Unsymmetrically substituted side-bridged cyclam derivatives and their Cu(II) and Zn(II) complexes†

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A series of new compounds built up on the skeleton of 1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (1,4-ethylene-bridged cyclam, 1,4-en-cyclam) were synthesized and characterized by means of NMR and MS spectroscopy and a single-crystal X-ray structure determination. The attempts to substitute the secondary amino group of the *p*-nitrobenzyl-1,4-en-cyclam **3**, using acetic acid derivatives as the alkylating agents, led to unexpected substitution of one of the piperazine ring nitrogen atoms, yielding the monoquaternary derivatives $\mathbf{4}^{\mathbf{Br}}$ and $\mathbf{5}^{\mathbf{Br}}$, respectively. In order to explain this reaction behaviour, the solution structure of the starting compound **3** was established using 2D-NMR techniques. The acid–base behaviour of the ligands and thermodynamic stability constants of their copper(II) and zinc(II) complexes were determined using potentiometric titrations. Stability constants of the investigated metal complexes are significantly lower than those of the cyclam complexes and comparable to those of the Me_4cyclam complexes. A copper(II) complex of amine **3** was prepared and characterized. In the solid state, this complex has the central copper atom surrounded by five donor atoms forming a coordination sphere with geometry between trigonal bipyramid and square pyramid.

Introduction

Cyclic amines derived from cyclam (1,4,8,11-tetraazacyclotetradecane) have been widely investigated as ligands suitable for copper(II) complexation. Introduction of one to four acidic pendant arms (acetates, methylphosphonates *etc.*) to the nitrogen atoms leads to macrocyclic chelators (*e.g.* TETA,[1] 1,8-H_4te2p)[2] forming good stability copper(II) complexes. Further improvements to the complex stability can be achieved by structural modifications of the cyclam skeleton, especially by limiting freedom of the macrocyles by introduction of a (carbon) bridge connecting two nitrogen atoms of the ring. The bridged azamacrocycles thus formed may be divided into two principal groups—the cross-bridged (with two distal nitrogen atoms connected) and the side-bridged (with two adjacent nitrogen atoms connected) ligands.[3] Whereas the compounds of the former group are known to form copper(II) complexes of a high kinetic inertness towards decomplexation,[4–7] data concerning the copper(II) complexes of the ligands of the latter groups are relatively scarce.[8,9]

In the search for an ideal copper(II)-encapsulating ligand suitable for *in vivo* applications[10] of radiolabelled complexes (^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu and ^{67}Cu, with half lives between 0.16 and 62 h) several aspects have to be regarded, including straightforward and uncomplicated ligand synthesis, good copper(II) complex inertness towards any type of decomposition and rapid complex formation under mild conditions. The ligands used today satisfy at most two of these requirements simultaneously. The cross-bridged cyclam-based ligands (Fig. 1) are usually easily prepared[11] and their copper(II) complexes exhibit enormous kinetic inertness towards decomplexation,[4–7] but formation of the complexes themselves requires either intensive heating (>80 °C for several hours) or a mild heating (~50 °C) for a prolonged time-period,[12] thus making these ligands unsuitable either for copper complexation after conjugation to a biomolecule (in the case of bifunctional chelators – BFCs) or for short-lived copper isotopes complexation. On the other hand, the known side-bridged cyclam-based ligands form copper(II) complexes much more easily but their kinetic inertness is significantly lower compared to the cross-bridged analogues (half-life in acid solutions in order of days, *vs.* years for the cross-bridged ligands).[5,6,9]

The ethylene-side-bridged cyclam **1** (Fig. 1) was prepared for the first time in the early 1980s[13] and the pathway leading

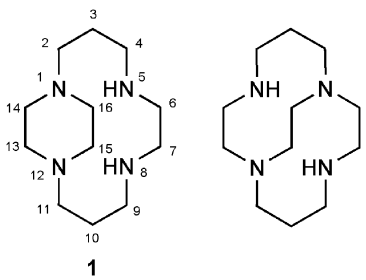

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Fig. 1 Structure and numbering scheme of 1,5,8,12-tetraazabicyclo[10.2.2]hexadecane **1** (side-bridged cyclam) and structure of the cross-bridged cyclam.

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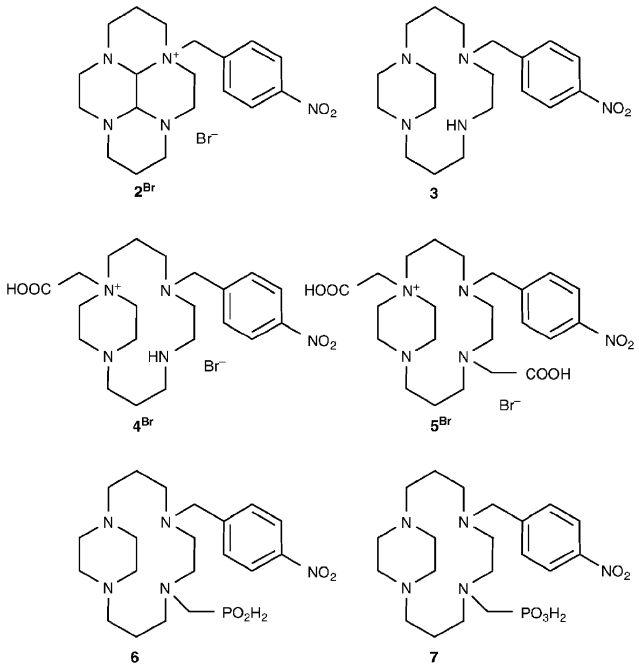


Fig. 2 An overview of compounds prepared in this work.

to mono-substituted derivatives of **1** was discovered in mid-1990s.[14] The kinetic inertness studies of copper(II) complex of the amine **1** revealed,[9] that the inertness of this complex towards acid-assisted decomplexation is comparable to that of the cyclam-copper(II) complex and, in addition, the thermodynamic stability of this complex, together with the protonation constants of the free ligand,[15] are also close to the values found for cyclam and its copper(II) complex, respectively.

Quite recently four papers dealing with mono-functionalized derivatives of the side-bridged cyclam were released by Archibald's group, concerning their use as copper(II) and zinc(II) chelators for medicinal use.[16]

The aim of our work was to prepare BFCs based on the side-bridged cyclam functionalized by *p*-nitrobenzyl group (as a spacer precursor) and by an acidic group to improve the complexation parameters of the side-bridged macrocycle (Fig. 2).

Results and discussion

Synthesis

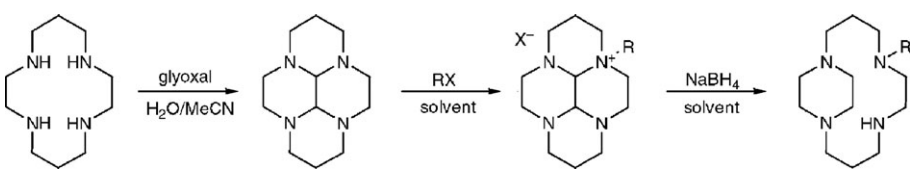
The general synthetic pathway leading to the monosubstituted 1,4-en-cyclam derivatives is shown in Scheme 1.[11,14] The first synthetic step, the glyoxal-cyclam bisaminal preparation, consists in an addition of aqueous solution of glyoxal (1,2-ethanedione) to a cyclam suspension in acetonitrile. Although the bisaminal yields were reported to be good to excellent (>80%),[11] in our hands the yield did not exceed 50%. One of the reasons of this result may be the composition of the commercially available 40% w/w (6 M) aqueous glyoxal solution which is known to contain concentration- and temperature-dependent amounts of the reactive monomeric species, this amount being substantially lowered with the increasing total concentration and the age of the material (oxidation on exposition to air).[17,18]

A suitable alternative source of glyoxal is its trimeric form. Dissolution of the trimer in hot distilled water (~70–80 °C) produces a solution in which the hydrated glyoxal monomer (ethane-1,1,2,2-tetraol) predominates (according to ^{1}H NMR measurements). This monomer reacts, after dilution by methanol, with cyclam to give the bisaminal in high and reproducible yields (~75–85%).

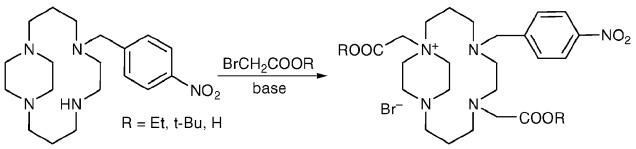
Alkylation of the bisaminal intermediate in a suitable solvent produces the monoquaternary ammonium salt in form of a precipitate (toluene or acetonitrile for R = benzyl,[11,19] acetonitrile for R = *p*-nitrobenzyl,[9] **2^{Br}**). Reduction of a suspension of the ammonium salt in ethanol by a 20-fold excess of $NaBH_4$ in 5 days produces the desired 1,4-en-cyclam derivative.[11] The amount of time needed to complete the reaction can be reduced under reflux conditions.[16b] It is possible to reduce the amount of the reducing agent used in the reaction either by conducting the reaction in methanol (10-fold excess of $NaBH_4$ is needed)[20] or in ethanol containing approx. 10% of water (2-fold excess of the reductant, see Experimental section). Use of the latter solvent also significantly reduces the time needed to complete the reaction (from 5 days to 8 h).

Substitution of the secondary amino nitrogen of the mono-substituted 1,4-en-cyclam derivative **3** has been attempted either by an alkylation reaction or by a Mannich-type reaction. Although the alkylation of similar derivatives in the presence of an additional base has been described,[20] alkylation of the *p*-nitrobenzyl-substituted compound by either ethyl bromoacetate or *tert*-butyl bromoacetate in a polar solvent (acetonitrile) in the presence of a base (Na_2CO_3, K_2CO_3, Et_3N or $^iPr_2NEt$) led to formation of monoquaternized dialkylated derivative **5^{Br}** (after acidic hydrolysis, Fig. 2, Scheme 2).

Analysis of the reaction mixtures had shown that yield of the diacetate **5^{Br}** was quantitative, relative to the amount of alkylating agent used in the reaction and only a trace amount of monoalkylated derivative (most probably **4^{Br}**, see below) and half of the unreacted starting material **3** were present. Results of the potentiometric titrations (see below) revealed that the starting amine **3** behaves as a very strong base. Thus, we decided to carry out the reaction without any additional base and with half an equivalent of bromoacetic acid (as the alkylating agent) in dry, non-polar solvent (diethyl ether).



Scheme 1



Scheme 2

Under such conditions amine **3** (the strongest base in the system) hydrobromide precipitation was expected, with the desired product **4a** left in solution. To our surprise, analysis of the precipitate had shown that monoquaternized monoalkylated compound $\mathbf{4}^{\mathbf{Br}}$ was prepared (Scheme 3).

The reasonable explanation of this behaviour could be found in the basicity of the secondary nitrogen atom of the starting compound **3**. This compound might have been isolated in its monoprotonated form as an ionic pair with hydroxide anion (see Experimental section). The relatively high basicity of the ligand **3** may facilitate existence of this ionic pair in benzene. According to the molecular mechanics (MM+) modelling results, the additional proton attached to the secondary nitrogen atom N8 would participate in the hydrogen bond system involving N12 and N5 nitrogen atoms, thus deactivating these atoms for further reaction with electrophiles. The only nitrogen atom in such systems available for further substitution is the N1 atom, which is too distant from the hydrogen bond system to participate in it (in the case of the twisted-boat piperazine ring conformation) or its lone electron pair is oriented outwards the macrocyclic ring (in the case of the piperazine ring chair conformation). The expected hydrogen-bond system is very similar to that found in the solid-state structure of $\mathbf{4}^{\mathbf{Br}}$ (see below). The alkylating agent attacks this nitrogen atom forming the 'tetraalkylammonium' quaternary centre. If the reaction proceeds in a non-polar solvent (diethyl ether) the product precipitates out of the reaction mixture in form of a yellow powder having the structure and composition shown in Scheme 3. In reaction media with higher polarity (acetonitrile), where the monoquaternized derivative remains in solution, and in the presence of an additional base, this molecule preferably reacts on the N8 atom with further equivalent of the alkylating agent, forming the compound $\mathbf{5}^{\mathbf{Br}}$. The reactivity of the secondary amine atom N8 of compound $\mathbf{4}^{\mathbf{Br}}$ must be significantly higher than the reactivity of the N1 nitrogen atom of the piperazine subunit in compound **3** as the final reaction mixture contains only a trace amount of the monoalkylated product $\mathbf{4}^{\mathbf{Br}}$ (detectable by the MS spectrometry) and a majority of the dialkylated compound $\mathbf{5}^{\mathbf{Br}}$ (together with half-amount of the unreacted compound **3**). This change of the N8-atom's reaction behaviour is related to a change of its basicity, which is lower in compound $\mathbf{4}^{\mathbf{Br}}$ due to the presence of an additional positive charge in the molecule.

The methylphosphinate and methylphosphonate derivatives have been synthesized *via* Mannich-type reactions of the secondary amine, paraformaldehyde and an appropriate phosphorus precursor (H_3PO_2, ambient temperature, to produce the methylphosphinate **6**; or $P(OEt)_3$ at elevated temperature, to produce (after acid hydrolysis) the methylphosphonate **7** in a low yield). Raising the temperature of the reaction mixture containing phosphinic acid results in the appearance of an inconsiderable amount of side-products, the most abundant among them being the hydroxymethylphosphinic acid (HO-CH_2(OH)(O)PCH_2N–) derivative.

NMR measurements

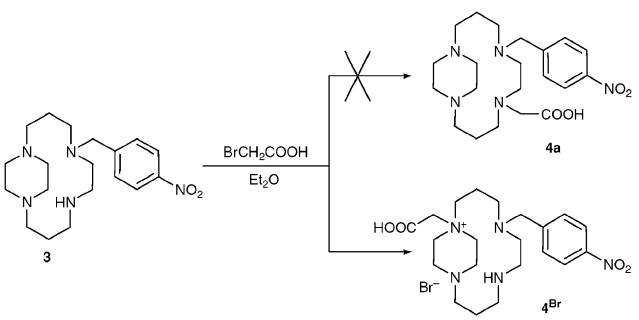
In the aromatic region of the proton NMR spectra, all the compounds shown in Fig. 2 exhibit a pair of doublets (an unresolved AA′BB′ pattern) at δ_H approx. 8 ppm, characteristic for the *p*-nitrophenyl group. With the exception of the structurally rigid ammonium salt $\mathbf{2}^{\mathbf{Br}}$ (Fig. 2) the aliphatic regions of the ^{1}H NMR spectra of the compounds measured in water contain sets of hardly distinguishable multiple signals. In addition to these signals, in the spectra of compound **6** a wide doublet assigned to the phosphorus-attached proton ($^1J_{HP}$ = 522 Hz) appears at ~6.9 ppm. In the ^{31}P NMR spectra of ligand **6** a corresponding doublet at δ 26.2 ppm is present. The value of the H–P coupling constant is in range of values typical for alkylphosphinic acids (R–PH(O)OH).[21]

To determine the structure of the ligand **3** in solution, several two-dimensional correlation NMR spectra have been measured (^{1}H–^{13}C gHSQC, gHMBC and ^{1}H–^{1}H COSY, NOESY). Results of the HSQC and HMBC experiments were used to assign the H–C and C–C connectivities. In contrast to our expectations, results of the NOESY measurements did not help to unambiguously establish the conformation of the piperazine subunit as the exchange signals are assignable to both possible conformations (*i.e.* chair and twisted boat).

The gHSQC and gHMBC experiments were also conducted in order to determine the H–C and C–C connectivities in the diacetate derivative $\mathbf{5}^{\mathbf{Br}}$. The second acetate group was localized at the nitrogen atom closer to nitrobenzyl-bearing nitrogen atom ('*cis*' to the nitrobenzyl group, '*trans*' to the second acetate group). This structural motif was later confirmed by the solid-state structure determination.

X-Ray structural studies

In order to determine the structure of the prepared compounds in the solid state, several attempts to prepare single crystals of the ligands or their metal complexes have been done. Crystals suitable for the single-crystal X-ray structure determination have been obtained from solutions of compound $\mathbf{4}^{\mathbf{Br}}$ and the copper(II) complex of ligand **3**—[Cu(**3**)Br][PF_6]. For the complete crystal, data collection and refinement details see the ESI.†



Scheme 3

Crystal structure of $4^{Br}\cdot 2.5H_2O$

The quaternary ammonium salt $\mathbf{4}^{Br}$ crystallizes with deprotonated carboxylate group and protonated N8 nitrogen atom (Fig. 3). The piperazine ring has the 'chair' conformation (the most stable for the six-membered cyclohexane-like rings) with the lone pair of the tertiary N12 atom heading towards the inner space of the macrocyclic ring and participating in the hydrogen bonds system among the N5, N8 and N12 nitrogen atoms (N8···N12 2.80 Å, N8···N5 2.91 Å, see Table 1. The carboxylate group O211 oxygen atom participates in a relatively strong intermolecular hydrogen bond including N8 and H82 atoms of the neighbouring molecule (O211#···N8 2.71 Å). One of the central propylene carbon atoms (C3) is disordered over two positions with relative population 62:38. The Br^- anion compensates the positive charge of the whole molecule. Furthermore, the crystal unit contains two solvate water molecules with full occupancy and one which was best fitted with 50% occupancy.

Copper(II) complex of ligand 3

The crystal structure of the [Cu(**3**)Br][PF_6] complex exhibits a five-coordinated copper(II) metal centre (Fig. 4). In the structure, a weak coordination interaction between copper and bromine atoms (Cu1–Br1A 2.7 Å, see Table 2) appears. The bromine atom has been found disordered in two almost equally populated positions (relative abundance 56 : 44), the less populated position being more distant from the copper centre (3.3 Å) than the position of the weakly coordinated bromine atom. The positions of the bromine atom are probably influenced by the proximity of the N8-bound hydrogen atom (N8···Br1A 3.122 Å, N8···Br1B 3.254 Å, but the hydrogen atom could not be located in the difference Fourier map).

The heavy atom (bromine) disorder and low diffraction data quality unfortunately shift the structure's uncertainty towards relatively high values (R' ~0.17, wR' ~0.49), however the other structural parameters (thermal parameters, bond distances deviations *etc.*) were satisfactory (Fig. 4).

The coordination sphere of the central copper atom (Table 2) could be described as an intermediate structure between square pyramid and trigonal bipyramid. The τ-parameter describing five-coordinated geometries along the Berry rearrangement between a trigonal bipyramid and a square pyramid ($\tau = (\beta - \alpha)/60$, with $\tau = 1$ for trigonal bipyramidal and $\tau = 0$ for square pyramidal geometry),[22] is 0.51 (β = N1–Cu1–N8, α = N5–Cu1–N12). The structural motif of this complex is essentially identical to that of a recently reported[17b] complex [Cu(**L**)Cl][$CuCl_2$] (where **L** = 5-benzyl-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane), with the τ-parameter equal to 0.54.

Table 1 Estimated distances (Å) and angles (°) in the H-bond system of $\mathbf{4}^+$ ion

H81···N5	2.47	N8···N5	2.91
H81···N12	2.06	N8···N12	2.80
H82···O211[a]	1.83	N8···O211[a]	2.71
N8–H81···N5	110	N8–H82···O211[a]	167
N8–H81···N12	139		

[a] $x, -y, z + 0.5$.

Potentiometric titrations

In order to determine the acid–base properties of the newly prepared ligands and the thermodynamic stability constants of their complexes with copper(II) and zinc(II), the pH-metric titration experiments were conducted. The resulting values of the protonation and dissociation constants of the ligands in aqueous solution are presented in Table 3, whereas the stability constants of their Cu^{II} and Zn^{II} complexes are listed in Table 4.

There could be four species with different degree of protonation found in the aqueous solutions of the monosubstituted compound **3**, depending on the pH value. The fully deprotonated species becomes predominant at pH value close to 12. The most basic nitrogen atom should be the secondary amine N8 (pK_a ~11). The second proton is probably caught by the piperazine-ring nitrogen atom in '*trans*' position to N8 (N1; pK_a ~8). The last two protons seem to be attached simultaneously to the ligand skeleton at the N5 and N12 atoms ($pK_a(H_3L) + pK_a(H_4L)$ ~3).

As expected,[23] the overall basicity of the ligand **6**, bearing an additional methylphosphinate group, is lower than the basicity of the parent amine **3**. The phosphinate compound is fully deprotonated at pH value above 11. The first proton

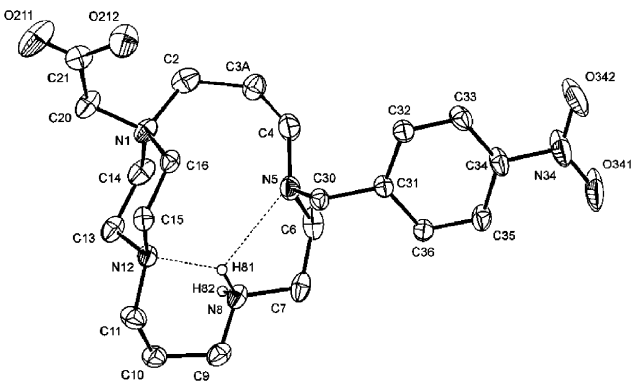


Fig. 3 The ORTEP view of $\mathbf{4}^+$ ion with 30% probability thermal ellipsoids (carbon-bound hydrogen atoms, and the ring-disorder are omitted for clarity).

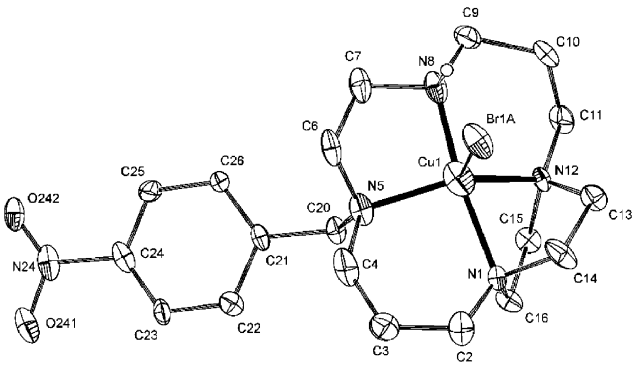


Fig. 4 The ORTEP view of the [Cu(**3**)Br] $^+$ ion with 30% probability thermal ellipsoids (hydrogen atoms and the bromine disorder are omitted for clarity).

Table 2 Selected bond distances (Å) and bond angles (°) in the $[Cu(\mathbf{3})Br]^+$ ion

Cu1–N1	2.076(10)	Cu1–N5	2.009(10)
Cu1–N8	1.850(13)	Cu1–N12	1.996(9)
Cu1–Br1A	2.718(8)	Cu1–Br1B	3.286(13)
N1–Cu1–N5	93.2(5)	N1–Cu1–N8	173.2(4)
N1–Cu1–N12	76.1(4)	N1–Cu1–Br1A	96.0(4)
N5–Cu1–N8	93.5(5)	N5–Cu1–N12	142.7(4)
N5–Cu1–Br1A	100.0(3)	N8–Cu1–N12	97.8(4)
N8–Cu1–Br1A	83.9(4)	N12–Cu1–Br1A	116.4(3)

(pK_a ~9.2) is probably attached either to the N5 atom (bearing the *p*-nitrobenzyl group) or N8 atom (bearing the methylphosphinate). In the next step (pK_a ~7.3) one of the piperazine ring nitrogen atoms is protonated. The lowest (the most acidic, pK_a ~0.8) dissociation constant detected corresponds to protonation of the remaining nitrogen atom and/or the methylphosphinate moiety (the value is similar to the constants obtained for aminomethylphosphinic acids).[24] The fifth expected dissociation constant was not detected due to the potentiometric method limitations (the constant is expected to be very low).

The acid–base behaviour of the investigated compounds can be well described as a combination of the cyclam and Me_4cyclam properties. The basicity of the secondary amino group in **3** is the same as in cyclam. The basicity of the remaining tertiary amino groups is much closer to Me_4cyclam than to cyclam. As expected, the acid–base behaviour of the compound **6** is similar to that of Me_4cyclam.

The complexation of Zn^{II} and Cu^{II} proceeded relatively slowly in the pH range used for the potentiometric experiments, thus the titrations involving the metal–ligand systems have been conducted using the 'out-of-cell' method (*i.e.* the solutions were prepared in the desired ligand–metal ratio, known amount of the base was added and the mixtures were left to equilibrate at 25 °C for 4 days).

The complexation of copper(II) and zinc(II) with ligand **3** shows usual behaviour (*cf.* Fig. 5). The ligands start to coordinate in acidic (Cu^{II}, $-\log[H^+]$ ~2) or slightly acidic region (Zn^{II}, $-\log[H^+]$ ~5.5), respectively, forming the expected $[M(L)]^{2+}$ species prevailing up to the strongly alkaline region (in the case of Cu^{II}). The Zn^{II}-complex decomposed at $-\log[H^+] > 9$ and some insoluble product precipitated out of the solution (probably $Zn(OH)_2$).

In the system M^{2+}–**6**, the complexation starts in strongly acidic region by formation of the $[M(HL)]^{2+}$ species, being low-abundant in the case of copper(II) (up to 20% at $-\log[H^+]$ ~2.5) but prevailing in Zn^{2+}–**6** system (up to ~90% at $-\log[H^+]$ ~4.5). On the basis of comparison of the pK_a values of the uncoordinated ligands and the complexes it seems reasonable that the first complexation step involves coordination of the phosphinate oxygen atom and at least one nitrogen atom of the macrocyclic ring (most probably the N8 atom bearing the methylphosphinate group) with the additional proton being attached to the piperazine ring N1 atom. This species transforms at higher $-\log[H^+]$ values to the $[M(L)]^+$ species, this being the major complex in the alkaline $-\log[H^+]$ region. For a complete set of distribution diagrams of the described systems see the ESI.†

Table 3 Protonation and dissociation constants of the investigated compounds determined in 0.1 M aq. KNO_3 at 25 °C

	3	**6**	**1**[a]	cyclam[b]	Me_4cyclam[bc]
$\log\beta_1$	11.35(8)	9.21(1)	—	—	—
$\log\beta_2$	19.61(1)	16.54(2)	—	—	—
$\log\beta_3$	—	18.13(4)	—	—	—
$\log\beta_4$	22.44(3)	18.9(1)	—	—	—
$pK_a(HL)$	11.36	9.21	12.54	11.4	9.36
$pK_a(H_2L)$	8.25	7.33	9.42	10.28	9.02
$pK_a(H_3L)$	—	1.59	0.73	1.6	2.54
$pK_a(H_4L)$	2.83[d]	0.8	—	2.1	2.25

[a] Data for **1** taken from ref. 15. [b] Data for cyclam and Me_4cyclam were taken from ref. 25. [c] Me_4cyclam = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane. [d] $pK_a(H_3L) + pK_a(H_4L)$.

When comparing to the copper(II) and zinc(II) complexes of cyclam and Me_4cyclam, respectively, the ligands **3** and **6** form complexes with a lower thermodynamic stability. The stability of complexes of the investigated compounds is significantly lower than the stability of the corresponding cyclam complexes (*e.g.* ~12 orders of magnitude for Cu(II) and ~7 orders of magnitude for the Zn(II) complex of **3**). On the other hand, comparison of Cu^{II} complex **3** stability constant (15.5) with the stability constant of [Cu(**1**)] (26.1)[15] shows the same trends in the values as in the case of Cu^{II} complexes of cyclam (28.1) and Me_4cyclam (18.3), respectively (a difference of approx. 10 orders of magnitude). The difference could be ascribed probably to lower basicity of **3** compared to **1** as an effect of presence of an additional substituent (*p*-nitrobenzyl group). Unfortunately, no data for a similar Zn^{II} complex are available.

The lower stability constant ratio ($\log\beta_{Cu} - \log\beta_{Zn}$) observed for the complexes of **6** (~3.2) over the similar complexes of Me_4cyclam (~7.9) could be ascribed to the

Table 4 Stability constants of copper(II) and zinc(II) complexes[a]

Equilibrium[b]	$\log\beta_{hlm}$	**1**[c]	**3**		**6**		Cyclam[d]		Me_4cyclam[d]	
		Cu^{2+}	Cu^{2+}	Zn^{2+}	Cu^{2+}	Zn^{2+}	Cu^{2+}	Zn^{2+}	Cu^{2+}	Zn^{2+}
M + L ⇌ ML	$\log\beta_{011}$	26.1	15.50(5)	8.5(1)	14.71(3)	11.53(9)	28.1	15.2	18.3	10.4
H + L + M ⇌ HML	$\log\beta_{111}$	—	—	—	16.81(9)	16.94(5)	—	—	—	—
HML ⇌ ML + H	pK_a	—	—	—	2.10	5.41	—	—	—	—

[a] Determined in 0.1 M KNO_3 at 25 °C. [b] Charges of the species are omitted for clarity. [c] Data for **1** were taken from ref. 15. [d] Data for cyclam and Me_4cyclam were taken from ref. 25.

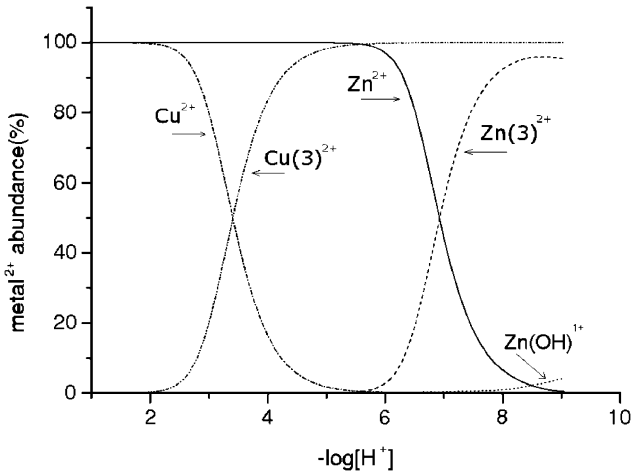


Fig. 5 Projection of species distributions in the Cu^{2+}–**3** and Zn^{2+}–**3** systems (0.1 M KNO_3, 25 °C, $c_M = c_L = 0.004$ M).

stabilizing effect of the hard phosphinate group present in ligand **6** for the zinc(II) complex formation.

Experimental

General

The analytical grade chemicals were purchased from Lachema (Czech Republic), Fluka, Sigma-Aldrich or Merck and were used as received. All the reactions were carried out under ambient atmosphere. Cyclam was prepared by a slightly modified literature procedure,[26] using glyoxal hydrate trimer and Raney-Nickel. Sulfonate cation exchange resin (Dowex 50, Fluka) and an anion exchange resin (Dowex 1, Fluka) were used for column chromatography.

Elemental analyses were conducted at the Institute of Macromolecular Chemistry of Academy of Sciences of the Czech Republic (Prague). Melting points were determined using a Kofler hot-stage apparatus (Boetius) and are uncorrected. NMR spectra were recorded on a Varian Unity Inova 400 spectrometer at 400.0 MHz for ^{1}H, 161.9 MHz for ^{31}P and 100.6 MHz for ^{13}C nuclei with internal references TMS for $CDCl_3$ solutions and *t*-BuOH for D_2O solutions, and external reference 85% H_3PO_4. The temperature (25 °C) was controlled by a VT-regulator, containing a thermocouple calibrated using MeOH and ethylene glycol according to a reported procedure.[27] Multiplicity of the signals is indicated as follows: s – singlet, d – doublet, t – triplet, q – quintet, m – multiplet, br – broad. The values of coupling constants (J) are given in Hz, chemical shifts (δ) are given in ppm. MS spectra were recorded on a Bruker Esquire 3000 spectrometer equipped with electrospray ion source and ion-trap detection in positive-ion mode.

Potentiometric measurements

The potentiometric titrations were carried out in a thermostated vessel at 25.0 ± 0.1 °C, at constant ionic strength $I(KNO_3) = 0.1$ mol dm^{-3}, using a PHM 240 pH-meter, a 2 ml ABU 900 automatic piston burette and a GK 2401B combined glass electrode (Radiometer). The ligand concentration in the titration vessel was *ca.* 0.004 mol dm^{-3}. The ligand-to-metal ratio was 1 : 1 in all cases. The initial volume was *ca.* 5 ml (in the protonation constants determination experiments) or *ca.* 1 ml (in the out-of-cell experiments involving metal complexes, see below). The measurements were taken with a HNO_3 excess added to the mixture to ensure a low starting pH value. The mixtures were titrated with the stock KOH solution (~0.2 M) in the region of $-\log[H^+] = 1.6$–12.0. Titrations for each system were carried out at least four times. Each titration consisted of *ca.* 40 points (protonation constants) or 25 points (metal complexation). Inert atmosphere was provided by constant passage of argon saturated with water vapour. The metal complexation reactions were too slow to be followed by standard titrations, thus the systems were studied by the 'out-of-cell' method. Each solution was mixed separately in the test tube and an appropriate amount of the KOH solution was added to each of the test tubes to simulate the common titration. The tubes were tightly closed and left to equilibrate for four days at ambient temperature (the amount of added KOH solution and equilibration times were determined in separate preliminary experiments). The amount of HX (X = Cl, Br) present in the ligand stock solutions was determined gravimetrically in form of AgX.

The constants with their standard deviations were calculated using the OPIUM program package.[28] The program minimises the criterion of the generalized least-squares method using the calibration function given in eqn (1).

$$E = E_0 + S\log[H^+] + j_1[H^+] + j_2K_w/[H^+] \qquad (1)$$

The term E_0 contains the standard potentials of the electrodes used and the contributions of inert ions to the liquid-junction potential. The term S corresponds to the Nernstian slope and the terms $j_1[H^+]$ and $j_2K_w/[H^+] = j_2[OH^-]$ are contributions of the H^+ and OH^- ions to the liquid-junction potential. The calibration parameters were determined from titration of the standard HNO_3 with the standard KOH solution before and after each titration of the ligand/metal ion system to give calibration–titration pairs used for calculations of the stability constants. The concentration stability constants are $\beta_{hlm} = [H_hL_lM_m]/([H]^h[L]^l[M]^m)$. The water ion product pK_w taken for calculations was 13.78. Stability constants of metal hydroxo complexes included in the calculations were taken from literature.[25]

Crystallography

The diffraction data were collected using a Nonius Kappa CCD diffractometer (Enraf-Nonius) at 150(1) K using Mo-Kα radiation ($\lambda = 0.71073$ Å) and analysed using the HKL program package.[29] The structures were solved using direct methods and refined by full-matrix least-squares techniques (SIR92[30] and SHELXL97).[31] Scattering factors for neutral atoms were included in the SHELXL97 program. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located in the electron density difference map; however they were fixed in theoretical or their original positions with thermal parameters $U_{eq}(H) = 1.2U_{eq}(C)$ or $1.3U_{eq}(N)$, as the free refinement led to several unreal bond lengths and to extreme increase of number of refined parameters. In the structure of $\mathbf{4}^{Br}\cdot 2.5H_2O$, solvate water molecules

were best refined in three positions, two of them fully and the last one half-occupied. Thermal ellipsoids of some oxygen atoms were very prolate, however, trials to refine these atoms in several positions did not improve the final fit. The hydrogen atoms attached to the solvate molecules could not be localized on the difference Fourier map. Crystal data quality of [Cu(**3**)Br][PF_6] was very low due to high mosaicity of the crystal. Trials for data correction for absorption lead to worsening of the *R*-factor, therefore, the refinement was done with uncorrected data.

Crystal data for 4^{Br}·2.5H_2O. $C_{21}H_{39}N_5O_{6.5}Br$, M_r = 545.28; colourless prism, monoclinic, space group *C*2/*c*, *a* = 19.4788(4), *b* = 19.7272(4), *c* = 13.7214(3), *β* = 97.7160(11)°, *V* = 5224.88(19) Å^3, *Z* = 8, D_c = 1.387 g cm^{-3}, θ_{max} = 27.50°, *μ*(Mo-K*α*) = 1.619 mm^{-1}, *T* = 150 K.

Crystal data for [Cu(3)Br][PF_6]. $C_{19}H_{31}CuN_5O_2BrF_6P$, M_r = 649.91; blue plate, triclinic, space group $P\bar{1}$, *a* = 6.9960(4), *b* = 10.2570(8), *c* = 17.8780(15) Å, *α* = 73.592(3), *β* = 84.539(5), *γ* = 80.636(4)°, *V* = 1212.60(16) Å^3, *Z* = 2, D_c = 1.780 g cm^{-3}, θ_{max} = 27.47°, *μ*(Mo-K*α*) = 2.688 mm^{-1}, *T* = 150 K.

CCDC reference numbers 652360 and 652361. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b709747f

Syntheses

Perhydro-3a,5a,8a,10a-tetraazapyrene. This compound was prepared using the reported procedure,[9] modified in the following manner: in a 50 ml flask, glyoxal trimer dihydrate (1.8 g, 8.6 mmol) was mixed with distilled water (20 ml) and heated to approximately 80 °C (until all solids dissolved). The solution was cooled to ~60 °C and diluted by methanol (20 ml). In a separate 500 ml flask, cyclam (5 g, 25 mmol) was dissolved in methanol (200 ml) and cooled using an ice-bath to ~3 °C. To this solution was added the above-prepared solution of glyoxal in a dropwise manner in ~30 min. The cooling bath was removed after complete addition and the resulting mixture was further stirred at ambient temperature for 2 h. The solvents were evaporated and 50 ml of acetonitrile were added to the mixture to precipitate the unreacted cyclam. The precipitate was filtered off and the solvent evaporated do give a slightly yellow oil, which was used without any further purification. Yield 4.9 g (87%, based on cyclam).

ESI-MS: *m*/*z* 223.2 (M + H$^+$), 245.2 (M + Na$^+$).

Perhydro-3a-(4-nitrobenzyl)-3a,5a,8a,10a-tetraazapyrenium bromide (2^{Br}). The oil prepared in the previous step was dissolved in anhydrous acetonitrile (25 ml) and 4-nitrobenzyl bromide (6 g, 27.8 mmol) was added to the solution. The mixture became cloudy after approximately 60 min of stirring and was further stirred for 48 h. The resulting light yellow precipitate was filtered off, washed with 10 ml of acetonitrile and 10 ml of methylene dichloride and dried *in vacuo* to give the product in form of a yellowish powder (9.1 g, quant. 84% based on cyclam); mp 189–190 °C; ^{1}H NMR (D_2O): *δ* 1.4 (br d, *J* = 13.99, 1H), 1.75 (br d, *J* = 14.33, 1H), 2.15 (qt, 2H), 2.29 (td, *J* = 13.6 and 4, 2 H), 2.4–2.5 (m, 2H), 2.61 (td, *J* = 12.2 and, 1H), 2.9–3.15 (m, 7H), 3.23 (td, *J* = 13.6 and 2.8, 1H), 3.31 (br d, *J* = 11.6, 1H), 3.45 (td, *J* = 13.6 and 4, 1H), 3.57 (td, *J* = 13.6 and 3.6, 1H), 3.70 (br s, 1H, C*H*), 4.19 (td, *J* = 14 and 4, 1 H), 4.32 (d, 1H, *J* = 1.6, C*H*), 4.81 and 5.23 (AB, *J* = 13.2, 2H, CH_2Ar), 7.75 (d, *J* = 8.8, 2H, Ar*H*), 8.27 (d, *J* = 8.8, 2H, Ar*H*); ^{13}C{^{1}H} NMR (D_2O): *δ* 18.0, 18.4, 41.9, 46.6, 48.6, 51.3, 51.9, 53.3, 53.9, 60.3, 61.1, 69.5, 82.6, 124.2, 132.8, 134.6, 149.0; ESI-MS: *m*/*z* 358.3 (M$^+$).

5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (3). Perhydro-3a-(4-nitrobenzyl)-3a,5a,8a,10a-tetraazapyrenium bromide (2^{Br}) (1 g, 2.3 mmol) was dissolved in an EtOH/H_2O mixture (30 ml EtOH + 5 ml H_2O) at ambient temperature. To the stirred solution sodium borohydride (0.3 g, 8 mmol) was added and the mixture was stirred at ambient temperature overnight. The reaction was quenched by careful addition of 10% aq. HCl (5 ml) and the solvents were evaporated. The remaining solid was dissolved in distilled water (30 ml) and the pH of the solution adjusted to ~13 by KOH. The mixture was extracted by benzene (3 × 25 ml), the organic phases were collected and dried over Na_2SO_4 and evaporated to yield an yellow oil, which was used in next reaction step without further purification (0.79 g, 96%). ^{1}H NMR ($CDCl_3$): *δ* 1.69 (q, *J* = 4.8, 2H, –$CH_2CH_2CH_2$–), 1.76 (q, *J* = 4.8, 2H, –$CH_2CH_2CH_2$–), 2.26 (ddd, 2H), 2.53 (t, 2H), 2.55–2.70 (m, 10H), 2.90 (t, *J* = 4, 2H, –$CH_2CH_2CH_2$–), 3.02 (ddd, 2H), 3.18 (ddd, 2H), 3.71 (s, 2H, –CH_2Ar), 7.47–7.50 and 8.16–8.20 (AA′BB′, 2H each, Ar*H*); ^{13}C{^{1}H} NMR ($CDCl_3$): *δ* 23.63, 26.10, 48.09, 48.33, 50.10, 51.22, 54.65, 54.79, 55.70, 56.95, 57.58, 123.29, 129.70, 146.89, 147.02 (for the complete signal assignment see ESI†); ESI-MS: *m*/*z* 362.4 (M + H$^+$).

The yellow oil was dissolved in 49% aq. HBr (5 ml). The solution was left in a glass desiccator filled with acetone. On vapour diffusion over several days, light yellow needles of the hydrate of hydrobromide salt of **3** precipitated out of the solution. The product was filtered off, washed with acetone and air-dried to yield yellowish needles of the product (1.20 g, 76%). mp = 182–184 °C. Found: C 27.20, H 5.30, N 8.31. Calc. for $C_{19}H_{31}N_5O_2$·5HBr·4H_2O: C 27.23, H 5.29, N 8.36%. ^{1}H NMR (D_2O): *δ* 1.9–2.2 (br m, 4H), 2.7–3.1 (br m, 8H), 3.2–3.7 (br m, 12H), 4.1 (br, 2H), 7.48 (d, *J* = 8.8, 2H, Ar*H*), 2.20 (d, *J* = 8.8, 2H, Ar*H*); ^{13}C{^{1}H} NMR (D_2O): *δ* 23.24, 25.78, 47.69, 48.02, 49.67, 50.92, 54.20, 54.36, 55.33, 56.57, 57.16, 122.87, 129.3, 146.53. 146.60; ESI-MS *m*/*z* 362.4 (M + H$^+$).

Attempted syntheses of 4a resulting in preparation of 5^{Br}. To the yellow oil prepared from 2 g of 2^{Br} as described above dissolved in acetonitrile (50 ml), 1 equiv. of a base (0.5 g of Et_3N, 0.6 g of DIPEA or 0.7 g of K_2CO_3) was added. To the mixture 1 equiv. of the alkylating agent (0.8 g of ethyl bromoacetate or 0.9 g of *tert*-butyl bromoacetate, respectively) was slowly added and the mixture was stirred overnight at ambient temperature. The resulting solution was evaporated (in the case of K_2CO_3 after filtration of the solids) and the resulting ester was hydrolysed (stirring the ethyl ester under reflux in 6 M aq. HCl or the *tert*-butyl ester at ambient temperature with trifluoroacetic acid–methylene dichloride

(1 : 1) overnight). The mixture was evaporated yielding an yellow oil, which was dissolved in ~5 ml of 49% aq. HBr. On addition of several drops of distilled water the product began to crystallise within 1 min and the mixture was left for crystallisation for further 5 min. The resulting crystalline material was filtered off, washed with cold ethanol (10 ml) and acetone (10 ml) and air-dried to yield off-white microcrystalline product **5^{Br}** (4.2 g, quantitative, based on the amount of added alkylating agent).

Mp = 171–172 °C. Found: C 32.33, H 5.28, N 7.89, Br 35.87. Calc. for $C_{23}H_{36}N_5O_6Br{\cdot}3HBr{\cdot}3H_2O$: C 32.30, H 5.30, N 8.19, Br 37.37%. ^{1}H NMR (D_2O): δ 2.26 (m, 2H, –CH_2CH_2CH$_2$–), 2.4 (m, 2H, –$CH_2CH_2CH_2$–), 3.2–3.41 (m, 8H), 3.63 (t, J = 5.2, 2H), 3.76–3.96 (m, 6H), 4.15 (t, J = 6.8, 2H), 4.20–4.32 (m, 4H), 4.44 (s, 1H), 4.46 (s, 1H), 7.73 (d, J = 8.8, 2H, Ar*H*), 8.33 (d, J = 8.8, 2H, Ar*H*); ^{13}C{^{1}H} NMR (D_2O): δ 20.04, 22.02, 45.88, 52.26, 52.74, 54.22, 55.12, 56.14, 56.32, 57.20, 58.86, 63.17, 126.61, 134.93, 139.1, 151.2, 168.2, 176.8; ESI-MS m/z 477.8 (M + H$^+$), 500 (M – H + Na$^+$).

1-Carboxymethyl-5-(4-nitrobenzyl)-5,8,12-triaza-1-azoniabicyclo[10.2.2]hexadecane bromide (4^{Br}). 5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane prepared from 2 g of **2^{Br}** as described above, was dissolved in diethyl ether (50 ml). Bromoacetic acid (0.3 g, 2.1 mmol, ~0.45 eq) solution in diethyl ether (10 ml) was then added in a dropwise manner to the macrocycle solution at ambient temperature with vigorous stirring. Immediately on mixing of the reagents a slightly yellow precipitate appears in the reaction mixture. After the complete addition of the alkylating agent the mixture was stirred for further 60 min, the liquid phase was decanted and the remaining solid was air-dried. The crude product was dissolved in an EtOH–H_2O mixture (5 ml, 1 : 1) and the solution carefully covered with a large amount of acetone. After 48 h of standing a drop of deep yellow oil separated on the bottom of the flask and some yellow crystals precipitated on the walls of the flask. The crystals were carefully separated, washed with acetone and air-dried, yielding 0.43 g of the product (19%, ~95% purity according to NMR measurements). 100 mg of the product were dissolved in hot distilled water in a NMR tube. On slow cooling to room temperature yellow crystals suitable for the single-crystal X-ray analysis appeared on the walls of the tube.

The oily substance remaining after isolation of the first batch of the product was dissolved in 4 M ethanolic HBr solution (10 ml). The solvents were evaporated under vacuum yielding the product in form of hydrobromide hydrate as a light yellow powder (1.06 g, overall yield ~50%) with purity similar to the first batch of crystals.

Mp = 186–190 °C. Found: C 31.22, H 5.40, N 8.44, Br 37.24. Calc. for $C_{21}H_{33}N_5O_4Br{\cdot}3HBr{\cdot}3.5H_2O$: C 31.29 , H 5.50, N 8.64, Br 39.65%. ^{1}H NMR (D_2O): δ 1.98 (q, 2H, –CH_2CH_2CH$_2$–), 2.05 (q, 2H, –$CH_2CH_2CH_2$–), 2.70–2.98 (m, 8H), 3.20–3.28 (m, 4H), 3.34 (t, J = 5.2, 2H), 3.39 (t, J = 5.3, 2H), 3.80–3.88 (br m, 4H), 3.90 (s, 2H), 4.15 (s, 2H), 7.53 (d, J = 8.8, 2H, Ar*H*), 8.26 (d, J = 8.8, 2H, Ar*H*); ^{13}C{^{1}H} NMR (D_2O): δ 20.69, 21.67, 45.51, 49.36, 50.79, 52.07, 54.82, 55.39, 55.52, 61.96, 63.74, 123.79, 131.17, 143.59, 147.18, 168.72; ESI-MS m/z 420.0 (M + H$^+$), 442.0 (M + Na$^+$).

[5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadec-8-yl]methylphosphinic acid (6). 5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (**3**), prepared from 2 g of **2^{Br}** as described above, was dissolved in 5 M aq. HCl (10 ml). To the stirred mixture paraformaldehyde (0.35 g, 12 mmol) and solid phosphinic acid (1.5 g, 23 mmol) were added and the suspension was stirred and heated to ~35 °C for 72 h. The resulting solution was evaporated *in vacuo* (with the water-bath temperature not exceeding 40 °C), dissolved in distilled water (5 ml) and chromatographed using cation-exchanging resin (Dowex 50 in H$^+$ form, elution H_2O, followed by 5% aq. ammonia). The ammonia eluate was evaporated, the residue dissolved in water and re-chromatographed using an anion-exchanging resin (Dowex 1 in OH$^-$ form, elution H_2O followed by 10% acetic acid). The acidic eluate was evaporated, the residue dissolved in mixture of ethanol (5 ml) and conc. aq. HCl (1 ml). Acetone (100 ml) was added to the solution to precipitate the product in form of a hydrochloride salt, which was filtered after overnight standing at ambient temperature (transformation of the amorphous precipitate to a microcrystalline powder) and dried under vacuum to yield 0.86 g of an off-white powder (27% based on **2^{Br}**).

Found: C 39.73, H 6.53, N 11.32, Cl 22.09. Calc. for $C_{20}H_{34}N_4O_5P{\cdot}4HCl{\cdot}H_2O$: C 39.81, H 6.68, N 11.61, Cl 25.63%. ^{1}H NMR (D_2O): δ 2.05 (br, 2H, –CH_2CH_2CH$_2$–), 2.20 (br, 2H, –$CH_2CH_2CH_2$–), 2.60–3.85 (br m, 18H), 4.40 (s, 2H, –CH_2Ar), 6.92 (d, J = 522, 1H, P–*H*), 7.70 (d, J = 8.8, 2H, Ar*H*), 8.20 (d, J = 8.8, 2H, Ar*H*); ^{31}P NMR (D_2O): δ 26.2 (d, J = 522, *P*–H); ESI-MS m/z 439.9 (M + H$^+$).

[5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadec-8-yl]methylphosphonic acid (7). 5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (**3**), prepared from 2 g of **2^{Br}** as described above, was dissolved in triethyl phosphite (10 ml) and paraformaldehyde (0.3 g, 10 mmol) was added. The heterogeneous mixture was warmed to 50 °C and stirred at this temperature for 72 h. The solution was cooled to ambient temperature and chromatographed using cation-exchanging resin (Dowex 50 in H$^+$-form, elution H_2O–ethanol 1 : 1, H_2O followed by conc. aq. NH_3–ethanol 1 : 1). The ammonia eluate was evaporated *in vacuo* to produce a diethyl ester of **7** as a yellow oil (ESI-MS m/z 512.3 (M + H$^+$). The crude ester was dissolved in 5 M aq. HCl (30 ml) and refluxed for 24 h. The solvent was evaporated, the residue dissolved in 49% aq. HBr (2 ml) and precipitated by addition of acetone (100 ml). On standing for 48 h the amorphous solid became more compact and was filtered off, washed with acetone (20 ml) and dried under vacuum to yield the product (0.31 g, 12% of expected amount based on **2**) in form of hydrobromide hydrate as a light yellow powder.

Mp = 179–180 °C. Found: C 30.23, H 5.19; N 8.45, Br 39.74. Calc. for $C_{20}H_{33}N_5O_4P{\cdot}4HBr{\cdot}2H_2O$: C 30.10, H 5.18, N 8.77, Br 42.66%; ^{1}H NMR (D_2O): δ 2.1–2.45 (m, 4H, –CH_2CH_2CH$_2$–), 2.75–4.15 (br m, 18H), 4.52 (s, 2H, –CH_2Ar), 7.83 (d, J = 8.8, 2H, Ar*H*), 8.36 (d, J = 8.8, 2H, Ar*H*); ^{31}P NMR (D_2O): δ 22.62 (s, pD ~1), 18.69 (s, pD ~13, NaOD); ^{13}C{^{1}H} NMR (D_2O, pD ~13): δ 21.7, 21.9, 44.0, 44.4, 47.5, 47.9, 50.1, 50.4, 51.1, 51.9, 53.8, 58.0, 123.5, 130.9, 145.4, 146.9; ESI-MS m/z = 455.8 (M + H$^+$).

Preparation of [Cu(3)Br][PF_6]. 5-(4-Nitrobenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (100 mg, 0.1 mmol) in the form of the HBr adduct prepared as described above, was dissolved in distilled water (1 ml). $CuCl_2{\cdot}2H_2O$ (21 mg, 0.1 mmol) was dissolved in another 1 ml of distilled water and this solution was added to the solution of ligand **3**. The violet-blue solution was refluxed for 10 min and an ethanolic solution of NH_4PF_6 (20 mg in 1 ml of EtOH) was added. The final solution was concentrated under reduced pressure to precipitate the complex, which was filtered off, washed with H_2O (1 ml) and ethanol (1 ml) and air-dried to yield a deep violet powder of the complex (54 mg, 70%). This product was recrystallized from acetonitrile (1 ml) to form blue–violet single crystals suitable for X-ray structure determination.

Conclusions

Synthesis of a series of new compounds built on the 1,4-encyclam skeleton is reported. During the synthetic procedure an unexpected alkylation pathway of the mono-*p*-nitrobenzyl-substituted derivative was observed. The protonation constants of the ligands together with the thermodynamic stability constants of their copper(II) and zinc(II) complexes are surprisingly lower than expected for the constrained azamacrocycles. Formation of the metal complexes is relatively slow at room temperature, thus the pH-metric experiment cannot be followed by common procedure but only by using the out-of-cell method; however, these complexes should be of use for complexation of copper radioisotopes with life-times of the order of hours (^{64}Cu and ^{67}Cu). The thermodynamic stability constant of the Cu^{II} complex of **3** is approx. 10 orders of magnitude lower than the constants of the similar complex of ligand **1** (15.5 *vs.* 26.1). The difference is in good agreement with the constants observed for copper(II) complexes of cyclam and Me_4cyclam (28.1 *vs.* 18.3).

The solid-state structure of the [Cu(**3**)Br][PF_6] complex was also determined; the copper central atom is surrounded by the macrocycle and the bromine atom forming a coordination sphere which is intermediate between trigonal bipyramidal and square pyramidal.

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