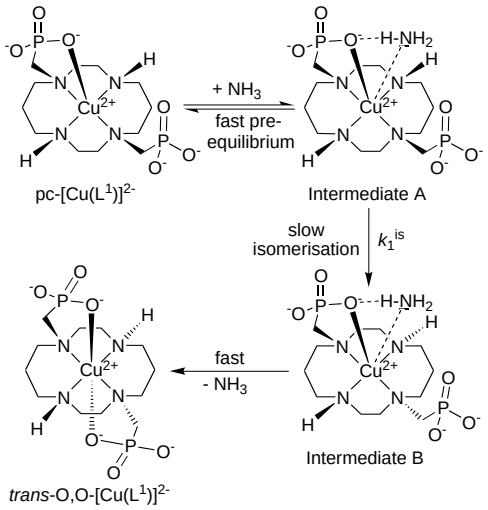
$$k_{obs}^{is} = k^{is} \times K^{is} \times [NH_3] = k_c^{is} \times [NH_3] \quad (3)$$

spectral changes were observed in the pc-$[Cu(L^1)]^{2-}$ solutions, even at the highest ammonia concentration (11M, room temperature), the equilibrium constant K^{is} must be much lower than 0.1 and, therefore, $K^{is} \times [NH_3]_t << 1$ ($[NH_3]_t$ is the total ammonia concentration), leading to Equation (3). The time course of the spectral changes for the isomerisation is depicted in Figure S5, the dependence of k_{obs}^{is} on the ammonia concentration in Figure S6 and temperature dependence of k^{is} in Figure S7. Results are given in Table 4.

Table 4. Kinetic parameters for isomerisation of pc-$[Cu(L^1)]^{2-}$ in presence of ammonia.

T [°C]	k_c^{is} [M^{-1}s^{-1}]	$\Delta H^{\neq}$ [kJ mol^{-1}]	$\Delta S^{\neq}$ [J K^{-1} mol^{-1}]	E_A [kJ mol^{-1}]
55	6.29×10^{-6}	94 ± 3	52 ± 9	97 ± 3
58	8.73×10^{-6}			
61.5	1.32×10^{-5}			
63	1.35×10^{-5}			
65	1.67×10^{-5}			
68	2.37×10^{-5}			
70	3.05×10^{-5}			
73	3.97×10^{-5}			

On the basis of Equation (3), we suggest the mechanism for the isomerisation shown in Scheme 3. Under the conditions employed, the pentacoordinated isomer is present as a fully deprotonated anionic species pc-$[Cu(L^1)]^{2-}$ (see Figure 4). At high concentrations of ammonia, phosphonate groups may be substituted or interact with NH_3 to a very low extent (intermediate **A**, Scheme 3). The structure of intermediate **A** may be 1) a square-pyramid (conformation **I** of the ring) with apical NH_3 coordination, as is usually observed for Cu^{II} complexes with tetrasubstituted cyclam derivatives[1a, 45] and/or 2) second-sphere solvation of the whole complex with NH_3, which is bonded to one or more phosphonate moieties or secondary nitrogen atoms through hydrogen bonds. The structure of intermediate **A** is probably closer to the second-sphere NH_3-adduct (with possible significant weakening of the phosphonate – metal bond), as no changes were observed in the UV/Vis spectrum of pc-$[Cu(L^1)]^{2-}$ dissolved in aqueous ammonia. Such a second-sphere adduct slowly isomerizes to more energetically favorable species with the *trans*-**III** conformation of the cyclam ring (intermediate **B**, Scheme 3). The isomerisation has to proceed by the breaking of two Cu–N bonds since an inversion must take place on two nitrogen atoms.



Scheme 3. Mechanism of isomerisation of pc-$[Cu(L^1)]^{2-}$ to *trans*-O,O-$[Cu(L^1)]^{2-}$.

The high positive activation enthalpy $\Delta H^{\neq}$ (94 kJ mol^{-1}) as well as the positive activation entropy $\Delta S^{\neq}$ (52 kJ mol^{-1}) correspond to the high energy loss and higher disorder owing to the Cu–N bond dissociation. The high activation energy E_A (97 kJ mol^{-1}) is associated mainly with the inversion of the nitrogen atoms. After conversion to the stable ring conformation, both phosphonate moieties are coordinated to give the final complex *trans*-O,O-$[Cu(L^1)]^{2-}$. The isomerisation is possible because ammonia solvates the negatively charged coordinated and free phosphonate groups in pc-$[Cu(L^1)]^{2-}$ through stable hydrogen bonds (moreover, the activity of water is highly reduced in such concentrated ammonia solutions). On formation of such educts, the electron density on the phosphonates and, consequently, on the nitrogen atoms is decreased, and Cu–N bond splitting is easier. Such solvation of phosphonate moieties can stabilize the intermediate **B** as well.

Direct isomerisation of Cu^{II} complexes with cyclam-like ligands has been observed;[48, 58] however, in contrast to our system, the CB mechanism was suggested. The difference may be explained by the presence of the negatively charged phosphonate moieties. The literature examples described are cationic complexes, for which proton dissociation of the N–H bond in the rate-determining step (the CB mechanism) is relatively easy. For pc-$[Cu(L^1)]^{2-}$, a double negative charge makes proton removal very unfavourable. As was mentioned above, ammonia can highly solvate the phosphonate moieties and can thus partly compensate for the high negative charge in intermediate **A**. However, the common CB mechanism may also operate in the presence of excess ammonia, as hydroxide anions may catalyze the nitrogen atom inversion.

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Therefore, hydroxide ions present in ammonia solutions can then assist the conversion of intermediate **A** to intermediate **B**. As mentioned above, a different isomerisation route, through a conformationally labile $[Cu(tmc)]^{+}$ complex, was recently observed for the $[Cu(tmc)]^{2+}$ and $[Cu(L^7)]^{2+}$ complexes.[34b, 47] A non-base-catalyzed isomerisation mechanism of $[Ni(tmc)]^{2+}$ (from *trans*-**III** to **I**) has been discussed;[57e] the isomerisation is highly promoted with strongly coordinating amines by means of partial replacement of the ring amine groups by solvent amine molecules. We tested several amines (Et_2NH, Et_3N, pyridine) for a possible catalytic effect on the isomerisation of pc-$[Cu(L^1)]^{2-}$. At 65 °C and at high amine concentration in water (1:1 *v*/*v* mixtures), the isomerisation was too slow (TLC control) to be easily followed by spectroscopic techniques; it was complete after more then one week. The rate of isomerisation was almost the same as in basic aqueous solution (NaOH, $-\log[H^+] \approx 11.5$). In 5 % aqueous NH_3 under the same conditions, the spot of pc-isomer disappeared after 20 h. The results confirm the catalytic effectiveness of ammonia.

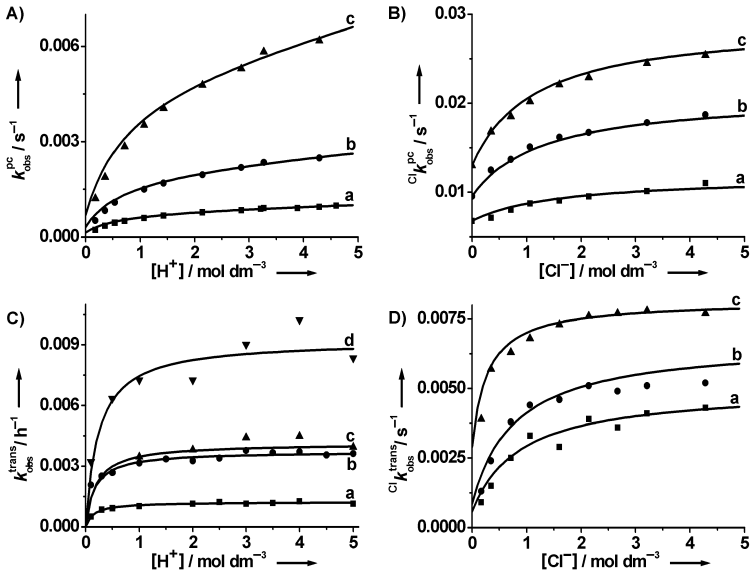

Figure 5. A) Dependence of k_{obs}^{pc} on concentration of acid at various temperatures; a) 25, b) 35, c) 45 °C. B) Dependence of $^{Cl}k_{obs}^{pc}$ on chloride anion concentration at $[H^+] = 4.28$ mol dm^{-3} and at various temperatures; a) 45, b) 50, c) 55 °C. C) Dependence of k_{obs}^{trans} on concentration of acid at various temperatures; a) 42, b) 50, c) 52, d) 60 °C. D) Dependence of $^{Cl}k_{obs}^{trans}$ on chloride anion concentration at $[H^+] = 4.28$ mol dm^{-3} and at various temperatures; a) 55, b) 60, c) 65 °C.

Kinetics of the acid-assisted dissociation of pc-$[Cu(H_2L^1)]$: The kinetics of the acid-assisted decomplexation of pc-$[Cu(H_2L^1)]$ were investigated in 0–5 mol dm^{-3} $HClO_4$ in 5 mol dm^{-3} (H,Na)ClO_4 in the 25–45 °C temperature region. Application of classic Equation (4) (k_0 and k_1 are acid-independent and acid-dependent rate constants, respectively; K is the corresponding protonation constant), commonly used in the literature for fitting experimental data of similar decompositions, leads to a very poor fit.

$$k_{obs} = \frac{k_0 + k_1 \times K \times [H^+]}{1 + K \times [H^+]} \quad (4)$$

The best fit for the rate constant k_{obs}^{pc} under pseudo-first order conditions in 5 mol dm^{-3} (H,Na)ClO_4 corresponds to Equation (5). The final results are presented in Table 5

$$k_{obs}^{pc} = \frac{k_1^{pc} \times K^{pc} \times [H^+] + k_2^{pc} \times K^{pc} \times [H^+]^2}{1 + K^{pc} \times [H^+]} \quad (5)$$

together with activation parameters obtained from the dependence of k_{obs}^{pc} on temperature. Figure 5A depicts the dependence of k_{obs}^{pc} on $[H^+]$ at various temperatures and Figure S8 the time course of spectra of the decomplexation reaction.

The approach using Equation (5) assumes an equilibrium protonation step with protonation constant K^{pc}. From similar systems,[26] it is known that such processes are associated with the protonations of amines of azacycles. Unfortunately, our results cannot directly give the number of protons attached to the complex molecule in the previous protonation steps. Therefore, we can only estimate the number of protons on the basis of the following considerations. The pK_A values for the third protonation are about 1.5 for the low-temperature isomer pc-$[Cu(H_2L^1)]$ (mostly at the noncoordinated phosphonate) and 1.2 for the high-temperature isomer *trans*-O,O-$[Cu(H_2L^1)]$ (at the coordinated phosphonate). Binding of the fourth proton to pc-$[Cu(H_3L^1)]^+$ to form pc-$[Cu(H_4L^1)]^{2+}$ is possible on the formally double bond oxygen atom of the coordinated phosphonate with pK_4 close to the value of 1.2 found for the high-temperature isomer. Such species, protonated on the phosphoryl oxygen atoms, are stable and have been found in Ni^{II} complexes of H_4L^1 even in the solid state.[43] The value of pK_5 for the fifth and decisive protonation step estimated from the kinetic data is about 0.3 (25 °C, Table 5). The fifth proton could only be anchored on the uncoordinated

Table 5. Kinetic parameters for acid-assisted decomplexation of pc-$[Cu(H_2L^1)]$.

Constant	T			$\Delta H^{\neq}$ or ΔH	$\Delta S^{\neq}$ or ΔS	E_A
	25.0 °C	35.0 °C	45.0 °C	[kJ mol^{-1}]	[J K^{-1} mol^{-1}]	[kJ mol^{-1}]
k_1^{pc} [s^{-1}]	$(8.5 \pm 0.3) \times 10^{-4}$	$(2.19 \pm 0.05) \times 10^{-3}$	$(5.3 \pm 0.2) \times 10^{-3}$	69.5 ± 0.2	-70.7 ± 0.6	72.0 ± 0.2
k_2^{pc} [M^{-1} s^{-1}]	$(5.1 \pm 0.6) \times 10^{-5}$	$(1.52 \pm 0.09) \times 10^{-4}$	$(4.4 \pm 0.5) \times 10^{-4}$	82 ± 1	-52 ± 4	85 ± 1
K^{pc} [M^{-1}]	1.9 ± 0.1	1.65 ± 0.07	1.5 ± 0.1	-8.3 ± 0.3	-22.7 ± 0.9	
log K^{pc}	0.27 ± 0.03	0.22 ± 0.02	0.18 ± 0.04			

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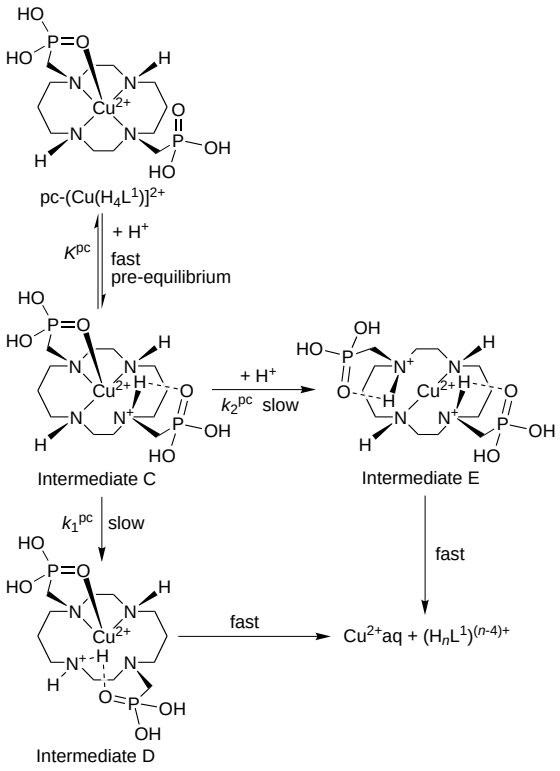
Table 6. Kinetic parameters for acid-assisted decomplexation of *trans*-O,O-[Cu(H_2L^1)].

Constant	T				$\Delta H^{\neq}$ or ΔH	$\Delta S^{\neq}$ or ΔS	E_A
	42.0 °C	50.0 °C	52.0 °C	60.0 °C	[kJ mol^{-1}]	[J K^{-1} mol^{-1}]	[kJ mol^{-1}]
k_1^{trans} [h^{-1}]	$(1.2\pm0.1)\times10^{-3}$	$(3.7\pm0.4)\times10^{-3}$	$(4.1\pm0.6)\times10^{-3}$	$(9\pm1)\times10^{-3}$	95 ± 7	-68 ± 23	98 ± 7
K^{trans} [M^{-1}]	6.8 ± 0.8	6.2 ± 0.6	5.3 ± 0.7	4.2 ± 0.7	-23 ± 5	-58 ± 15	
$\log K^{trans}$	0.83 ± 0.05	0.79 ± 0.04	0.72 ± 0.06	0.63 ± 0.07			

phosphonate to form $-P(OH)_3^+$, on a ring nitrogen atom, or also on both of these groups together (forming a hydrogen bond). The negative value of ΔS (-22.7 J K^{-1} mol^{-1}, Table 5) indicates the formation of an intramolecular hydrogen bond between the phosphonate moiety and the α-amino nitrogen atom (Intermediate **C**), which has also been observed for simple aminophosphonic acids.[60] Another explanation may be a difference in solvation of the protonated and deprotonated species. The formation of a hydrogen bond between the P–OH moiety and the adjacent nitrogen atom is supported[61] by the observation that the reaction is slightly exothermic (-8.3 kJ mol^{-1}, Table 5). Nevertheless, proton transfer to the amine and, consequently, destabilization of the Cu–N bond and formation of [Cu(H_5L^1)]$^{3+}$ (Intermediate **C**) is assumed to be a decisive step in the mechanism (Scheme 4) of the acid-assisted decomplexation given below. Slow rearrangement of



Scheme 4. Mechanism of acid-assisted decomplexation of pc-[Cu(H_2L^1)].

intermediate **C** leads to intermediate **D**, which has a hydrogen bond between the phosphonate group and the nitrogen atom spanning over the ethylene chain. The presence of such strong intramolecular hydrogen bonds between the uncoordinated phosphonate and protonated secondary amine group was observed in the solid state as well as in a solution of the free ligand (Scheme 1).[41]

In our previous work,[26] we suggested inclusion of similar hydrogen bond formation in the mechanism of the acid-assisted decomplexation of [Cu(H_2tetp^{Ph})], in which the process was characterised by a very negative value of $\Delta S^{\neq}$ (-121 J mol^{-1} K^{-1}). The value of $\Delta S^{\neq}$ corresponding to k_1^{pc} (-71 J mol^{-1} K^{-1}) is more negative than that for k_2^{pc} (-52 J mol^{-1} K^{-1}) and supports the suggestions mentioned above. So intermediate **D** quickly decomposes to final products. Subsequent slow protonation of intermediate **C** (taking place on the opposite nitrogen atom) and slow phosphonate decomplexation (characterised by rate constant k_2^{pc}) leads to intermediate **E** and is followed by fast decomplexation. Values of $\Delta H^{\neq}$ for both of the steps (67 and 88 kJ mol^{-1}, respectively) are similar to those found for [Cu(cyclen)]$^{2+}$ (74 kJ mol^{-1})[59] and [Cu(H_2tetp^{Ph})] (46 kJ mol^{-1}).[26] After decomplexation, the final product should be a ligand species protonated on all nitrogen atoms. This form is present in strongly acidic solution as follows from the dependence of δ_H and δ_P on $-\log[H^+]$ for H_4L^1, H_4L^2, and H_4L^3[41] and the crystal structure of $(H_6L^3)^{2+}\cdot2Cl^-\cdot4H_2O$.[63]

Kinetics of the acid-assisted dissociation of *trans*-[Cu(H_2L^1)]: Kinetics of the acid-assisted decomplexation of *trans*-O,O-[Cu(H_2L^1)]$^{2-}$ could not be investigated by conventional techniques, as the complex dissociation required several months. Therefore, the acidic solutions (0–5 mol dm^{-3} $HClO_4$ in 5 mol dm^{-3} (H,Na)ClO_4) sealed in glass ampoules were heated in an oven at 42–60 °C. The samples were removed at such time intervals to cover at least seven half-lives. Dependence of the rate constant k_{obs}^{trans} on [H$^+$] (Figure 5C) was best fitted using Equation (6).

$$k_{obs}^{trans}=\frac{k_1^{trans}\times K^{trans}\times[H^+]}{1+K^{trans}\times[H^+]} \quad (6)$$

The final results are listed in Table 6 together with activation parameters obtained from the dependence of k_{obs}^{trans} on temperature. Figure S9 depicts the decrease in intensity of the CT band at 276 nm.

On the basis of the previous discussion on the decomplexation of pc-[Cu(H_2L^1)], the decomposition of *trans*-O,O-[Cu(H_2L^1)] is possible only after protonation of one or more of the ring nitrogen atoms. The dissociation constant of the three-protonated species is known (pK_3 1.2) from potentiometric measurements, and the third proton is bound to the oxygen of the P=O group. Analogously to pc-[Cu(H_2L^1)], the fourth protonation of *trans*-O,O-[Cu(H_2L^1)] is assumed to take place on the other P=O group. Only the fifth proton is directed to the nitrogen atom to form intermediate **F** (Scheme 5). In contrast to intermediates **C**–**E** in Scheme 4, intermediate **F** still has the *trans*-**III** ring conformation. In the rate-determining step, protonation of a nitrogen atom should

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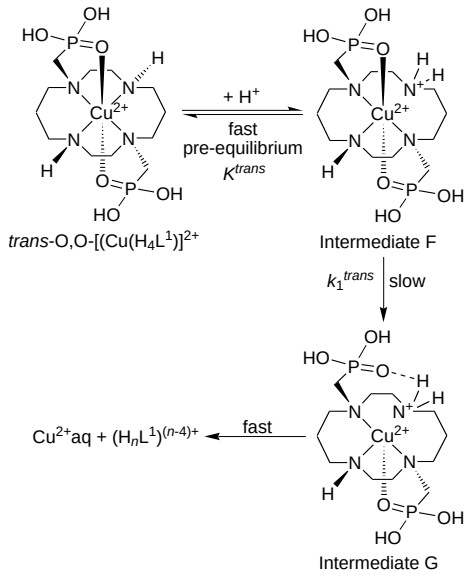

Scheme 5. Mechanism of acid-assisted decomplexation of *trans*-O,O-[Cu(H_2L^1)].

induce decoordination of a phosphonate moiety and immediate formation of intermediate **G**. This is followed by complex dissociation. In Scheme 5, intermediate **G** has a conformation distinct from that of intermediate **D** in Scheme 4. However the exceptional slowness of the kinetic step may be accompanied by inversion on the nitrogen atoms in addition to phosphonate decomplexation. This conformational change is supported by the very high activation energy of the process ($E_A = 98\ kJ\,mol^{-1}$, Table 6). In that case, intermediate **G** would be identical to intermediate **D**. The *trans*-**III** ring conformation is thermodynamically the most stable conformation in metal complexes of cyclam derivatives.[1a, 43] Therefore, the barrier for decomplexation of the *trans* isomer is higher than for the pentacoordinated isomer (Table 5). The acid-assisted decomplexation of the *trans* isomer is about 3600 times slower than that of the pentacoordinated complex and the deceleration is caused by the different conformation of the cycle as well as by the coordination of the second phosphonate group.

A comparison of kinetic inertness in acid-assisted decomplexation is shown for several Cu^{II} complexes in Table 7. As apparent from the table, there is only one example of comparable kinetic inertness among the Cu^{II} complexes, a complex of the structurally reinforced cyclam derivative L^9.[64] The complex of ligand H_2L^6 with two acetate arms may be kinetically more inert but data on the acid-assisted decomplexation were not published.[40] The kinetic inertness of $[Cu(L^9)]^{2+}$ is mainly caused by the nonflexibility of the cycle as well as by steric hindrance provided by the additional ethylene bridge. For our complexes, the explanation is partly different. Similarly, the large phosphonate moieties hinder access of protons to the nitrogen atoms. However, electrostatic repulsion is probably more important. Both of the isomers should be protonated on all phosphonate oxygen atoms at high $[H^+]$ as was discussed above. Such species are highly positively charged and, therefore, additional protons are repelled from the species. In accordance with this hypothesis, chloride ions accelerate (see below) the reactions through the formation of ion pairs (decreasing the positive charge in an indirect way) or coordination to the Cu^{II} ion (a direct way).

Influence of an additional nucleophile on the decomplexation of [Cu(H_2L^1)] complexes: Using different mixtures of (H,Na)(Cl,ClO_4) at $I = 5.0\ mol\,dm^{-3}$ led to the acceleration

Table 7. Comparison of kinetic inertness of Cu^{II} complexes with different macrocyclic ligands in acidic medium ($[H^+] = 1.0$ M), $[H^+] = 0.1$ M for lower ionic strength $I < 1.0$ M).

Ligand	T [°C]	Ionic medium	k_{obs}	$\tau_{1/2}$	Ref.
cyclen	25	5.0 M (Na,H)ClO_4	$2.54 \times 10^{-4}\ s^{-1}$	45.5 min	[62]
cyclam	25	5.0 M (Na,H)NO_3	$5.52 \times 10^{-4}\ s^{-1}$[a]	20.9 min	[65]
meso-5,5,7,12,12,14-Me_6-cyclam (blue form)	25	5.0 M (Na,H)NO_3	$4.4 \times 10^{-4}\ s^{-1}$[a]	26.3 min	[66]
rac-5,5,7,12,12,14-Me_6-cyclam (blue form)	25	5.0 M (Na,H)NO_3	$1.33 \times 10^{-5}\ s^{-1}$[a]	14.5 d	[67]
meso-5,5,7,12,12,14-Me_6-cyclam (red form)	25	5.0 M (Na,H)NO_3	$4.59 \times 10^{-4}\ s^{-1}$[a]	25.2 min	[68]
thec-12[b]	25	1.5 M (Na,H)NO_3	$2.81 \times 10^{-5}\ s^{-1}$	6.9 h	[69]
thec-14	25	1.0 M (Na,H)ClO_4	$3.44\ s^{-1}$	0.2 s	[70]
thec-14	25	1.5 M (Na,H)NO_3	$2.44\ s^{-1}$	0.3 s	[69, 71]
thec-15	25	1.5 M (Na,H)NO_3		≈18 s	[69]
thpc-14	25	1.0 M ($HClO_4$ + NaCl)	$4.01\ s^{-1}$	0.2 s	[72]
H_3do3a	25	1.0 M (K,H)NO_3	$5.80 \times 10^{-5}\ s^{-1}$	3.3 h	[12a]
Hcpta	25	1.0 M (K,H)Cl		≈24 d	[15b]
1,4,8,11-tetraazacyclotetradecane-5,7-dione	25	0.1 M (H,K)NO_3	$19.5\ s^{-1}$	35.6 ms	[73]
1,4,7,10-tetraazacyclotridecane-11,13-dione	25	0.1 M (H,K)NO_3	$304.0\ s^{-1}$	2.3 ms	[74]
H_4dotp^{Ph}	25	5.0 M (Na,H)ClO_4	$2.12 \times 10^{-3}\ s^{-1}$	5.4 min	[26]
H_4tetp^{Ph}	25	0.43 M (Na,H)Cl	$2.26 \times 10^{-2}\ s^{-1}$	30.7 s	[26]
L^9	40	1 M $HClO_4$		> 6 years	[64]
pc-[Cu(H_2L^1)]	25	5.0 M (Na,H)ClO_4	$5.85 \times 10^{-4}\ s^{-1}$	19.7 min	this work
trans-O,O-[Cu(H_2L^1)]	42	5.0 M (Na,H)ClO_4	$1.06 \times 10^{-3}\ h^{-1}$	27.2 days	this work
trans-O,O-[Cu(H_2L^1)]	25	5.0 M (Na,H)ClO_4	$1.45 \times 10^{-4}\ h^{-1}$	6.7 months	this work

[a] k_2 for the mechanism: $[Cu(L)]^{2+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Cu(HL)]^{3+} \xrightarrow{k_2} H_4L^{4+} + Cu^{II}$. [b] Abbreviations: thec-12 = *N,N′,N″,N‴*-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane; thec-14 = *N,N′,N″,N‴*-tetrakis(2-hydroxyethyl)-1,4,8,11-tetraazacyclotetradecane; thec-15 = *N,N′,N″,N‴*-tetrakis(2-hydroxyethyl)-1,4,8,12-tetraazacyclopentadecane; thpc-14 = *N,N′,N″,N‴*-tetrakis(2-hydroxypropyl)-1,4,8,11-tetraazacyclotetradecane; Hcpta = 1,4,8,11-tetraazacyclotetradecane-1-(methyl(phenyl-4-carboxylic acid)).

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of acid-assisted decomplexation. Thus, we investigated the influence of chloride as an external ligand/nucleophile. The reaction was studied under the same conditions, that is at the same proton concentration and temperature but in the presence of Cl^- ions. For both of the complexes, the dependences of ${}^{Cl}k_{obs}^{pc}$ and ${}^{Cl}k_{obs}^{trans}$ on $[H^+]$ are similar (Figure 5B and D) and the rate laws are the same as above. However, another pre-equilibrium and a formation of a mixed chloride complex must be included into a model mechanism. For equations used for fitting in the presence of chloride ions, see the Supporting Information.

It is apparent that the acceleration of the decomplexation in the presence of Cl^- is much more pronounced for the *trans*-O,O-[Cu(H_2L^1)] complex, for which the relative acceleration (with or without Cl^-) is several orders of magnitude higher (${}^{Cl}k_1^{trans}/k_1^{trans} \approx 2680$ at 60 °C, see Tables S1 and 6, respectively) than for the pentacoordinated isomer (${}^{Cl}k_1^{pc}/k_1^{pc} \approx 2$, Tables S2 and 5, respectively). Such behaviour accounts for interactions of Cl^- ions with the complexes. There are two possible weak Cl^- interactions with the complex (similar to those suggested for ammonia in the mechanism of isomerisation; see above): 1) Cl^- – phosphonate group exchange in the first coordination sphere or 2) an outer-sphere interaction between positively charged protonated phosphonate and chloride anions through hydrogen bonds. Such relatively strong P–O–H ··· Cl^- hydrogen bonds were found in the solid state structures of differently protonated forms of *cis*-O,O- and *trans*-O,O-[Ni(H_xL^1)]$Cl_{x-2} \cdot y H_2O$ ($x = 2-4$)[43] and may be present in solution as well. Both of these possibilities cause a destabilization of the phosphonate coordination bond and/or a decrease in the positive charge on phosphonate moieties, which enables access to protons (removal of electrostatic repulsion between protons and positively charged complex species). It would lead to faster decomplexation as was observed here, mainly for the *trans* isomer. This fact is also supported by a lower activation energy ($E_a = 45$ kJ mol^{-1} for the *trans* isomer, Table S1) in comparison with the non-catalyzed reaction ($E_a = 98$ kJ mol^{-1}, Table 6). As expected, the final products of decomplexation in this case are $[CuCl_x]^{2-x}$ complexes.[81]

Conclusion

We have prepared two isomers of [Cu(H_2L^1)] and determined their structure in the solid state. Complexes of ligands derived from H_4L^1 by a sequential attachment of methyl groups at secondary nitrogen atoms are not able to isomerise in the same way under similar conditions. On the basis of spectral parameters, the solid-state structures should be preserved in aqueous solution as well. On the basis of the values of stability constants, these complexes are among the most stable Cu^{II} complexes. The most striking result is their extraordinary kinetic inertness, especially that of the octahedral isomer. To the best of our knowledge, the complex is kinetically the second most robust Cu^{II} complex ever known. However, the sterically constrained cyclam derivative L^9 is difficult to handle, as it acts as a proton sponge[64] and cannot be easily modified to prepare bifunctional ligands. On the other hand, complexes of its acetic derivative H_2L^6 may be even more kinetically inert and can be modified to obtain bifunctional ligands, however H_2L^6 suffers from slow complexation rate.[39, 40]

The above properties of H_4L^1 are very promising for the design of new ligands as carriers for radioisotopes of copper, owing to their high selectivity for Cu^{II} in comparison with other metal ions,[63] fast kinetics of complexation at pH near to physiological, high hydrophilicity as a consequence of the presence of phosphonate groups, easy synthesis and modification, and, mainly, kinetic inertness. Work in this direction is under way in our laboratories.

Experimental Section

General: Ligands H_4L^1, H_4L^2, and H_4L^3 were synthesized by a published method.[41] Hydrates of [$CuCl_2$], [$Cu(ClO_4)_2$], and [$Cu(NO_3)_2$] were obtained from Lachema (Czech Republic) and recrystallized from water before use. The other chemicals were purchased from Fluka or Merck in the highest purity available and were used as obtained. Most kinetic experiments were run on an HP 8453A (Hewlett – Packard) diode-array spectrophotometer. A UV-300 (Pye – Unicam) was used for kinetic experiments with of *trans*-O,O-[Cu(H_2L^1)] and for UV/Vis characterization (200 – 1100 nm) of the complexes (abundance of species present at particular $-\log[H^+]$ was estimated from a distribution diagram involving all complex protonation constants). MALDI/TOF mass spectra were recorded on a Kratos Kompact MALDI III and Kratos Axima-CFR (both Shimadzu) in positive-ion mode using 2,5-dihydroxybenzoic acid as a matrix. Thermogravimetry was done on a TG-750 Statton – Redcroft apparatus at 25 – 300 °C (5 °C min^{-1}) in air. Elemental analyses were carried out at the Institute of Macromolecular Chemistry of the Academy of Sciences of the Czech republic. Thin-layer chromatography (TLC) was run on silica gel aluminium-backed sheets (Silufol; Kavalier, Czech Republic) with propan-2-ol/conc. aq. NH_3/water 7:3:3 as a solvent phase. Water used in physico-chemical measurements was purified with a Milli-Q System (Millipore).

pc-[Cu(H_2L^1)] · 5 H_2O: $H_4L^1 \cdot 4H_2O$ (0.10 g, 0.22 mmol) and [$CuCl_2$] · 2 H_2O (0.038 g, 0.23 mmol) were dissolved in water (10 mL) and the solution was left at room temperature for 2 h. The product was precipitated by slow addition of acetone. The solid was filtered off and recrystallized from an aqueous solution by diffusion of acetone vapour. Deep blue leaves of complex were filtered off, washed with acetone, and dried in air, yielding 0.094 g (85 %). Single crystals suitable for diffraction studies were picked out of the bulk product obtained by recrystallization. $R_f = 0.20$ (blue spot); UV/Vis (water): $-\log[H^+] = 3.68$ (fresh solution of pure solid pc-[Cu(H_2L^1)]): λ_{max} (ε) = – 970 (155), 596 (296), 313 (8100), 275sh nm (7000 mol^{-1} dm^3 cm^{-1}); $-\log[H^+] = 9.10$ (pure pc-[Cu(L^1)]$^{2-}$): λ_{max} (ε) = – 967 (168), 583 (342), 325 (7750), 269 nm (5000 mol^{-1} dm^3 cm^{-1}); $-\log[H^+] = 0.10$ (more protonated species): λ_{max} (ε) = – 976 (147), 830sh, 730sh, 609 (175), 310sh (6500), 270 nm (7050 mol^{-1} dm^3 cm^{-1}); in 25 % aq. NH_3: λ_{max} (ε) = – 970 (90), 587 nm (244 mol^{-1} dm^3 cm^{-1}); MALDI/MS: calcd for $C_{12}H_{28}CuN_4P_2O_6$: 450.9 [M+H]$^+$, found 447.3; elemental analysis calcd (%) for $C_{12}H_{28}CuN_4P_2O_6 \cdot 5H_2O$ (539.1): C 26.71, H 7.10, N 10.39; found C 26.83, H 6.85, N 10.31; thermogravimetry: water removal in two unresolved steps (60 – 100 °C, Δm 4.93 %; ≈ 1.5 H_2O) immediately followed with slow decomposition and quick decomposition above 250 °C.

***trans*-O,O-[Cu(H_2L^1)] · 2 H_2O**: $H_4L^1 \cdot 4H_2O$ (0.10 g, 0.22 mmol) and [$CuCl_2$] · 2 H_2O (0.038 g, 0.23 mmol) were dissolved in water (10 mL) and the blue solution was evaporated under vacuum. The residue was dissolved in water (10 mL) and the solution was refluxed for 20 h. Progress of the reaction was followed by TLC. The solution was cooled and evaporated under vacuum to about 2 mL. The suspension was dissolved by addition of several drops of conc. aq. ammonia and the solution was chromatographed on Amberlite 50CG (50 mL) with water elution. Some hydrochloric acid was eluted first followed by the complex. Fractions containing the complex were evaporated to dryness and the residue was dissolved in boiling water (5 mL). After cooling to room temperature, the product was precipitated

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by slow addition of acetone. A violet solid was filtered off, washed with acetone and dried in air, yielding 0.085 g (80 %). Violet cubes suitable for diffraction studies were grown by diffusion of acetone vapour into aqueous solution. $R_f = 0.30$ (violet spot); UV/Vis (water): $-\log[H^+]$ 3.25 (fresh solution of pure solid *trans*-O,O-[Cu(H_2L^1)]): λ_{max} (ε) = – 974 (92), 746sh, 553 (88), 275 nm (6900 $mol^{-1} dm^3 cm^{-1}$); $-\log[H^+]$ 8.14 (pure *trans*-O,O-[Cu(L^1)]$^{2-}$): λ_{max} (ε) = – 974 (115), 740sh, 551 (122), 280 nm (7100 $mol^{-1} dm^3 cm^{-1}$); $-\log[H^+]$ 0.10 (more protonated species): λ_{max} (ε) = – 975 (95), 550 (97), 270 nm (8000 $mol^{-1} dm^3 cm^{-1}$); MALDI/MS: calcd for $C_{12}H_{28}CuN_4P_2O_6$ $[M+H]^+$: 450.9; found 451.4; elemental analysis calcd (%) for $C_{12}H_{28}CuN_4P_2O_6 \cdot 2H_2O$ (485.10): C 29.68, H 6.65, N 11.55; found C 29.82, H 6.48, N 11.42; thermogravimetry: Δm 7.66 % (calcd for $2H_2O$: 7.43 %) in the temperature range 90–150 °C; decomposition above 300 °C.

pc-[Cu(H_2L^2)]·3H_2O: $H_4L^2 \cdot 5.5H_2O$ (0.11 g, 0.22 mmol) and $[CuCl_2] \cdot 2H_2O$ (0.038 g, 0.23 mmol) were dissolved in water (10 mL) and the solution was left at room temperature for 2 h. The complex was precipitated by slow addition of acetone. The solid was filtered off and recrystallized from aqueous solution by diffusion of acetone vapour. Sky blue needles of the complex were filtered off, washed with acetone and dried in air, yielding 0.065 g (57 %). Single crystals suitable for diffraction studies were picked out of the bulk product obtained by recrystallization. $R_f = 0.20$; UV/Vis (water): $-\log[H^+]$ 2.95 (fresh solution of pure solid pc-[Cu(H_2L^2)]): λ_{ma} (ε) = – 967 (103), 653 (217), 322 (6100), 285sh nm (5200 $mol^{-1} dm^3 cm^{-1}$); MALDI/MS: calcd for $C_{13}H_{30}CuN_4P_2O_6$ $[M+H]^+$: 464.3; found 464.9; elemental analysis calcd (%) for $C_{13}H_{30}CuN_4P_2O_6 \cdot 3H_2O$ (517.95): C 30.15, H 7.01, N 10.82; found C 30.50, H 6.91, N 10.52; thermogravimetry: slow decomposition above 70 °C in unresolved steps, fast decomposition above 250 °C.

[Cu(H_2L^3)]·4H_2O: $H_4L^3 \cdot 6H_2O$ (0.10 g, 0.19 mmol) and $[CuCl_2] \cdot 2H_2O$ (0.035 g, 0.21 mmol) were dissolved in water (5 mL) and the solution was evaporated to dryness on a rotavapor. The residue was dissolved in water (5 mL) and evaporated again and the process was repeated three times. Finally, the residue was dissolved in water (5 mL) and the complex was precipitated by slow addition of acetone. The solid was filtered off and recrystallized from aqueous solution by diffusion of acetone vapour. Green-blue leaves of complex were filtered off, washed with acetone and dried in air, yielding 0.075 g (71 %). $R_f = 0.20$; UV/Vis (water): $-\log[H^+]$ 2.95 (fresh solution of pure solid [Cu(H_2L^3)]): λ_{max} (ε) = – 969 (132), 687 (252), 315 nm (6200 $mol^{-1} dm^3 cm^{-1}$); MALDI/MS: calcd for $C_{14}H_{32}CuN_4P_2O_6$ $[M+H]^+$: 479.6; found 478.9; elemental analysis calcd (%) for $C_{14}H_{32}CuN_4P_2O_6 \cdot 4H_2O$ (549.99): C 30.57, H 7.33, N 10.19; found C 30.61, H 6.71, N 10.00; thermogravimetry: water removal in two unresolved steps (Δm 8.3 % up to 100 °C ($\approx 2.5 H_2O$)) followed with slow decomposition (up to 250 °C) and fast decomposition (> 250 °C).

Crystal structure determination: Suitable crystals were mounted on glass fibres in random orientation with epoxy glue. Using a CAD4 diffractometer (Enraf–Nonius), diffraction data for pc-[Cu(H_2L^1)]·5.5H_2O, *trans*-O,O-[Cu(H_2L^1)]·2H_2O, and pc-[Cu(H_2L^2)]·3H_2O were collected at 293 K. The lattice parameters of the compounds were always determined from 25 reflections. The intensities were collected by the $\omega - 2\theta$ scan; three standard reflections were always measured after 1 h, no decrease of intensity was observed. A Lorenzian–polarization correction was used for all compounds using the JANA 98 program;[75] absorption corrections were not applied. The structures were solved by direct methods, and refined by full-matrix least-squares techniques (SIR 92,[76] SHELXL97,[77]). The hydrogen atoms were found by difference Fourier map and refined isotropically. In the structure of pc-[Cu(H_2L^2)]·3H_2O, oxygen atoms of the uncoordinated phosphonate group are disordered in two staggered positions with a relative occupancy of 79:21. Crystal data and structure refinement parameters are listed in Table 8.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-179990 (pc-[Cu(H_2L^1)]·5.5H_2O), -179991 (*trans*-O,O-[Cu(H_2L^1)]·2H_2O), and -179992 (pc-([Cu(H_2L^2)]·3H_2O). Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html (or from the

Table 8. Experimental and refinement data for the X-ray diffraction studies of pc-[Cu(H_2L^1)]·5.5H_2O, *trans*-O,O-[Cu(H_2L^1)]·2H_2O and pc-[Cu(H_2L^2)]·3H_2O complexes.[a,b]

Parameters	pc-[Cu(H_2L^1)]·5.5H_2O	*trans*-O,O-[Cu(H_2L^1)]·2H_2O	pc-[Cu(H_2L^2)]·3H_2O
empirical formula	$C_{12}H_{39}CuN_4O_{11.5}P_2$	$C_{12}H_{32}CuN_4O_8P_2$	$C_{13}H_{36}CuN_4O_9P_2$
M_w	548.95	485.90	517.94
T [K]	293(2)	293(2)	293(2)
crystal system	triclinic	triclinic	monoclinic
space group	$P\bar{1}$ (No. 2)	$P\bar{1}$ (No. 2)	$P2_1/c$ (No. 14)
a [Å]	9.605(5)	8.162(2)	9.4540(4)
b [Å]	14.474(5)	8.2230(10)	15.6240(6)
c [Å]	16.786(5)	9.161(3)	14.3830(4)
α [°]	89.250(5)	112.45(2)	90
β [°]	88.000(5)	104.34(3)	97.199(2)
γ [°]	80.140(5)	110.94(2)	90
V [Å^3]	2297.7(16)	475.3(2)	2107.75(13)
Z	4	1	4
ρ_{calcd} [g cm^{-3}]	1.587	1.698	1.632
λ [Å]	0.71069	0.71069	0.71069
μ [mm^{-1}]	1.151	1.367	1.242
θ range of data [°]	1.87–24.01	2.69–24.97	1.93–26.08
F(000)	1160	255	1092
hkl range	$-10 \le h \le 10$	$-9 \le h \le 9$	$0 \le h \le 11$
	$0 \le k \le 16$	$-9 \le k \le 9$	$-19 \le k \le 19$
	$-19 \le l \le 19$	$0 \le l \le 10$	$-17 \le l \le 17$
method of refinement	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	7213/0/862	1640/0/188	4164/0/435
goodness-of-fit on F^2	1.048	1.095	1.089
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0295$	$R1 = 0.0203$	$R1 = 0.0361$
	$wR2 = 0.0799$	$wR2 = 0.0550$	$wR2 = 0.0850$
R indices (all data)	$R1 = 0.0367$	$R1 = 0.0234$	$R1 = 0.0432$
	$wR2 = 0.0840$	$wR2 = 0.0564$	$wR2 = 0.0884$
largest difference peak/hole [e Å^{-3}]	0.674/ – 0.512	0.321/ – 0.380	0.545/ – 0.484

[a] $w = 1/[\sigma^2(F_0^2) + (A \cdot P)^2 + B \cdot P]$; where $P = (F_0^2 + 2F_c^2)/3$ (SHELXL97).[77] [b] $R = \Sigma | F_0 - F_C | / \Sigma | F_C |$; $R' = [\Sigma w(F_0^2 - F_c^2)^2 / \Sigma w(F_0^2)^2]^{1/2}$ (SHELXL97).[77]

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Potentiometric titrations: The concentration of a H_4L^1 stock solution was determined from the weight of anhydrous sample.[41] The published protonation constants[41] of the ligand were used for the calculation of the stability constants of the complexes. Metal stock solutions were prepared by dissolution of $[Cu(NO_3)_2]\cdot 3H_2O$ or $[CuCl_2]\cdot 2H_2O$ in water. The metal content of the solutions was determined by titration with Na_2H_2edta solution. A nitric acid solution was prepared by passing aqueous potassium nitrate solution through a Dowex 50W-8 column in the H^+ form because of traces of NO and NO_2 present in the concentrated acid. Azeotropic HCl was used for the preparation of a standard HCl solution. The KOH solution was standardized against potassium hydrogen phthalate, and HNO_3 and HCl solutions against the KOH solution.

Titrations at 25 °C were carried out in a thermostatted vessel at 25 ± 0.1 °C, at an ionic strength $I(KNO_3) = 0.1$ mol dm^{-3} and in the presence of an excess of HNO_3 in the region of $-\log[H^+] = 1.6-11.8$ using a PHM 240 pH-meter, a 2 cm^3 Radiometer ABU 900 automatic piston burette and a GK 2401B combined electrode (Radiometer). The initial volume was 5 cm^3 and the concentration of ligand was 0.004 mol dm^{-3}. The metal:ligand ratio was 1:1; parallel titrations were carried out five times. Each titration consisted of about 40 points. An inert atmosphere was ensured by constant passage of argon saturated with the solvent vapour during measurements. The stability constants for the $Cu^{II}-OH^-$ systems included in the calculations and $pK_w = 13.78$ were taken from ref. [78]. The protonation and stability constants β_{pqr} are concentration constants and are defined by $\beta_{pqr} = [H_pM_qL_r]/[H]^p \times [M]^q \times [L]^r$. The constants and the analytical concentrations of titrated complexes were calculated using the OPIUM program.[79] The program minimizes the criterion of the generalized least squares method using the calibration function $E = E_0 + S \times \log[H^+] + j_A \times [H^+] + j_B \times (K_w/[H^+])$, in which the additive term E_0 contains standard potentials of the electrodes used and contributions of inert ions to the liquid-junction potential; S corresponds to the Nernstian slope, the value of which should be close to the theoretical value; and the $j_A \times [H^+]$ and $j_B \times [OH^-]$ terms are contributions of the H^+ and OH^- ions to the liquid-junction potential. Clearly, j_A and j_B cause deviation from a linear dependence between E and $-\log[H^+]$ only in strong acid and strong alkali solutions. In the titration of Cu^{II}-H_4L^1, it was necessary to wait (to reach a stable $-\log[H^+]$ reading) for about 15 min for the first point and about 2.5 min for the next ten points ($-\log[H^+] < 2.1$). Equilibrium was established quickly (< 30 s) in less acidic solutions ($-\log[H^+] > 2.1$).

Titrations involving formation of *trans*-O,O-$[Cu(L^1)]^{2-}$ were carried out by the "out of cell" method. Because of decomposition of the starting and final complexes in nitrate-containing solutions at high temperatures, the titrations were done at $I(KCl) = 0.1$ mol dm^{-3} with a standard HCl solution. Solutions were prepared under the same conditions as above in ampoules at room temperature. The ampoules were sealed under argon and placed in a drying oven at 90 ± 0.5 °C for 7 d to reach equilibrium (checked using CZE[59]). The equilibrium was frozen by cooling to room temperature; the $-\log[H^+]$ values of the solutions in ampoules were measured at 25.0 ± 0.1 °C and the constants were calculated as above. Four parallel titrations were made, each titration consisting of about 30 points.

To find the third protonation constants of the complexes employable for interpretation of kinetic data, we titrated solutions of the pure complexes pc-$[Cu(H_2L^1)]$ or *trans*-O,O-$[Cu(H_2L^1)]$ (prepared from solid samples) in the region of $-\log[H^+] = 1.8-11.8$ under the above conditions (0.1 mol dm^{-3} KNO_3, 25 °C). Exact concentrations of the complexes in the titrated solutions were fitted together with determination of their protonation constants (OPIUM).[79]

Kinetic measurements: The formation kinetics of pc-$[Cu(H_2L^1)]$ was followed under pseudo-first-order conditions ($c_{Cu} = 4.2$ mm, $c_L = 0.42$ mm) in the $-\log[H^+]$ range of 1–3.1 at 310 nm ($I = 0.1$ mol dm^{-3} (K,H)Cl, 25 °C) using a diode-array spectrophotometer. The full Cu^{II} concentration range used in the measurements was $c_{Cu} = 1-10$ mm (ratio [M]:[L] = 10:1). In the $-\log[H^+]$ range of 3–5, the stopped-flow technique with indicator method was applied.[55] Compared with the standard method (measurement of absorbance of the evolved complex in buffered solutions) both methods gave results with satisfactory precision. The measurements were made on a home-made modular stopped-flow apparatus equipped with a Hewlett–Packard 6267BDD power supply, a 100 W tungsten lamp, and a water UV monochromator with fibre-optics light-guide (Jobin Yvon).[80]

Isomerization kinetics of pc-$[Cu(L^1)]^{2-}$ ($c_{complex} = 0.20$ mm) were determined at different total ammonia concentrations (2–11 mol dm^{-3}) in the 55–75 °C temperature range with no other control of ionic strength.

Dissociation kinetics measurement on pc-$[Cu(H_2L^1)]$ were performed in the $[H^+]$ range of 0.2–4.7 mol dm^{-3} ($c_{complex} = 0.28$ mm, $I = 5.00$ mol dm^{-3} (Na,H)ClO_4, 25–45 °C (± 0.1 °C)). The decomplexation was followed by a decrease of the intensity of the CT band of pc-$[Cu(H_2L^1)]$ at 306 nm with time.

Because of the very long duration of the experiments (months), the solutions used for the investigation of the acid-assisted decomplexation of *trans*-$[Cu(H_2L^1)]$ were sealed in glass ampoules. Weighed amounts of the complex were dissolved in an appropriate mixture of $HClO_4$ and $NaClO_4$ standard solutions to give complex concentrations of about 0.3 mm at 5.00 mol dm^{-3} (H,Na)ClO_4. This solution was divided into ampoules, which were sealed under argon. A relevant set of ampoules was placed in a drying oven at the required temperature (42, 50, 52, and 60 °C; ± 0.5 °C). Samples were withdrawn regularly and measured over a period up to 7–8 half-lives (about 30 points). The course of decomplexation was followed by a decrease in intensity of the CT band of *trans*-O,O-$[Cu(H_2L^1)]$ at 276 nm.

Measurements of the dissociation kinetics of both complexes (pc-$[Cu(H_2L^1)]$ and *trans*-$[Cu(H_2L^1)]$) in the presence of Cl^- ions were obtained under following experimental conditions: $c_{complex} = 0.28$ mm, $I = 5.00$ mol dm^{-3} (Na,H)(Cl,ClO_4), temperature range 45–65 °C (± 0.1 °C), $[H^+] = 1-4.3$ mol dm^{-3}, $[Cl^-] = 0.2-4.3$ mol dm^{-3}. All other experimental details were the same as for measurement without chloride ions.

Data from kinetic experiments were processed by nonlinear regression using spectrometer software and Excel 97[82] with identical results. All measured absorbances were corrected for background absorbance (due to free aqueous Cu^{II} and/or chlorocopper(II) complexes in the presence of Cl^-).

Electrochemical study: Cyclic voltammetry was performed on a PA 4 (Laboratorní přístroje, Prague, Czech Republic) in a three-electrode arrangement with a hanging mercury electrode working electrode, platinum auxiliary electrode, and saturated calomel reference electrode at 20 °C. The background electrolyte was 0.1 mol dm^{-3} KNO_3 in water. The scan rate was 100 mV s^{-1}.

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