Highly Substituted Cyclams: Stereoselective Synthesis and Coordination Properties

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We report here a new synthetic route to highly-substituted tetraazamacrocycles. Raney nickel hydrogenation of macrocyclic phenylenediamine–acetylacetone condensation products gives cyclams in high yield with complete *all-cis* stereoselectivity. The extensive C-substitution of the cyclam **2a** changes its ligand properties markedly. The X-ray structure analyses of Ni^{II}, Cu^{II}, and Zn^{II} complexes of **2a** reveal a deviation of the metal ion coordination geometry from the usual square-planar arrangement. This may account for the differences in the redox properties of the Ni^{II} and Cu^{II} complexes of **2a** compared to **3**. The highly-substituted structure of the ligand **2a** leads to more positive oxidation and reduction potentials compared to the analogous unsubstituted cyclam complexes. While the binding constant between $Zn(ClO_4)_2$ and **2a** is lower by a factor of 10^5 compared to cyclam, the subsequent binding of uridine to the zinc-cyclam complexes in methanol/water is slightly stronger in the case of **2a** · $Zn(ClO_4)_2$.[

Aza-crowns, such as 1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,8,11-tetraazacyclotetradecane (cyclam), are excellent ligands for metal ion complexation. The increasing interest in these compounds is fostered by the use of metal ions in various new medicinal concepts for diagnosis and therapy, such as magnetic resonance imaging[1] and radioimmunotherapy[2]. To reduce their toxicity and to adapt their physical properties to specific applications, a tight coordination of the metal ion with a functionalized ligand is necessary. In many cases aza-crowns and *N*-alkylated derivatives have been employed as effective metal ion binding sites since their transition metal complexes usually show very high thermodynamic and kinetic stability[3]. Whereas several practical methods for the selective *N*-alkylation of commercial aza-crowns are available[4], the synthesis of *C*-substituted derivatives remains difficult[5]. We report here a new, economic strategy for the synthesis of *C*-substituted cyclams.

A second important feature of aza-crown macrocycles is their use in anion recognition[6]. Protonated azamacrocycles can bind anions, such as azides[7], carboxylates[8], or phosphates[9]. The binding selectivity and strength depends largely on the size, conformation, and substitution of the host molecule. We report herein the influence of extensive *C*-substitution on the pK_a values, binding ability and complex properties of a cyclam macrocycle.

Results and Discussion

Ligand Synthesis

The chemistry of template-assisted phenylenediamine-1,3-dicarbonyl condensation reactions has been thoroughly investigated by Jäger[10] and others[11]. The parent system **1a** can be further functionalized by lithiation of the acidic methyl groups followed by the addition of an electrophile[12]. Treatment of **1a** with 1 equiv. of *n*BuLi in THF followed by an alkylation reagent results in a clean substitution of one methyl group (**1b–c**), whereas 2 or more equiv. of base and electrophile yield a 1:1 mixture of the 5′,12′- and 5′,14′-disubstituted products[13]. Hydrogenation of **1a–c** on Raney nickel[14] leads to fully saturated cyclam macrocycles. Reaction of **1a** with 15 MPa of H_2 in ethanol for 36 h at 100 °C affords **2a** in 74% isolated yield. Under these conditions, all hydrogens were added to the double bonds of the macrocycle from one side, resulting in the exclusive formation of the *all-cis-R,S,R,S* compound. At lower temperatures, hydrogenation of **1a** is not observed, while higher temperatures and increased H_2 pressure give rise to a loss of stereoselectivity and lower yields. The stereochemistry of the saturated product was confirmed by X-ray analysis[12a]. Although the detailed mechanism of the heterogeneous perhydrogenation remains uncertain, the central nickel(II) atom in **1a** seems to be important. Hydrogenation of the analogous metal-free macrocycle[11b,12b] under the same conditions gives a mixture of several partially hydrogenated products without a defined stereochemistry. The hydrogenation of the mono-substituted derivatives **1b–c** proceeds at slightly higher temperatures than that used in the case of the parent system[15]. Alkylation of the sterically hindered nitrogen atoms of **2a** with electrophiles, such as benzyl bromide, *N,N*-diethylchloroacetamide or ethyl bromoacetate, did not proceed under standard conditions[16].

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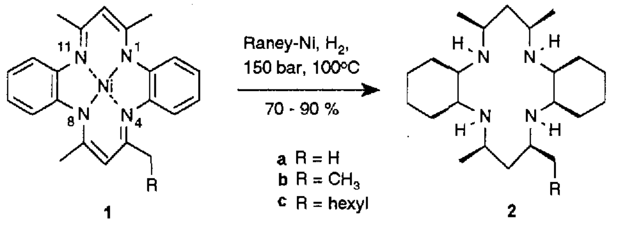
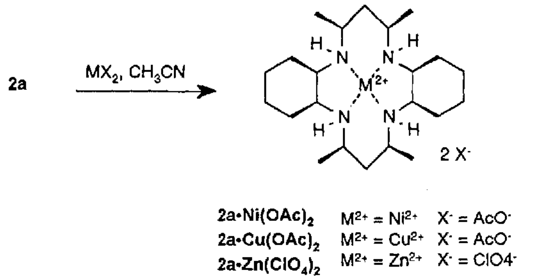
Scheme 1. Stereoselective hydrogenation of nickel macrocycles to cyclams



Metal Complexes

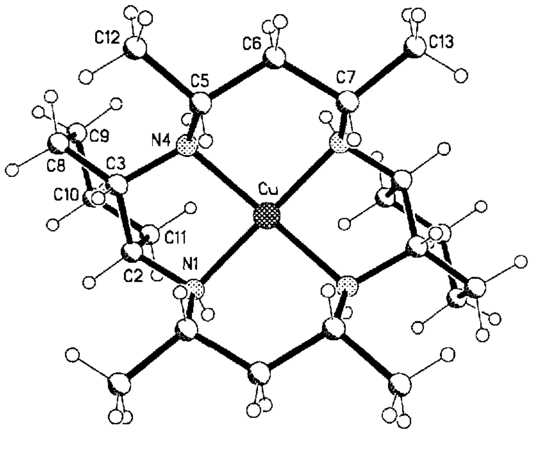
As expected, **2a** coordinates metal ions tightly. With $Ni(OAc)_2$ and $Cu(OAc)_2$ the corresponding complexes **2a** · $Ni(OAc)_2$ and **2a** · $Cu(OAc)_2$ were obtained from methanol solution at room temperature. For the preparation of the zinc perchlorate complex **2a** · $Zn(ClO_4)_2$ it was necessary to reflux the reaction mixture overnight.

Scheme 2. Cyclam metal complex formation



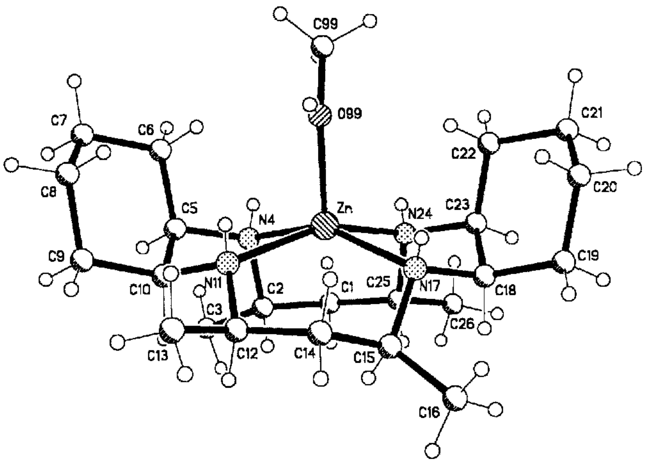
All complexes were characterized by X-ray analysis[17]. Figure 1 shows the structure of **2a** · $Cu(OAc)_2$ in the crystal. The molecule displays crystallographic twofold symmetry. As in the case of **2a** · $Ni(OAc)_2$, a distorted square planar coordination of the central copper ion is observed[18]. The copper-nitrogen distances of 195.9(2) pm for Cu–N(1) and 201.1(2) pm for Cu–N(4) and the N–Cu–N angles of 87.6(1)° and 93.1(1)° show the slight deviation of the coordination from the ideal square-planar geometry. The interplanar "twist" angle between N(1)–Cu–N(4) and N(1')–Cu–N(4') is 17.8°. Neither the acetate ion nor the solvent of crystallization (two water and two toluene molecules per molecule of complex) coordinates to the metal.

Figure 1. Structure of [**2a** · $Cu(OAc)_2(H_2O)_2(toluene)_2$] in the solid state. Solvent molecules and counterions are omitted for clarity



The structure of the zinc complex **2a** · $Zn(ClO_4)_2$ (Figure 2), which was crystallized from methanol, shows that a methanol molecule is bound to the central zinc ion in the solid state. The zinc ion is coordinated by the four cyclam nitrogens with Zn–N 210.2–218.8(4) pm. The offset of the zinc ion from the best plane through all four nitrogen atoms is 45 pm. The methanol molecule is bound in the cavity of the two cyclohexane substituents with a zinc–oxygen distance of 207.3(4) pm.

Figure 2. Structure of [**2a** · $Zn(MeOH)(ClO_4)_2$] in the crystal. Counterions are omitted



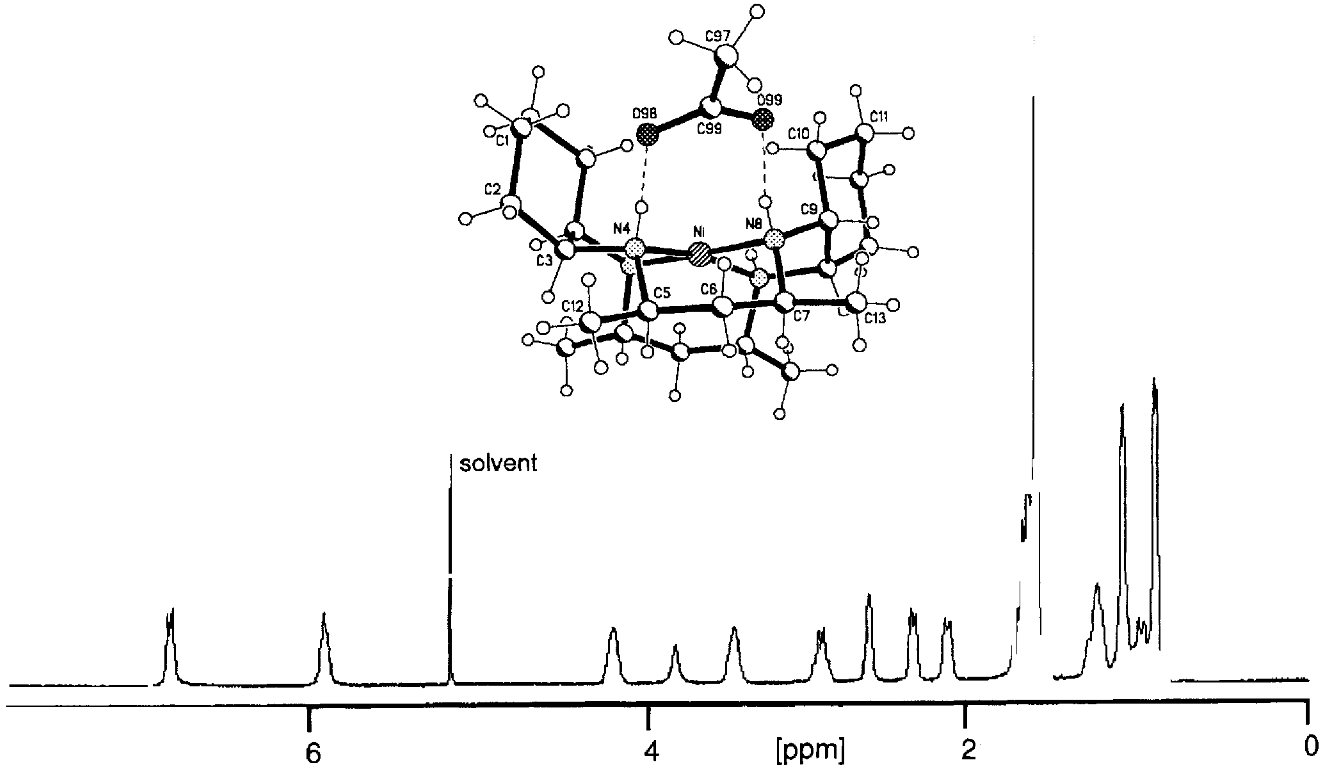
All cyclams **2a–c** and their metal complexes gave poorly resolved NMR spectra at room temperature due to restricted mobility on the NMR time scale caused by the extensive substitution[19]. However, spectra of higher resolution were obtained at −70 °C; whereas the proton NMR spectrum of **2a** remained complex because of superimposed coupling patterns, the simple ^{13}C-NMR spectrum revealed the expected ten signals. Figure 3 shows the ^{1}H-NMR spectrum of **2a** · $Ni(OAc)_2$ at −70 °C. As observed in the solid state by X-ray analysis[12a], one acetate counterion remains tightly bound to the N–H groups even in solution. As a result, the NMR spectrum shows two different signals for the free and the hydrogen-bonded N–H protons at $\delta = 6.0$ and $\delta = 7.0$, respectively.

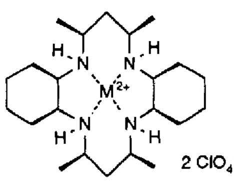
Electrochemical Measurements

Cyclic voltammograms of the nickel and copper complexes **2a** · $Ni(ClO_4)_2$, **2a** · $Cu(ClO_4)_2$, **3** · $Ni(ClO_4)_2$, and **3** · $Cu(ClO_4)_2$ were recorded to compare their redox properties. Table 1[20,21] summarizes the redox potentials.

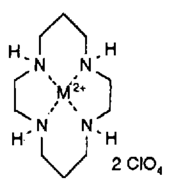
The nickel [**2a** · $Ni(ClO_4)_2$] and copper [**2a** · $Cu(ClO_4)_2$] complexes of **2a** show more positive reduction and oxidation potentials compared to the cyclam complexes **3** · $Ni(ClO_4)_2$ and **3** · $Cu(ClO_4)_2$. The reduction of Ni^{II} to Ni^{I} in **2a** · $Ni(ClO_4)_2$ was found at a potential nearly 600 mV more positive than in **3** · $Ni(ClO_4)_2$. The oxidation of **2a** · $Ni(ClO_4)_2$ to a Ni^{III} species, as in the case of **3** · $Ni(ClO_4)_2$, was not observed within the limits of the experiment. With compound **2a** · $Ni(ClO_4)_2$ an irreversible reduction to Ni^{0} occurs at −2.05 V vs. Ag/AgCl[22]. The copper complexes show a similar trend: the reduction of Cu^{II} to Cu^{I} in **2a** ·

Figure 3. ^{1}H NMR spectra (CH_2Cl_2, 400 MHz) of **2a** · $Ni(OAc)_2$ at −70 °C





2a·Ni(ClO$_4$)$_2$ $M^{2+} = Ni^{2+}$
2a·Cu(ClO$_4$)$_2$ $M^{2+} = Cu^{2+}$



3 free ligand
3·Ni(ClO$_4$)$_2$ $M^{2+} = Ni^{2+}$
3·Cu(ClO$_4$)$_2$ $M^{2+} = Cu^{2+}$

Table 1. Redox potentials[a] of the Ni^{II}- and Cu^{II}-complexes of **2a** and cyclam (**3**)

Compound	M^+/M^0 E_D [V]	M^+/M^{2+} $E_{1/2}$ [V]	M^{2+}/M^{3+} $E_{1/2}$ [V]
2a · $Ni(ClO_4)_2$	−2.05	−1.11	–
3 · $Ni(ClO_4)_2$[20]	–	−1.70	+0.67
2a · $Cu(ClO_4)_2$	−1.58	−0.46	+1.82
3 · $Cu(ClO_4)_2$[21]	−1.17	−0.93	+1.52

[a] Potentials were measured at an analyte concentration of 5×10^{-4} mol/l in 0.1 M Bu_4PF_6 acetonitril solution; scan rate 100 mV/s. All potentials vs. Ag/AgCl in LiCl sat. ethanol; the ferrocene/ferrocenium redox potential is at +0.53 V under these conditions[22].

$Cu(ClO_4)_2$ takes place at a potential 470 mV more positive than in the cyclam complex **3** · $Cu(ClO_4)_2$. The potential necessary for the oxidation to the cyclam Cu^{III} species is 300 mV more positive for **2a** · $Cu(ClO_4)_2$ than for **3** · $Cu(ClO_4)_2$. A possible rationale for the difference in the redox potentials of metal complexes of **2a** and cyclam (**3**) can be derived from their coordination geometries. The strong, square-planar coordination of the cyclam ligand increases the energy of the metal $d_{x^2-y^2}$ orbital and, to a lesser extent, that of the d_{xy} orbital. The coordinated metal ion is therefore more difficult to reduce, but more easily oxidized than the free metal ion. The X-ray structure analyses show a significant deviation of the coordinated metal ion in **2a** from an ideal, square-planar geometry. If this geometry is retained in solution, it will reduce the energy of the $d_{x^2-y^2}$ orbital, leading to a more positive reduction and an increased oxidation potential.

Figure 4 shows the quasi-reversible reduction of **2a** · $Cu(ClO_4)_2$ to the Cu^I complex and the irreversible reduction and deposition of Cu^0. The oxidation current at +0.2 V corresponds to the anodic dissolution of the deposited copper layer.

Potentiometric Titrations[23]

To investigate the influence of the highly-substituted structure of **2a** on its binding abilities, the pK_a values, the binding constant of Zn^{2+} ions and the binding constant of water to the complexed metal ion were determined by potentiometric titration and compared to the corresponding data for the parent macrocycle **3**. The limited solubility of **2a** in water necessitated the use of 95:5 methanol/water as solvent. All titrations were performed at 20 °C at an ionic strength of I = 0.1 mol/l tetraethylammonium perchlorate (TEAP).

Figure 4. Cyclic voltammogram of **2a** · $Cu(ClO_4)_2$. For conditions see Table 1

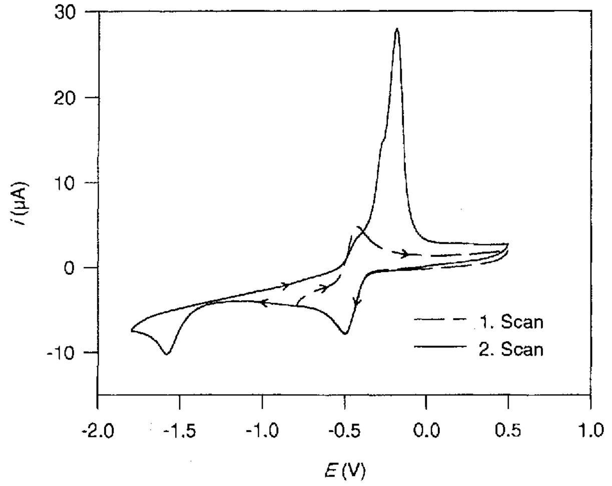
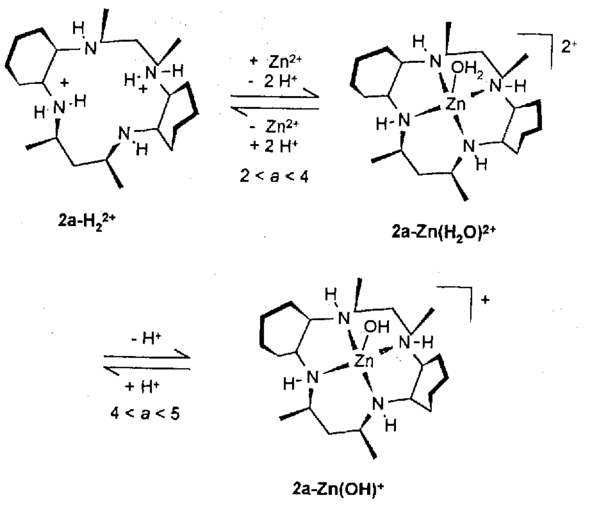


Table 2 summarizes the pK_a values and binding constants of **2a** and cyclam (**3**). The pH titration of **2a** with and without $Zn(ClO_4)_2 \cdot 6\ H_2O$ is shown in Figure 5. The pK_a values of cyclam and **2a** are of the same order of magnitude. The pH titration reveals that **2a**H_4^{4+} has two very acidic and two less acidic protons, as is found in the parent system. The binding constant of **2a** · $Zn(H_2O)^{2+}$, however, was determined to be five orders of magnitude smaller than that of **3** · $Zn(H_2O)^{2+}$. Increased steric hindrance and restricted flexibility of ligand **2a** may explain this result[24].

Scheme 3. Zinc complex formation of **2a**



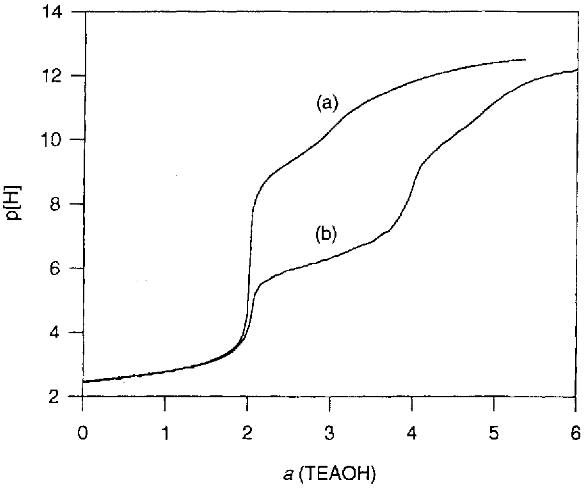
The pK_a values of the bound water molecules in **3** · $Zn(H_2O)^{2+}$ and **2a** · $Zn(H_2O)^{2+}$ are indicative of the Lewis acidity of the coordinated zinc(II) ion. In the case of zinc cyclen complexes, this has been utilized to bind nucleosides in aqueous solution[25]. We have measured the binding of the nucleoside uridine to **3** · $Zn(H_2O)^{2+}$ and **2a** · $Zn(H_2O)^{2+}$ in order to investigate the influence of the extensive substitution in **2a** on binding strength and structure of the supramolecular assembly.

Table 2. pK_a values, binding constant of Zn^{2+} and complex bound water of **2a** and **3**[a]

	2a	**3**
log K_1	11.67(4)[b]	11.37(3)
log K_2	9.29(7)	10.16(4)
log K_3	2.0(3)	2.0(1)
log K_4	2.0(2)	2.0(1)
log K_{ZnL}[c]	11.37(6)	15.13(4)
pK_a	9.83(6)	10.82(8)

[a] All values for 95% methanol/water at I = 0.1 mol/l tetraethylammonium perchlorate. – [b] The uncertainty of the last digit is given in brackets. – [c] binding constant of $Zn(H_2O)^{2+}$ to **2a** resp. **3**.

Figure 5. pH-Titration of **2a** in the absence (a) and presence (b) of $Zn(ClO_4)_2$



Scheme 4. Uridine binding to [**3** · $Zn(ClO_4)_2$] and [**2a** · $Zn(ClO_4)_2$]

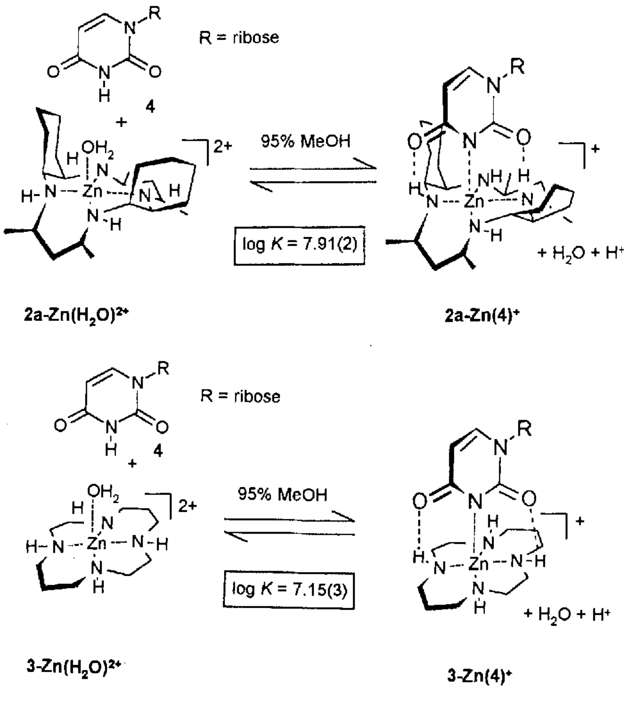
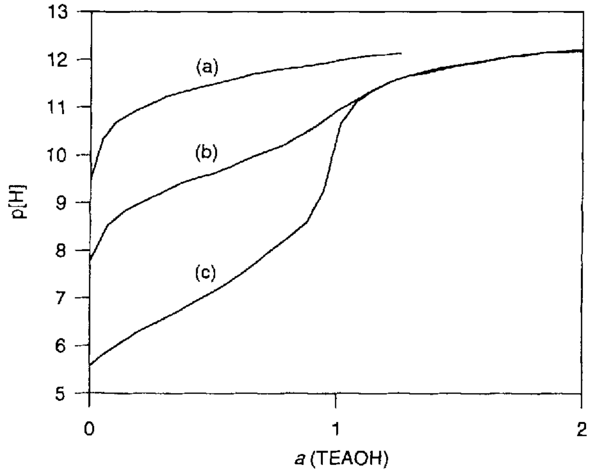


Figure 6. pH-Titration curve for [**2a** · $Zn(ClO_4)_2$]-uridine binding. (a) 2 × 10^{-3} M uridine, (b) 2 × 10^{-3} M [**2a** · $Zn(ClO_4)_2$], (c) 2 × 10^{-3} M uridine and 2 × 10^{-3} M [**2a** · $Zn(ClO_4)_2$]



All measurements were performed in 95% methanol/water, at 20°C and I = 0.1 mol/l (TEAP)[26]. The binding constant of uridine to **3** · $Zn(H_2O)^{2+}$ was determined as $\log K = 7.15(3)$, whereas the value for **2a** · $Zn(H_2O)^{2+}$ was slightly higher at $\log K = 7.91(2)$. The binding of uridine is essentially complete at pH = 8. The slightly different properties exhibited by the two compounds can be explained in terms of an enhanced Lewis acidity of the zinc ion when coordinated by ligand **2a**. The distorted coordination geometry of the complex prevents optimal overlap of the nitrogen ligands with the metal ion orbitals. This might result in a lower electron density, and therefore a higher Lewis acidity, at the metal ion, in comparison with the zinc cyclam **3** · $Zn(H_2O)^{2+}$[27].

Conclusions

The heterogeneous Raney nickel hydrogenation of fully-conjugated macrocycles, such as **1a**, is an efficient route to highly-substituted cyclams. Metal complexes of the cyclam **2a** thus obtained show a distorted square-planar coordination geometry in the solid state. Their redox and binding properties in solution are significantly different from those of the parent cyclam complexes. The copper(II) and nickel(II) complexes of **2a** are easier to reduce and more difficult to oxidize than the analogous cyclam complexes. The binding constant of the zinc complex of **2a** was determined to be 5 orders of magnitude smaller than that of the cyclam zinc complex, whereas the Lewis acidity of the zinc ion is higher when coordinated by **2a**.The lipophilic character of **2a** and of its metal complexes, together with the fact that it is readily accessible, makes it a suitable ligand for many applications directed towards metal ion coordination.

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Experimental Section

General methods: Melting points were taken on a hot-plate microscope apparatus and are uncorrected. – NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C) in [D]chloroform solution, unless otherwise stated. The multiplicities of the ^{13}C signals were determined with the DEPT technique and are quoted as: (+) for CH_3 or CH, (–) for CH_2 and (C_{quat}) for quaternary carbons. – CC denotes column chromatography on silica gel. – 1,8-Dihydro-5,7,12,14-tetramethyldibenzo[*b,i*][1,4,8,11]tetraazacyclotetradeca-4,6,11,13-tetraene (**1a**) was synthesized according to ref.[11b].

5-Ethyl-7,12,14-trimethyldibenzo[1,4,8,11]tetraazacyclotetradecahexaenatonickel(II) (**1b**): To a solution of **1a** (2 g, 5 mmol) in 40 ml of dry THF at 0°C was added LDA (6 mmol in 10 ml THF). The mixture was stirred for 3 h, and then 0.37 ml (6 mmol) of MeI was added. The solvent was removed in vacuo, the solid residue was dissolved in CH_2Cl_2 (100 ml), washed with water (2 × 60 ml) and dried over K_2CO_3. The solvent was removed to yield 2 g (97%) of **1b** as a deep-green solid, m.p. 93°C. – IR (KBr): $\tilde{\nu}$ = 1463 cm^{-1}, 1400, 743. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 192 nm (4.583), 392 (4.456), 584 (3.664). – ^1H NMR: δ = 1.19 (t, $^3J(H,H)$ = 7.4 Hz, 3H), 2.07 (m, 6H), 2.10 (s, 3H), 2.44 (q, $^3J(H,H)$ = 7.3 Hz, 2H), 4.85 (s, 1H), 4.91 (s, 1H), 6.56 (m, 4H), 6.63 (m, 1H), 6.68 (m, 3H). – ^{13}C NMR: δ = 14.0 (+), 21.9 (+), 22.0 (+), 22.1 (+), 25.8 (–), 109.5 (+), 112.1 (+), 120.0 (+), 120.8 (+), 120.9 (+), 121.7 (+), 121.8 (+), 121.9 (+), 147.0 (C_{quat}), 147.1 (C_{quat}), 147.2 (C_{quat}), 147.3 (C_{quat}), 155.3 (C_{quat}), 155.4 (C_{quat}), 155.6 (C_{quat}). – MS (70 eV, EI); *m/z* (%): 414 (100) [M^+]; $C_{22}H_{22}N_4Ni$ (414.6): calcd. C 66.54, H 5.83, N 13.50; found C 66.47, H 5.85, N 13.37. – Mol. mass 414 (MS).

5-Heptyl-7,12,14-trimethyldibenzo[1,4,8,11]tetraazacyclotetradecahexaenatonickel(II) (**1c**): Following the procedure described above for **1b**, 5 g (12.5 mmol) of **1a** was deprotonated with 10 ml (15 mmol) of *n*BuLi (1.5 M) and treated with 1.8 ml (12.5 mmol) of 1-bromohexane. CC (CH_2Cl_2) afforded 5.8 g (96%) of **1c** (R_f = 0.7) as a dark-green solid, m.p. 110°C. – IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1}, 1462, 743. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 192 nm (4.647), 392 (4.551), 584 (3.773). – ^1H NMR: δ = 0.85 (m, 3H), 1.20 (m, 10H), 2.07 (bs, 9H), 2.40 (m, 2H), 4.78 (d, $J(H,H)$ = 2.0 Hz, 1H), 4.81 (d, $J(H,H)$ = 2.0 Hz, 1H), 6.60 (m, 8H). – ^{13}C NMR: δ = 14.0 (+), 21.8 (+), 21.9 (+), 22.0 (+), 22.5 (–), 28.9 (–), 29.5 (–), 29.6 (–), 31.7 (–), 32.8 (–), 110.1 (+), 111.1 (+), 120.1 (+), 120.8 (+), 121.7 (+), 121.8 (+), 147.2 (C_{quat}), 147.3 (C_{quat}), 155.3 (C_{quat}), 155.4 (C_{quat}), 160.4 (C_{quat}), 160.5 (C_{quat}). – MS (70 eV, EI), *m/z* (%): 484 (80) [M^+], 400 (100). – $C_{28}H_{34}N_4Ni$ (484.4): calcd. C 69.30, H 7.06, N 11.54; found C 69.33, H 7.15, N 11.29.

cis-2:9;9:10-Dicyclohexane-1,4,8,11-tetraazacyclotetradecane (**2a**): A mixture of **1a** (4.0 g, 10 mmol) and Raney nickel (6 g, 0.1 mol) in 500 ml of EtOH was hydrogenated for 36 h at 100°C and 15 MPa H_2 pressure. The catalyst was removed by filtration through Celite, the solvent was evaporated in vacuo and the oily residue was dissolved in CH_2Cl_2. Slow evaporation of the solvent gave large colourless crystals of **1a**; yield 3.1 g (74%), m.p. 60°C. – IR (KBr): $\tilde{\nu}$ = 3292 cm^{-1}, 2950, 1474, 761. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 192 nm (3.957), 250 (2.523). – ^1H NMR: δ = 0.98 (m, 14H), 1.38 (m, 22H), 2.68 (bs, 4H), 2.96 (bs, 4H). – ^{13}C NMR (CH_2Cl_2, –70°C): δ = 20.3 (+), 20.32 (–), 23.3 (+), 25.2 (–), 28.5 (–), 31.8 (–), 46.4 (–), 48.6 (+), 54.2 (+), 56.0 (+). – MS (70 eV, EI), *m/z* (%): 364 (26) [M^+], 125 (100). – $C_{22}H_{44}N_4$ (364.6): calcd. C 72.47, H 12.16, N 15.57; found C 72.20, H 12.06, N 15.41.

cis-2:3;9:10-Dicyclohexane[5,7,12,14]tetramethyl[1,4,8,11]-N,N,N,N-tetramethyl[1,4,8,11]tetraazacyclotetradecane (**2a**-Me): To a solution of 150 mg (0.4 mmol) **2a** in 15 ml of THF at 0°C, was added MeLi (2.7 ml, 4.1 mmol, 1.5 M) and the mixture was stirred for 1 h. Then, MeI (0.25 ml, 4.1 mmol) was added, the reaction mixture was stirred for a further 1 h, quenched with 75 ml of satd. aq. NH_4Cl solution and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were dried over $NaSO_4$ and evaporated in vacuo to yield 155 mg (92%) of **2a**-Me as a white solid, m.p. 85 °C. – IR (KBr): $\tilde{\nu}$ = 2957 cm^{-1}, 1646, 1393, 1158. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 192 nm (4.367), 206 (4.229), 248 (4.040). – ^{13}C NMR: δ = 15.6 (+), 22.4 (–), 24.7 (–), 25.6 (–), 32.5 (+), 43.6 (+), 58.8 (+), 59.3 (+). – MS (70 eV, EI), *m/z* (%): 420 (30) [M^+], 112 (100).

cis-2:3;9:10-Dicyclohexane[5]ethyl[7,12,14]trimethyl[1,4,8,11]-tetraazacyclotetradecane (**2b**): 2.5 g (6 mmol) of **1b** was allowed to react following the procedure described for **2a**. The solution of the product was dried over $NaSO_4$ and evaporated to dryness to yield 1.59 g (70%) of **2b** as a white solid, m.p. 65 °C. – IR (KBr): $\tilde{\nu}$ = 3291 cm^{-1}, 2950, 1474, 751. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 192 nm (3.842). – ^1H NMR: δ = 0.81 (m, 16H), 1.21 (m, 22H), 2.53 (m, 4H), 2.76 (m, 4H). – MS (70 eV, EI), *m/z* (%): 378 (10) [M^+], 125 (100). – $C_{23}H_{46}N_4$ (378.4): calcd. C 72.96, H 12.25, N 14.80; found C 72.43, H 12.54, N 15.37.

cis-2:3;9:10-Dicyclohexane[5]heptyl[7,12,14]trimethyl[1,4,8,11]-tetraazacyclotetradecane (**2c**): A mixture of 5 g (10.3 mmol) of **1c** and 5 g (90 mmol) of Raney nickel in 750 ml of EtOH was hydrogenated at 15 MPa H_2 for 48 h at 100 °C followed by 48 h at 120 °C. The Raney nickel was removed by filtration through Celite and the solvent was evaporated in vacuo to yield 4.28 g (92%) of **2c** as an oil. – IR (KBr): $\tilde{\nu}$ = 3243 cm^{-1}, 2854, 1574, 1086. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 197 nm (4.709), 206 (4.177), 222 (3.575). – ^1H NMR: δ = 0.88 (m, 3H), 1.02 (m, 14H), 1.13–1.53 (bm, 31H), 2.82 (bs, 4H), 2.82 (bs, 4H). – MS (70 eV, EI), *m/z* (%): 448 (12) [M^+], 364 (100) [$M^+ - C_6H_{12}$]. – $C_{28}H_{56}N_4$ (EtOH)(H_2O): calcd. C 70.52, H 12.24, N 10.97; found C 70.15, H 11.70, N 11.46.

cis-2,3;9:10-Dicyclohexane[5,7,12,14]tetramethyl[1,4,8,11]tetraazacyclotetradecanenickel(II) Acetate [**2a** · $Ni(OAc)_2$]: A mixture of **2a** (800 mg, 2.2 mmol) and $Ni(OAc)_2(H_2O)_4$ (248 mg, 2.3 mmol) in 40 ml of degassed MeOH was stirred overnight under nitrogen. Slow evaporation of the solvent from the yellow solution gave large yellow crystals of [**2a** · $Ni(OAc)_2$]. The crystals were dried in vacuo at 40 °C to yield 762 mg (64%) of [**2a** · $Ni(OAc)_2$] as a yellow powder; m.p. 250 °C (dec.), R_f (alumina) = 0.35 [CH_2Cl_2/MeOH (90:10)]. – IR (KBr): $\tilde{\nu}$ = 3089 cm^{-1}, 2837, 1076, 698. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 194 nm (4.080), 222 (3.841), 244 (3.655). – ^1H NMR: δ = 0.98 (m, 14H), 1.38 (m, 22H), 2.68 (bs, 4H), 2.96 (bs, 4H). – MS (70 eV, EI), *m/z* (%): 420 (100) [M^+], 125 (100) [$M^+ - C_9H_{17}$]. – $C_{22}H_{44}N_4Ni(OAc)_2$ (541.4): calcd. C 57.47, H 9.65, N 10.31; found C 57.68, H 9.31, N 10.35.

cis-2:3;9:10-Dicyclohexane[5,7,12,14]tetramethyl[1,4,8,11]tetraazacyclotetradecanecopper(II) Acetate [**2a** · $Cu(OAc)_2$]: A mixture of **2a** (364 mg, 1.0 mmol) and $Cu(OAc)_2$ (199 mg, 1.0 mmol) in 30 ml of degassed MeOH was stirred under nitrogen overnight. The solvent was removed in vacuo and the brown residue was dissolved in 20 ml of a mixture of toluene/MeOH/H_2O (80:15:5). Slow evaporation of the solvent mixture gave red crystals, which were dried in vacuo to yield 310 mg (54%) of [**2a** · $Cu(OAc)_2$] as a red powder; m.p. 250 °C (dec.). – IR (KBr): $\tilde{\nu}$ = 3120 cm^{-1}, 2858, 1045, 615. – UV/Vis (CH_3CN): λ_{max} (lg ε) = 270 nm (3.633), 504 (1.948). – MS (FAB^+; NBA), *m/z* (%): 486 (36) [$M(OAc)^+$], 426 (100) [M^+]. – $C_{22}H_{44}N_4Cu(OAc)_2(MeOH)$ (578.3): calcd. C 56.08, H 9.41, N 9.69; found C 55.98, H 9.32, N 9.92.

cis-2:3;9:10-Dicyclohexane[5,7,12,14]tetramethyl[1,4,8,11]tetraazacyclotetradecanezinc(II) Perchlorate [**2a** · $Zn(ClO_4)_2$]: A solution of **2a** (200 mg, 0.55 mmol) and $Zn(ClO_4)_2$· 6 H_2O (205 mg, 0.55 mmol) in 50 ml of MeOH was refluxed under nitrogen for 12 h. The reaction mixture was filtered and the solvent was removed in vacuo until precipitation began. Methanol was then added to redissolve the precipitate material. Slow evaporation of the solvent gave colourless crystals of [**2a** · $Zn(ClO_4)_2$], which were dried in vacuo to yield 338 mg (95%) of [**2a** · $Zn(ClO_4)_2$] as a white powder; m.p. 280 °C (dec.). – IR (KBr): $\tilde{\nu}$ = 3254 cm^{-1}, 2935, 1625, 625. – ^1H NMR: δ = 1.24 (m, 14H), 1.55 (m, 22H), 2.94 (bs, 4H), 3.03 (bs, 4H). – MS (FAB^+; NBA), *m/z* (%): 527 (100) [$M(ClO_4)^+$]. – $C_{22}H_{46}N_4O_9Cl_2Zn$ (646.9): calcd. C 40.85, H 7.17, N 8.66; found C 40.69, H 7.22, N 8.62.

X-ray Structure Determination[17] *of the Copper Complex* [**2a** · $Cu(OAc)_2(H_2O)_2(toluene)_2$]: *Crystal data:* $C_{33}H_{62}CuN_4O_6$, M_r = 674.41, monoclinic, space group *C2/c*, *a* = 1197.9(1), *b* = 1406.7(1), *c* = 2196.8(2) pm, β = 104.533(8)°, *V* = 3.5835(6) nm^3, *Z* = 4, D_x = 1.250 g cm^{-3}, $\lambda(MoK_\alpha)$ = 0.71073 Å, μ = 0.65 mm^{-1}, *T* = –100 °C. – *Data collection and reduction:* An orange tablet 0.5 × 0.5 × 0.35 mm was mounted in inert oil. Data were collected to $2\Theta_{max}$ 55° on a Siemens R3 diffractometer fitted with an LT-2 low temperature attachment. Of 4439 data, 4103 were unique. An absorption correction based on ψ-scans was applied, with transmissions 0.75–0.94. – *Structure solution and refinement:* The structure was solved by direct methods and refined anisotropically on F^2 using all reflections (program SHELXL-93, G. M. Sheldrick, University of Göttingen). Hydrogen atoms were included with a riding model or as rigid methyls, but not all solvent H's could be located. The acetate ion is disordered over two positions. The final $wR(F^2)$ was 0.121 for 240 parameters, conventional *R(F)* 0.043. *S* = 0.97; max Dρ 1344 e nm^{-3}.

Structure Determination[17] *of the Zinc Complex* [**2a** · Zn(MeOH)$(ClO_4)_2$]: *Crystal data:* $C_{23}H_{48}Cl_2N_4O_9Zn$, M_r = 660.92, orthorhombic, space group *Pbca*, *a* = 1465.2(2), *b* = 1629.3(2), *c* = 2486.0(3) pm, *V* = 5.935 nm^3, *Z* = 8, D_x = 1.479 g cm^{-3}, μ = 1.06 mm^{-1}, *T* = –100 °C. – *Data collection and reduction:* Colourless block 0.6 × 0.45 × 0.4 mm, $2\Theta_{max}$ 50°, 12945 data, 5218 unique, transmissions 0.84–0.94. – *Structure solution and refinement:* $wR(F^2)$ 0.132 for 409 parameters, *R(F)* 0.068, *S* 1.05, max Dρ 555 e nm^{-3}. All other details as above. One perchlorate ion is disordered over two positions; atoms C7–9 show high displacement parameters and may also be disordered.

Electrochemical Measurements: All potentials were determined in 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$)[28]

Scheme 5

$$\text{(1)}\quad L + H^+ \rightleftharpoons HL^+ \qquad K_1 = \frac{[HL]}{[L][H]}$$

$$\text{(2)}\quad HL^+ + H^+ \rightleftharpoons H_2L^{2+} \qquad K_2 = \frac{[H_2L]}{[HL][H]}$$

$$\text{(3)}\quad H_2L^+ + H^+ \rightleftharpoons H_3L^{3+} \qquad K_3 = \frac{[H_3L]}{[H_2L][H]}$$

$$\text{(4)}\quad H_3L^+ + H^+ \rightleftharpoons H_4L^{4+} \qquad K_4 = \frac{[H_4L]}{[H_3L][H]}$$

$$\text{(5)}\quad L + Zn^{2+} \rightleftharpoons ZnL^{2+} \qquad K_{ZnL} = \frac{[ZnL]}{[L][Zn]}$$

$$\text{(6)}\quad LZn(H_2O)^{2+} \rightleftharpoons ZnL(OH)^+ + H^+ \qquad K_a = \frac{[ZnL]}{[L][Zn]}$$

$$\text{(7)}\quad \text{urdine} \rightleftharpoons \text{uridine}^- + H^+ \qquad K_a = \frac{[\text{uridine}^-][H^+]}{[\text{uridine}]}$$

$$\text{(8)}\quad \text{uridine}^- + ZnL^{2+} \rightleftharpoons ZnL(\text{uridine})^+ \qquad K_{ZnLU} = \frac{[ZnL(\text{uridine})]}{[\text{uridine}^-][ZnL]}$$

solution in CH_3CN at 20°C. Potentiostat/galvanostat Autolab PGSTAT20 (Eco Chemie) with program GPES V3.0; working electrode: glassy carbon, counter electrode: platinum wire, reference electrode: Ag/AgCl in EtOH satd. with LiCl. All measurements were performed under exclusion of air and moisture.

Potentiometric Titrations: Titrations were performed with a computer controlled pH meter (WTW 3000) and dosimat (Metrohm Dosimat 655). 0.1 M Perchloric acid (Merck, 60%, p.a.) and 0.1 M tetraethylammonium hydroxide (TEAOH) (Merck, 20%) in 95% methanol, with tetraethylammonium perchlorate to maintain an ionic strength of $I = 0.1$, were used for all titrations. TEAOH solutions were calibrated with benzoic acid. A titration of the perchloric acid with the TEAOH solution was used for calibration and to determine $\log K_w$ and A_j[29]. The following equilibria and equations were considered for calculations[30]: (1)−(4) determination of pK_a values; (1)−(6) binding constant of $Zn(H_2O)^{2+}$ and pK_a of bound water; (6)−(8) binding of uridine (Scheme 5).

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