# *cis*-Diprotected cyclams and cyclens: a new route to symmetrically or asymmetrically 1,4-disubstituted tetraazamacrocycles and to asymmetrically tetrasubstituted derivatives

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The use of cyclam and cyclen oxamides as intermediates for the synthesis of $N^1,N^4$-disubstituted tetraazamacrocycles is reported. This pathway affords a general strategy for the preparation of symmetrically or asymmetrically disubstituted derivatives in good yields. Also these intermediates proved convenient synthons for the preparation of asymmetrically tetrasubstituted macrocycles, leading to a new class of potentially dinucleating ligands.

## Introduction

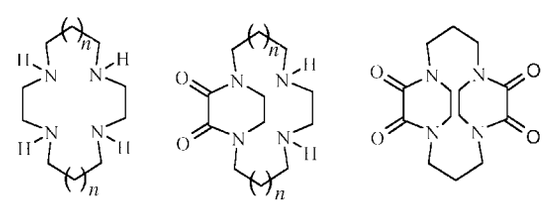
Substituted tetraazamacrocycles, derivatives of cyclam and cyclen, constitute a wide family of ligands acting as receptors for a large range of metallic cations. Their versatility with regard to coordination of the metals is under the control of a number of factors including the functionalisation of the coordinating nitrogen. Indeed N-functionalisation has been revealed to be a remarkable tool for the synthesis of ligands possessing enhanced selectivity towards metal-ion coordination.[1] As a matter of fact, these substitution reactions afford the preparation of derivatives with tailored properties.

While a number of methods for the mono-N-alkylation of tetraazamacrocycles, such as either cyclen or cyclam, have been developed,[2–5] very few strategies for their dialkylation have been reported. Selective dialkylation of cyclen has been described *via* derivatives temporarily diprotected by tosyl,[6] methyl[7] and phosphoryl[8] groups, carbamates moieties,[9] metal carbonyl[10] or silicon intermediates.[11] In the case of cyclam, most dialkylated derivatives have been prepared according to multistep reaction schemes involving tosyl[2] or Boc[12] as protective groups. Unfortunately, the corresponding diprotected macrocycles are formed as a mixture also containing both the monoprotected and triprotected ones. In order to avoid such a drawback, new modes of protection have been recently described involving the use of dioxomacrocycles,[13] cyclam formamidinium salt[14] or methylene-bridged cyclam.[15] However, most of these procedures only allow $N^1,N^7$-functionalisation. To our knowledge only one $N^1,N^4$-dialkylation has been reported.[16]

In the present paper we report a general strategy for the selective $N^1,N^4$-dialkylation of both cyclen and cyclam. Through the preparation of various derivatives, the extension of this method is established. Moreover it appears that this new synthetic approach opens the way to a new class of dimetallic chelating ligand.

## Results and discussion

As a strategy for the selective dialkylation of cyclam and cyclen tetraazamacrocycles, the use of diprotective groups has been envisaged. Molecular mechanics calculations predicted that the oxamide group should properly fit the distance between the two adjacent nitrogens, *i.e.* $N^1,N^4$ and the formation of the corresponding six-membered ring is preferred. Hereafter the numbering **a** and **b** designates, respectively, cyclam and cyclen derivatives.



| | | | |
|---|---|---|---|
| $n$=1 | **1a** | **2a** | **3a** |
| $n$=0 | **1b** | **2b** | |

Acylation of cyclam with diethyl oxalate leads to cyclamoxamide. A method previously reported by Krajewski[17] gave a low overall yield (50%), unsatisfactory with regard to a synthetic demand. We attempted to enhance the yield of this reaction by acylation of cyclam **1a** with oxalyl dichloride but this reaction led to a mixture containing unchanged **1a**, cyclamoxamide **2a** and the dibridged **3a**. Optimisation of the yield and purity of the desired synthon was realised through reaction of cyclam **1a** with equimolar amounts of diethyl oxalate by refluxing in ethanol under strictly anhydrous conditions; this afforded white needles of **2a** in 82% yield after recrystallisation. We have extended this synthetic procedure to cyclen. Equimolar amounts of diethyl oxalate and cyclen **1b** were allowed to react in absolute ethanol at room temperature, and the cyclenoxamide **2b** was obtained in 96% yield. This new derivative was characterised by its five resonances in $^{13}C$ NMR (42.9, 44.9, 47.6, 47.7, 160.2 ppm) and two signals in $^{15}N$ NMR spectroscopy (−357.2, −270.4 ppm) corresponding, respectively, to two amine and two amide functions: these spectroscopic data established the proposed structure **2b** according to symmetry criteria.

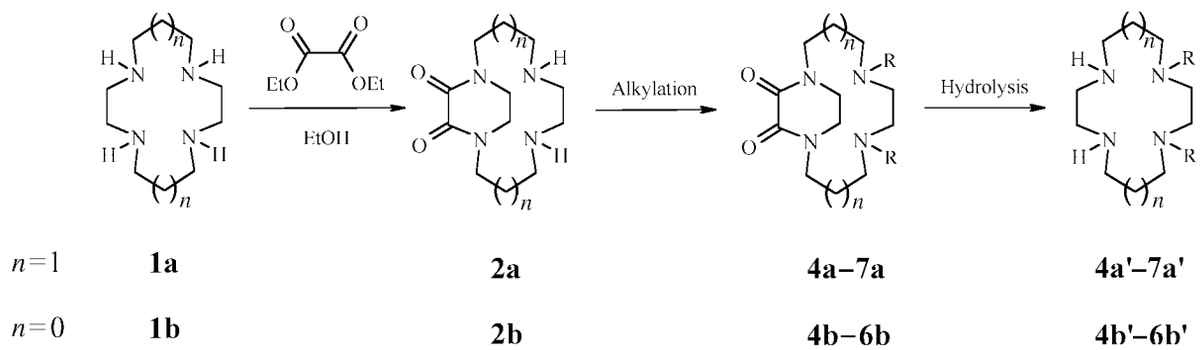
The oxamide intermediate was revealed to be a powerful bisnucleophile. Under $S_N2$ conditions, oxamides **2a** and **2b** were efficiently converted to the corresponding $N^1,N^4$-dialkylated

**Table 1** Alkylation of cyclam **1a** and cyclen **1b** with various electrophiles

| Electrophile | $N^1,N^4$-functionalised cyclamoxamide | | Yield (%) | $N^1,N^4$-functionalised cyclam | | Yield (%) |
|---|---|---|---|---|---|---|
| $PhCH_2Br$ | $R' = R'' = CH_2Ph$ | **4a** | 87 | $R' = R'' = CH_2Ph$ | **4a′** | 82 |
| $PyCH_2Cl$, HCl | $R' = R'' = CH_2Py$ | **5a** | 86 | $R' = R'' = CH_2Py$ | **5a′** | 89 |
| $^tBuOCOCH_2Cl$ | $R' = R'' = CH_2COOBu^t$ | **6a** | 96 | $R' = R'' = CH_2CO_2H$ [a] | **6a′** | 52 |
| PrBr | $R' = R'' = Pr$ | **7a** | 85 | $R' = R'' = Pr$ | **7a′** | 72 |

| Electrophile | $N^1,N^4$-functionalised cyclenoxamide | | Yield (%) | $N^1,N^4$-functionalised cyclen | | Yield (%) |
|---|---|---|---|---|---|---|
| $PhCH_2Br$ | $R' = R'' = CH_2Ph$ | **4b** | 93 | $R' = R'' = CH_2Ph$ | **4b′** | 81 |
| $PyCH_2Cl$, HCl | $R' = R'' = CH_2Py$ | **5b** | 94 | $R' = R'' = CH_2Py$ | **5b′** | 79 |
| PrBr | $R' = R'' = Pr$ | **6b** | 74 | $R' = R'' = Pr$ | **6b′** | 71 |

[a] Compound obtained as its tetrahydrochloride salt.




**Scheme 1**

compounds **4a**–**7a**, **4b**–**6b**. These were readily hydrolysed under mild acidic or basic conditions into the corresponding $N^1,N^4$-dialkylated cyclams or cyclens **4a′**–**7a′**, **4b′**–**6b′**. After subsequent purification, these derivatives were isolated in good yields (Scheme 1, Table 1). Moreover, resolution of X-ray structures for single crystals of the dibenzylated dioxocyclen **4b** (Fig. 2) and of the dibenzylated cyclam [**4a′**, $Ni^{II}$] complex (Fig. 3) highlighted the $N^1,N^4$ locations of the substituents. The metal ion is tetracoordinated in a square planar geometry; the central unit [$NiN_4$] is planar within 0.09 Å. The macrocycle is in a *trans*-III configuration, as expected for 1,8-dialkylated cyclams.[18] Ni–N bonds are in the normal range;[16] Ni–N(1), Ni–N(2) distances [respectively 1.979(7), 1.954(7) Å] are slightly longer than Ni–N(3) and Ni–N(4) ones [respectively 1.942(7), 1.943(7) Å] as a consequence of the alkylation on N(1) and N(2) atoms. Incidentally, these structures provide further evidence for the structures of the intermediate oxamide synthons.

Addition of the oxamides **2a** and **2b** to a Michael acceptor, *e.g.* acrylonitrile, opens up new interesting prospects since, according to experimental conditions, either symmetrical or asymmetrical dialkylation can be attained. Thus, in ethanol as solvent, excess of acrylonitrile led to the expected dinitriles $N^1,N^4$-cyclam or cyclen oxamide **8a**, **8b**. In pure acrylonitrile, mononitriles **9a** and **9b** were the major products, isolated in 78% and 67% yield (after chromatography) and only small amounts of dinitriles were detected. Under these conditions the kinetics for the linkage of the second group are sufficiently slowed to produce selectively the monoalkylated derivatives **9a** and **9b**.

The latter compounds proved useful for the grafting of another pendant arm to the macrocyclic skeleton and, for example, **9a** and **9b** after reaction with picolyl chloride and hydrolysis led to the asymmetrical macrocycles **9a″** and **9b″** (Scheme 2, Table 2).

Clearly, this synthetic scheme opens up the way to a new kind of tetraalkylated macrocycle. As an illustration, when dipicolylcyclam **5a′** was allowed to react with tosylaziridine in acetonitrile solution[19] and the resulting tosylamide hydrolysed, the octamine **10′** is obtained in 78% yield (Scheme 3). This ligand appears to be a potentially binucleating agent towards metal ions.

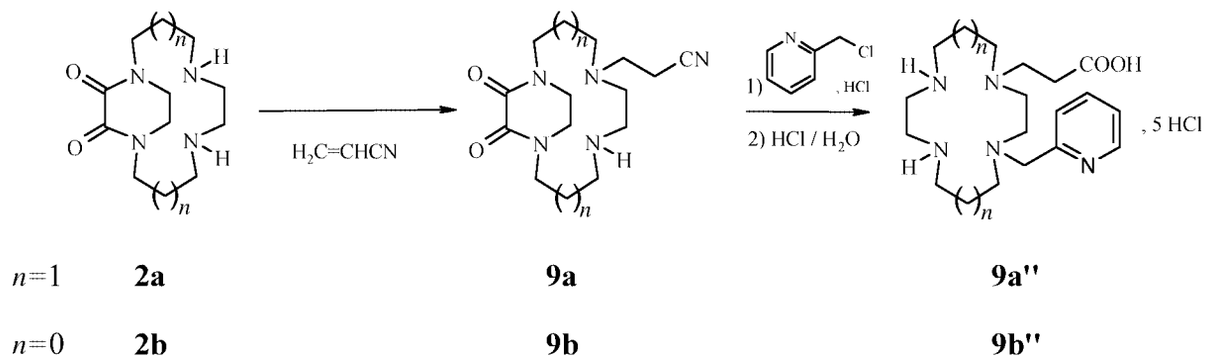
## Conclusions

These results emphasise the efficiency of the dioxo-bridge as a protective group for $N^1,N^4$-functionalisation of cyclams and cyclens. The synthesis of cyclam and cyclen oxamides is easy and quantitative; removal of the protective group is carried out under mild basic or acidic conditions. This pathway allows the N-attachment of a wide variety of substituents, leading to disubstituted and even tetrasubstituted ligands.

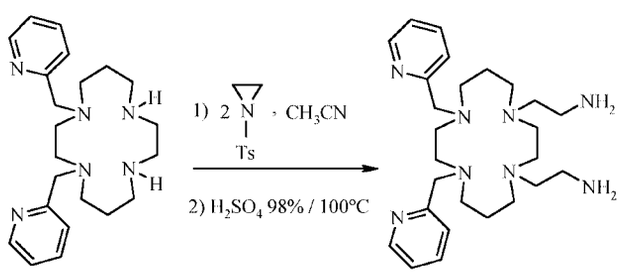
**Table 2** Alkylation of cyclam **1a** and cyclen **1b** with acrylonitrile

| | $N^1,N^4$-functionalised cyclamoxamide | | Yield (%) | $N^1,N^4$-functionalised cyclam | | Yield (%) |
|---|---|---|---|---|---|---|
| [a] | R′ = R″ = $CH_2CH_2CN$ | **8a** | 98 | R′ = R″ = $CH_2CH_2CO_2H$ [c] | **8a′** | 59 |
| [b] | R′ = $CH_2CH_2CN$, R″ = H | **9a** | 78 | R′ = $CH_2CH_2CO_2H$, R″ = $CH_2Py$ [c] | **9a″** | 51 |
| | $N^1,N^4$-functionalised cyclenoxamide | | Yield (%) | $N^1,N^4$-functionalised cyclen | | Yield (%) |
| [a] | R′ = R″ = $CH_2CH_2CN$ | **8b** | 87 | R′ = R″ = $CH_2CH_2CO_2H$ [c] | **8b′** | 82 |
| [b] | R′ = $CH_2CH_2CN$, R″ = H | **9b** | 67 | R′ = $CH_2CH_2CO_2H$, R″ = $CH_2Py$ [c] | **9b″** | 49 |

[a] In ethanol solution. [b] In pure acrylonitrile. [c] Compound obtained as its tetrahydrochloride salt.




**Scheme 2**




**Scheme 3**

Finally, protected disubstituted cyclens and cyclams can also be considered as precursors of reinforced cyclen and cyclam. This family of compounds has been shown to display (i) greater selectivity towards metal ions in terms of size matching[20] and (ii) some efficiency as proton sponges.[21] Further work concerning all these aspects is currently in progress.

## Experimental

$^1H$ and $^{13}C$ NMR spectra (400 and 100.62 MHz respectively) were acquired on a Bruker AC 400 spectrometer; *J* values are given in Hz. $^{15}N$ NMR spectra were obtained as $^1H/^{15}N$ correlations with HMBC sequence using a TBI probe. IR spectra were recorded on a Perkin-Elmer 1430. Mass spectra were obtained on a Navigator Finnigan in APCI positive mode (the samples were diluted in MeOH or $CH_3CN$), and high-resolution mass spectra were recorded using ZabSpecETOF FAB+ (*m*-NBA). TLC analyses were performed on silica or alumina plates (Merck 60 $F_{254}$). All the reactions were run under nitrogen using freshly distilled and dry solvents.

### 1,5,8,12-Tetraazabicyclo[10.2.2]hexadecane-13,14-dione 2a (cyclamoxamide)

Cyclam **1a** (5 mmol, 1.0 g) was dried by azeotropic distillation in 60 mL of toluene. After removal of solvent under reduced pressure, the residue was dissolved in dry ethanol (15 mL), and diethyl oxalate (5 mmol, 680 μL) was added. The reaction mixture was refluxed for 12 h. The solvent was rotary evaporated and the crude product was recrystallised in acetone–ethanol (20 : 1) to yield white crystals (82%), mp 166–168 °C; $\delta_H$ ($CDCl_3$) 1.87 (2H, m, C$H_2$$CH_2N$), 1.97 (2H, m, C$H_2$$CH_2N$), 2.66 (4H, m, $CH_2N$), 2.75 (2H, m, $CH_2N$), 2.85 (2H, m, $CH_2NCO$), 2.98 (2H, m, $CH_2N$), 3.58 (2H, m, $CH_2NCO$), 3.94 (2H, m, $CH_2NCO$), 4.55 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 25.3 ($CH_2$-$CH_2N$), 44.1, 47.7 ($CH_2NCO$), 49.3, 49.8 ($CH_2N$), 158.1 (CO); *ν* ($CH_2Cl_2$)/$cm^{-1}$ 1675 (CO); *m*/*z* (APCI) 255.9 (M + $H^+$).

### 1,4,7,10-Tetraazabicyclo[8.2.2]tetradecane-11,12-dione 2b (cyclenoxamide)

Cyclen (1,4,7,10-tetraazacyclododecane) **1b** (2 mmol, 416 mg) was dried by azeotropic distillation in 50 mL of toluene. After removal of solvent under reduced pressure, the residue was dissolved in dry ethanol (10 mL), and diethyl oxalate (2 mmol, 272

μL) was added. The reaction mixture was stirred for 48 h. Chromatography on silica gel ($CHCl_3$–isopropylamine, 5:1) yielded a white solid (96%), mp 96–98 °C; $R_f$ 0.20; $\delta_H$ 2.55 (2H, m, $CH_2N$), 2.63–2.70 (4H, m, $CH_2N$), 2.87–3.02 (4H, m, $CH_2N$ and $CH_2NCO$), 3.47–3.59 (4H, m, $CH_2NCO$), 3.68 (1H, d, *J* 13.6, $NCH_2Py$), 3.82 (1H, m, $CH_2NCO$), 4.12 (1H, m, $CH_2NCO$), 4.36 (1H, m, $CH_2NCO$), 4.47 (1H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 42.9, 47.7 ($CH_2NCO$), 44.9, 47.6 ($CH_2N$), 160.2 (CO); *ν* (neat)/$cm^{-1}$ 1660 (CO); *m*/*z* HRMS (M + $H^+$) (Calc. for $C_{10}H_{19}N_4O_2$: *M*, 227.1508; C, 53.0; H, 8.06; N, 24.7. Found: $M^+$, 227.1502; C, 52.7; H, 8.0; N, 24.0%).

### 1,5,8,12-Tetraazatricyclo[10.2.2.2$^{5,8}$]octadecane-6,7,13,14-tetraone 3a (cyclamdioxamide)

Cyclam **1a** (2 mmol, 400 mg) was dried by azeotropic distillation in 30 mL of toluene. After removal of solvent under reduced pressure, the residue was dissolved in dichloromethane (40 mL), and triethylamine (10 mmol, 1.4 mL) was added. The reaction mixture was cooled in an ice-bath, oxalyl dichloride (4 mmol, 350 μL) was added dropwise, and the mixture was stirred at room temperature overnight. The solvent and excess of triethylamine were rotary evaporated and the residue was recrystallised in acetonitrile to yield white crystals, suitable for X-ray analysis (36%), $\delta_H$ ($CDCl_3$) 2.16 (4H, m, $CH_2CH_2N$), 2.87 (4H, dt, $^3J$ 5.3, $^2J$ 13.8, $CH_2NCO$), 3.42 (8H, s, $CH_2N$), 4.41 (4H, dt, $^3J$ 5.8, $^2J$ 13.8, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 21.1 ($CH_2CH_2N$), 43.9, 47.9 ($CH_2NCO$), 158.8 (CO); *ν* ($CH_2Cl_2$)/$cm^{-1}$ 1670 (CO); *m*/*z* (APCI) 309.2 (M + $H^+$).

### General procedure for dialkylation

Cyclamoxamide **2a** (1 mmol, 260 mg) or cyclenoxamide **2b** (1 mmol, 230 mg) in DMF (10 mL) was treated in the presence of $Na_2CO_3$ (2.2 mmol, 235 mg) with 2.2 equivalents of alkyl halide. The resulting reaction mixture was stirred for 3–6 h at 100 °C. After removal of solvent under reduced pressure, the residue was dissolved in dichloromethane and filtered. The crude product was chromatographed through alumina or silica gel.

**5,8-Dibenzyl-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane-13,14-dione 4a.** This compound was purified by chromatography on alumina gel ($CHCl_3$) to yield a white solid (87%), $R_f$ 0.45; $\delta_H$ ($CDCl_3$) 1.65 (2H, m, $CH_2CH_2N$), 1.89 (2H, m, $CH_2CH_2N$), 2.41 (8H, m, $CH_2N$), 2.72 (2H, m, $CH_2NCO$), 3.46 (6H, m, $CH_2NCO$ and $NCH_2Ph$), 4.05 (2H, m, $CH_2NCO$), 4.38 (2H, m, $CH_2NCO$), 7.15–7.28 (10H, m, Ph); $\delta_C$ ($CDCl_3$) 23.7 ($CH_2CH_2N$), 44.4, 46.2 ($CH_2NCO$), 52.0, 52.2 ($CH_2N$), 57.5 ($NCH_2Ph$), 126.9, 128.0, 129.6, 137.5 (Ph), 158.4 (CO); *ν* (neat)/$cm^{-1}$ 1670 (CO); *m*/*z* (APCI) 435.3 (M + $H^+$).

**5,8-Dipicolyl-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane-13,14-dione 5a.** This compound was purified by chromatography on silica gel (acetone–isopropylamine, 20:1) to yield a brown solid (86%), $R_f$ 0.22; $\delta_H$ 1.70 (2H, m, $CH_2CH_2N$), 1.88 (2H, m, $CH_2CH_2N$), 2.51–2.57 (8H, m, $CH_2N$), 2.70 (2H, m, $CH_2NCO$), 3.41 (2H, m, $CH_2NCO$), 3.58 (2H, d, *J* 13.9, $NCH_2Py$), 3.64 (2H, d, *J* 13.9, $NCH_2Py$), 4.02 (2H, m, $CH_2NCO$), 4.41 (2H, m, $CH_2NCO$), 7.12 (2H, m, $H_{Ar}$), 7.28 (2H, d, *J* 7.8, $H_{Ar}$), 7.59 (2H, dd, *J* 7.7, 1.7, $H_{Ar}$), 8.49 (2H, d, *J* 4.1, $H_{Ar}$); $\delta_C$ ($CDCl_3$) 22.8 ($CH_2CH_2N$), 43.4, 45.3 ($CH_2NCO$), 53.0 (2C) ($CH_2N$), 58.4 ($NCH_2Py$), 121.1, 123.2, 135.3, 148.0, 157.5 ($C_{Ar}$), 157.6 (CO); *ν* (neat)/$cm^{-1}$ 1660 (CO); *m*/*z* (APCI) 437.4 (M + $H^+$); HRMS (M + $H^+$) Calc. for $C_{24}H_{33}N_6O_2$: *m*/*z*, 437.2665. Found: *m*/*z*, 437.2669.

**5,8-Bis(*tert*-butoxycarbonylmethyl)-1,5,8,12-tetraazabicyclo-[10.2.2]hexadecane-13,14-dione 6a.** This compound was purified by chromatography on alumina gel ($CHCl_3$) to yield a colourless oil (96%), $R_f$ 0.38; $\delta_H$ ($CDCl_3$) 1.38 [18H, s, $(CH_3)_3C$], 1.64 (2H, m, $CH_2CH_2N$), 1.80 (2H, m, $CH_2CH_2N$), 2.54–2.75 (10H, m, $CH_2N$), 3.13 (2H, d, *J* 16.8, $NCH_2CO_2Bu^t$), 3.25 (2H, d, *J* 16.8, $NCH_2CO_2Bu^t$), 3.34 (2H, m, $CH_2NCO$), 3.90 (2H, m, $CH_2NCO$), 4.37 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 22.5 ($CH_2CH_2N$), 27.6 [$(CH_3)_3C$], 43.8, 46.1 ($CH_2NCO$), 51.1, 52.1, 53.5 ($CH_2N$), 81.1 [$(CH_3)_3C$], 157.9 (NCO), 169.8 ($CO_2Bu^t$); $\delta_N$ ($CDCl_3$) −347.3 ($NCH_2CO_2Bu^t$), −263.2 ($CH_2NCO$); *ν* (neat)/$cm^{-1}$ 1670 ($CO_{oxamide}$), 1725 ($CO_{ester}$).

**5,8-Dipropyl-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane-13,14-dione 7a.** This compound was purified by chromatography on alumina gel ($CHCl_3$) to yield a white solid (85%), $R_f$ 0.58; $\delta_H$ ($CDCl_3$) 0.65 (6H, t, *J* 7.3, $CH_3CH_2$), 1.19 (4H, m, $CH_3CH_2CH_2N$), 1.47–1.70 (4H, m, $CH_2CH_2N$), 2.06–2.27 (12H, m, $CH_2N$), 2.59 (2H, m, $CH_2NCO$), 3.22 (2H, m, $CH_2NCO$), 3.80 (2H, m, $CH_2NCO$), 4.17 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 11.6 ($CH_3CH_2$), 17.0 ($CH_3CH_2CH_2N$), 23.4 ($CH_2CH_2N$), 43.8, 45.9 ($CH_2NCO$), 51.8, 52.0, 54.6 ($CH_2N$), 158.0 (CO); $\delta_N$ ($CDCl_3$) −340.5 ($NCH_2CH_2CH_3$), −264.2 ($CH_2NCO$); *ν* (neat)/$cm^{-1}$ 1660 (CO); *m*/*z* (APCI) 339.4 (M + $H^+$).

**5,8-Bis(2-cyanoethyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane-13,14-dione 8a.** This compound was prepared from cyclamoxamide (1 mmol, 260 mg) in a mixture of ethanol (10 mL) and acrylonitrile (5 mL). The reaction mixture was refluxed for 48 h, and the solvent and the excess of reagent were evaporated to yield a colourless oil (98%), $\delta_H$ 1.81 (4H, m, $CH_2CH_2N$), 2.43–2.63 (14H, m, $CH_2N$ and $CH_2CN$), 2.71–2.80 (4H, m, $CH_2N$ and $CH_2NCO$), 3.42 (2H, m, $CH_2NCO$), 3.91 (2H, m, $CH_2NCO$), 4.40 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 13.6 ($CH_2CN$), 23.0 ($CH_2CH_2N$), 43.5, 45.6 ($CH_2NCO$), 48.6, 51.9, 52.3 ($CH_2N$), 119.0 ($CH_2CN$), 157.8 (CO); *ν* (neat)/$cm^{-1}$ 1660 (CO), 2240 (CN); *m*/*z* (APCI) 361.4 (M + $H^+$, 90%), 721.5 (dimer + $H^+$, 100).

**5-(2-Cyanoethyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane-13,14-dione 9a.** This compound was prepared from cyclamoxamide (1 mmol, 260 mg) in acrylonitrile (10 mL). The reaction mixture was refluxed for 48 h and the excess of reagent was evaporated. Chromatography on silica gel ($CHCl_3$–isopropylamine, 50:1) yielded a colourless oil (78%), $R_f$ 0.46; $\delta_H$ 1.56–1.77 (4H, m, $CH_2CH_2N$), 2.30–2.91 (16H, m, $CH_2N$, $CH_2CN$ and $CH_2NCO$), 3.61 (2H, m, $CH_2NCO$), 4.47 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 12.6 ($CH_2CN$), 22.1, 25.8 ($CH_2CH_2N$), 41.7, 43.6, 45.3, 46.5 (2C), 47.6, 48.5, 52.0, 53.2 ($CH_2N$), 118.9 ($CH_2CN$), 157.4, 157.7 (CO); *ν* (neat)/$cm^{-1}$ 1660 (CO), 2240 (CN); *m*/*z* (APCI) 308.3 (M + $H^+$).

**5-(2-Cyanoethyl)-8-(2-picolyl)-1,5,8,12-tetraazabicyclo-[10.2.2]hexadecane-13,14-dione 9a′.** 5-(2-Cyanoethyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane-13,14-dione (0.5 mmol, 155 mg) was dissolved in DMF (10 mL). $Na_2CO_3$ (2 mmol, 212 mg) and 2-picoline hydrochloride (0.5 mmol, 135 mg) were added. The reaction mixture was stirred at 100 °C for 4 h. After removal of solvent under reduced pressure, the residue was dissolved in dichloromethane and filtrated. Chromatography on silica gel ($CHCl_3$–isopropylamine, 10:1) yielded a yellow oil (81%), $R_f$ 0.41; $\delta_H$ 1.77–2.06 (6H, m, $CH_2CH_2N$ and $CH_2CN$), 2.32–2.81 (16H, m, $CH_2N$ and $CH_2NCO$), 3.34 (1H, m, $CH_2NCO$), 3.46 (1H, m, $CH_2NCO$), 3.57 (1H, d, *J* 13.6, $NCH_2Py$), 3.68 (1H, d, *J* 13.6, $NCH_2Py$), 3.82 (1H, m, $CH_2NCO$), 4.12 (1H, m, $CH_2NCO$), 4.36 (1H, m, $CH_2NCO$), 4.47 (1H, m, $CH_2NCO$), 7.17 (1H, m, $H_{Ar}$), 7.32 (1H, d, *J* 7.7, $H_{Ar}$), 7.66 (1H, m, $H_{Ar}$), 8.63 (1H, m, $H_{Ar}$); $\delta_C$ ($CDCl_3$) 12.9 ($CH_2CN$), 22.5, 23.2 ($CH_2CH_2N$), 43.1, 43.6, 45.0, 47.6, 47.8, 48.5, 51.2, 51.7, 52.5 ($CH_2N$), 118.9 ($CH_2CN$), 121.5, 123.3, 135.6, 148.2, 157.2 ($C_{Ar}$), 157.6, 157.8 (CO); *ν* (neat)/$cm^{-1}$ 1660 (CO), 2240 (CN); *m*/*z* (APCI) 399.2 (M + $H^+$).

**1,4-Dipicolyl-8,11-bis(*p*-tolylsulfonamidoethyl)-1,4,8,11-tetraazacyclotetradecane 10.** This compound was prepared from **5a′**

(1 mmol, 382 mg) by reaction with tosylaziridine (2 mmol, 392 mg) in acetonitrile (15 mL). The reaction mixture was refluxed for 48 h. Chromatography on silica gel ($CHCl_3$–isopropylamine, 10:1) yielded a brown oil (91%), $R_f$ 0.61; $\delta_H$ ($CDCl_3$) 1.59 (4H, m, $CH_2CH_2N$), 2.31 (4H, m, $CH_2N$), 2.40 (10H, m, $CH_2N$ and $CH_3C_6H_4SO_2$), 2.52 (10H, m, $CH_2N$), 3.01 (4H, m, $CH_2NHTs$), 3.51 (4H, s, $NCH_2Py$), 7.10 (2H, m, $H_{Py}$), 7.28 (4H, m, $C_6H_4$), 7.40 (2H, d, $J$ 7.6, $H_{Py}$), 7.49 (2H, m, $H_{Py}$), 7.77 (4H, m, $C_6H_4$), 8.46 (2H, d, $J$ 4.1, $H_{Py}$); $\delta_C$ ($CDCl_3$) 20.9 ($CH_3C_6H_4SO_2$), 23.9 ($CH_2CH_2N$), 40.1 ($CH_2NHTs$), 49.6 (2C), 50.7 (2C), 51.6 ($CH_2N$), 59.8 ($NCH_2Py$), 121.4, 122.3, 135.6, 147.9 ($C_6H_4$), 126.3, 129.1, 137.1, 142.2, 159.7 ($C_{Py}$); *m/z* (FAB) 777.3945 ($M + H^+$, 100%).

**1,4-Bis(2-aminoethyl)-8,11-dipicolyl-1,4,8,11-tetraazacyclotetradecane 10′.** Compound **10** (1 mmol, 778 mg) was detosylated in conc. sulfuric acid (5 mL). The reaction mixture was stirred at 90 °C for 72 h. Ethanol (30 mL) and diethyl ether (30 mL) were slowly added to the cooled black mixture. The protonated octamine sulfate was precipitated, filtered off and washed with diethyl ether (2 × 10 mL). The sulfate salt was neutralised with cooled 10 M NaOH solution. The product was extracted with dichloromethane. The octamine was obtained as a colourless oil (86%), $\delta_H$ ($CDCl_3$) 1.70 (4H, m, $CH_2CH_2N$), 2.50–2.60 (20H, m, $CH_2N$), 2.95 (4H, m, $CH_2NH_2$), 3.57 (4H, s, $NCH_2Py$), 5.25 (4H, s, NH), 7.13 (2H, m, $H_{Py}$), 7.33 (2H, d, $J$ 7.8, $H_{Py}$), 7.56 (2H, m, $H_{Py}$), 8.51 (2H, d, $J$ 4.5, $H_{Py}$); $\delta_C$ ($CDCl_3$) 24.5 ($CH_2CH_2N$), 37.8 ($CH_2NH_2$), 50.8 (2C), 51.6, 52.0, 52.1 ($CH_2N$), 60.4 ($NCH_2Py$), 122.0, 123.5, 136.3, 148.9, 159.3 ($C_{Py}$); $\delta_N$ ($CDCl_3$) −73.3 ($N_{Py}$), −343.2, −350.2 ($CH_2N$), −359.4 ($CH_2NH_2$); *m/z* (APCI) 469.5 ($M + H^+$).

**4,7-Dibenzyl-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione 4b.** This compound was purified by chromatography on silica gel ($CHCl_3$–isopropylamine, 15:1) to yield a white solid (93%), mp 150–152 °C. Crystals, suitable for X-ray analysis, were obtained in toluene. $R_f$ 0.41; $\delta_H$ ($CDCl_3$) 2.29 (2H, m, $CH_2N$), 2.40–2.66 (6H, m, $CH_2N$), 2.90 (2H, m, $CH_2NCO$), 3.34–3.51 (6H, m, $CH_2NCO$ and $NCH_2Ph$), 4.11–4.23 (4H, m, $CH_2NCO$), 7.12 (4H, m, $H_{Ar}$), 7.30 (6H, m, $H_{Ar}$); $\delta_C$ ($CDCl_3$) 46.4, 48.7, 51.8, 54.7 ($CH_2N$), 57.9 ($NCH_2Ph$), 126.7, 127.7, 129.3, 137.7 ($C_{Ar}$) 159.3 (CO); $\nu$ (neat)/$cm^{-1}$ 1670 (CO); *m/z* HRMS ($M + H^+$) Calc. for $C_{24}H_{31}N_4O_2$: *m/z*, 407.2447. Found: *m/z*, 407.2466.

**4,7-Dipicolyl-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione 5b.** This compound was purified by chromatography on silica gel (acetone–isopropylamine, 20:1) to yield a brown solid (94%), mp 138–140 °C; $R_f$ 0.23; $\delta_H$ 2.34–2.60 (8H, m, $CH_2N$), 2.82 (2H, m, $CH_2NCO$), 3.35 (2H, m, $CH_2NCO$), 3.47 (4H, m, $NCH_2Py$), 3.95 (2H, m, $CH_2NCO$), 4.14 (2H, m, $CH_2NCO$), 7.04 (4H, m, $H_{Ar}$), 7.50 (2H, t, $J$ 7.6, 1.7, $H_{Ar}$), 8.40 (2H, m, $H_{Ar}$); $\delta_C$ ($CDCl_3$) 45.5, 47.9 ($CH_2NCO$), 51.6, 54.4 ($CH_2N$), 58.0 ($NCH_2Py$), 121.6, 123.7, 135.8, 148.3, 157.9 ($C_{Ar}$), 159.5 (CO); $\nu$ (neat)/$cm^{-1}$ 1670 (CO); *m/z* HRMS ($M + H^+$) Calc. for $C_{22}H_{29}N_6O_2$: *m/z*, 409.2352. Found: *m/z*, 409.2359.

**4,7-Dipropyl-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione 6b.** This compound was purified by chromatography on silica gel ($CHCl_3$–isopropylamine, 7:1) to yield a yellow solid (74%), $R_f$ 0.56; $\delta_H$ 0.87 (6H, t, $J$ 7.3, $CH_3$), 1.42 (4H, m, $CH_2CH_3$), 2.17 (2H, m, $CH_2N$), 2.31–2.40 (6H, m, $CH_2N$ and $CH_2NCO$), 2.49 (2H, m, $CH_2N$), 2.72–2.84 (4H, m, $CH_2N$), 3.47 (2H, m, $CH_2NCO$), 4.17 (4H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 11.8 ($CH_3$), 19.5 ($CH_2CH_3$), 47.0, 49.6, 52.2, 55.9, 56.0 ($CH_2N$), 159.4 (CO); $\nu$ (neat)/$cm^{-1}$ 1660 (CO); *m/z* (FAB) 311.2448 ($M + H^+$, 100%).

**4,7-Bis(2-cyanoethyl)-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione 8b.** This compound was prepared from cyclenoxamide (1 mmol, 230 mg) in a mixture of ethanol (10 mL) and acrylonitrile (5 mL). The reaction mixture was refluxed for 48 h and the solvent and the excess of reagent were evaporated to yield a white solid, which was chromatographed on silica gel ($CHCl_3$–isopropylamine, 10:1) (87%), mp 180–182 °C; $R_f$ 0.35; $\delta_H$ 2.45 (10H, m, $CH_2N$ and $CH_2CN$), 2.76 (8H, m, $CH_2N$ and $CH_2NCO$), 3.51 (2H, m, $CH_2NCO$), 3.83 (2H, m, $CH_2NCO$), 4.24 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 13.4 ($CH_2CN$), 45.0, 47.4, 47.6, 50.7, 53.3 ($CH_2N$), 119.0 ($CH_2CN$), 159.4 (CO); $\nu$ (neat)/$cm^{-1}$ 1660 (CO), 2240 (CN); *m/z* (APCI) 333.3 ($M + H^+$).

**4-(2-Cyanoethyl)-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione 9b.** This compound was prepared from cyclenoxamide (1 mmol, 230 mg) in acrylonitrile (10 mL). The reaction mixture was refluxed for 48 h and the excess of reagent was evaporated. Chromatography on silica gel ($CHCl_3$–isopropylamine, 7:1) yielded a yellow solid (67%), mp 182–184 °C; $R_f$ 0.29; $\delta_H$ 2.32–2.94 (14H, m, $CH_2N$, $CH_2CN$ and $CH_2NCO$), 3.19 (1H, m, $CH_2NCO$), 3.44 (1H, m, $CH_2NCO$), 3.63 (2H, m, $CH_2NCO$), 4.23 (2H, m, $CH_2NCO$); $\delta_C$ ($CDCl_3$) 14.3 ($CH_2CN$), 42.4, 44.6, 45.7, 46.6, 48.3, 48.4, 48.7, 49.2, 53.8 ($CH_2N$), 118.7 ($CH_2CN$), 159.3, 160.7 (CO); $\nu$ (neat)/$cm^{-1}$ 1660 (CO), 2240 (CN); *m/z* (APCI) 280.2 ($M + H^+$).

**4-(2-Cyanoethyl)-7-(2-picolyl)-1,4,7,10-tetraazabicyclo[8.2.2]-tetradecane-11,12-dione 9b′.** 4-(2-Cyanoethyl)-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione **9b** (0.5 mmol) was dissolved in DMF (10 mL). $Na_2CO_3$ (2 mmol, 212 mg) and 2-picoline hydrochloride (0.5 mmol, 135 mg) were added. The reaction mixture was stirred at 100 °C for 4 h. After removal of solvent under reduced pressure, the residue was dissolved in dichloromethane and filtered. Chromatography on silica gel ($CHCl_3$–isopropylamine, 7:1) yielded a brown solid (83%), mp 148–150 °C; $R_f$ 0.47; $\delta_H$ 2.33 (2H, t, $J$ 6.6, $CH_2CN$), 2.43–2.93 (8H, m, $CH_2N$), 3.46–3.53 (4H, m, $CH_2NCO$), 3.68 (1H, d, $J$ 13.6, $NCH_2Py$), 3.77 (1H, d, $J$ 13.6, $NCH_2Py$), 3.84 (1H, m, $CH_2NCO$), 4.05 (1H, m, $CH_2NCO$), 4.26 (2H, m, $CH_2NCO$), 7.12 (1H, m, $H_{Ar}$), 7.30 (1H, d, $H_{Ar}$), 7.60 (1H, m, $H_{Ar}$), 8.45 (1H, m, $H_{Ar}$); $\delta_C$ ($CDCl_3$) 13.0 ($CH_2CN$), 44.5 (2C), 46.7, 47.0 (2C), 50.3, 50.7, 53.1, 53.2, 57.1 ($CH_2N$), 118.6 ($CH_2CN$), 121.3, 123.3, 135.5, 147.8, 157.0 ($C_{Ar}$), 159.0, 159.4 (CO); $\nu$ (neat)/$cm^{-1}$ 1670 (CO), 2240 (CN); *m/z* (APCI) 371.3 ($M + H^+$).

### General procedure for hydrolysis

Disubstituted cyclamoxamide or cyclenoxamide was dissolved in water (5 mL) and NaOH (10 M; 5 mL) was added. The reaction mixture was stirred at 90 °C overnight. The product was extracted with dichloromethane. The solvent was rotary evaporated. The disubstituted tetramine was transformed into the hydrochloride salt for elemental analysis. Dropwise addition of HCl–ethanol solution induced precipitation of the hydrochloride salt, which was washed twice with ethanol and dried *in vacuo*.

**1,4-Dibenzyl-1,4,8,11-tetraazacyclotetradecane 4a′.** This compound was prepared from **4a** following the general procedure (colourless oil, 82%), $\delta_H$ ($CDCl_3$) 1.78 (4H, m, $CH_2CH_2N$), 2.39 (8H, m, $CH_2N$), 2.78 (2H, m, $CH_2N$), 2.87 (4H, s, $CH_2N$), 3.43 (4H, s, $NCH_2Ph$), 7.21–7.30 (10H, m, Ph); $\delta_C$ ($CDCl_3$) 25.4 ($CH_2CH_2N$), 46.5, 46.9, 51.5, 51.6 ($CH_2N$), 57.6 ($NCH_2Ph$), 126.7, 127.9, 129.1, 138.4 (Ph), 158.4 (CO); *m/z* (APCI) 381.4 ($M + H^+$).

**Complex [Ni(4a′)](ClO$_4$)$_2$.** A methanolic solution of $Ni(ClO_4)_2 \cdot 6H_2O$ (0.1 mmol, 36 mg) was added to a methanolic solution of the ligand **4a′** (0.1 mmol, 37 mg). The mixture was refluxed for 1 h. After cooling, the precipitate was recrystallised

in $CH_3CN$ (79% yield), $\lambda_{max}(CH_3CN)$ 478 nm. Orange rhombohedral crystals, suitable for X-ray analysis, were obtained by slow evaporation of an acetonitrile solution.

**1,4-Dipicolyl-1,4,8,11-tetraazacyclotetradecane 5a′.** This compound was prepared from **5a** following the general procedure (yellow oil, 89%), $\delta_H$ ($CDCl_3$) 1.75 (4H, m, C$H_2$CH$_2$N), 2.46 (8H, m, CH$_2$N), 2.72 (2H, m, CH$_2$N), 2.83 (4H, s, CH$_2$N), 3.58 (4H, s, NC$H_2$Py), 7.10 (2H, m, H$_{Ar}$), 7.41 (2H, d, *J* 7.8, H$_{Ar}$), 7.58 (2H, m, H$_{Ar}$), 8.49 (2H, d, *J* 4.1, H$_{Ar}$); $\delta_C$ ($CDCl_3$) 25.4 (*C*H$_2$CH$_2$N), 45.9, 46.6, 51.1, 51.9 (CH$_2$N), 59.0 (N*C*H$_2$-Py), 121.4, 122.9, 135.6, 148.4, 158.8 (C$_{Ar}$); *m*/*z* HRMS (M + H$^+$) Calc. for $C_{22}H_{35}N_6$: *m*/*z*, 383.2923. Found: *m*/*z*, 383.2922 (Calc. for $C_{22}H_{40}Cl_6N_6$: C, 43.9; H, 6.7; N, 14.0%. Found: C, 44.0; H, 6.5; N, 14.0).

**1,4-Bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane tetrahydrochloride 6a′.** This compound was prepared from **6a** hydrolysed in 6 M HCl (10 mL). The acidic solution was stirred at 90 °C for 14 h. The solvent was rotary evaporated and the crude product was recrystallised in water–ethanol to yield a white solid (52%),† $\delta_H$ ($D_2O$) 2.02 (4H, m, C$H_2$CH$_2$N), 3.04 (8H, m, CH$_2$N), 3.35 (4H, m, CH$_2$N), 3.48 (4H, s, CH$_2$N), 3.70 (4H, s, NC$H_2$CO$_2$H); $\delta_C$ ($D_2O$) 22.5 (*C*H$_2$CH$_2$N), 42.2, 45.6, 52.2, 54.3 (CH$_2$N), 57.7 (N*C*H$_2$CO$_2$H), 173.2 (CO$_2$H); *ν* (KBr)/cm$^{-1}$ 1730 (CO$_2$H); *m*/*z* (APCI) 317.3 (M + H$^+$).

**1,4-Dipropyl-1,4,8,11-tetraazacyclotetradecane 7a′.** This compound was prepared from **7a** following the general procedure (colourless oil, 72%), $\delta_H$ ($CDCl_3$) 0.84 (6H, t, *J* 7.4, C$H_3$CH$_2$), 1.45 (4H, m, CH$_3$C$H_2$CH$_2$N), 1.70 (4H, m, C$H_2$-CH$_2$N), 2.31 (2H, m, CH$_2$N), 2.46 (10H, m, CH$_2$N), 2.64 (4H, m, CH$_2$N), 2.72 (4H, s, CH$_2$N), 2.84 (2H, s, NH); $\delta_C$ ($CDCl_3$) 11.8 (*C*H$_3$CH$_2$), 18.6 (CH$_3$*C*H$_2$CH$_2$N), 25.4 (*C*H$_2$CH$_2$N), 46.5, 46.6, 51.4, 51.9, 54.8 (CH$_2$N); *m*/*z* (APCI) 285.4 (M + H$^+$); HRMS (M + H$^+$) Calc. for $C_{16}H_{37}N_4$: *m*/*z*, 285.3018. Found: *m*/*z*, 285.3025.

**1,4-Bis(2-carboxyethyl)-1,4,8,11-tetraazacyclotetradecane tetrahydrochloride 8a′.** This compound was prepared from **8a** hydrolysed in 6 M HCl (10 mL). The acidic solution was stirred at 90 °C for 48 h. The solvent was rotary evaporated and the crude product was recrystallised in water–ethanol to yield a white solid (59%), mp 160–162 °C; $\delta_H$ ($D_2O$) 2.18 (4H, m, C$H_2$CH$_2$N), 2.94 (4H, s, NCH$_2$C$H_2$CO$_2$H), 3.28–3.79 (20H, m, CH$_2$N); $\delta_C$ ($D_2O$) 20.5 (*C*H$_2$CH$_2$N), 31.9 (NCH$_2$*C*H$_2$CO$_2$H), 39.6, 43.2, 47.1, 50.9, 54.2 (CH$_2$N), 176.3 (CO$_2$H); *ν* (KBr)/cm$^{-1}$ 1720 (CO) (Calc. for $C_{16}H_{36}Cl_4N_4O_4$. 2H$_2$O: C, 36.5; H, 7.7; N, 10.6%. Found: C, 36.3; H, 7.9; N, 10.5).

**1-(2-Carboxyethyl)-4-picolyl-1,4,8,11-tetraazacyclotetradecane 9a″.** This compound was prepared from **9a′** hydrolysed in 6 M HCl (10 mL). The acidic solution was stirred at 90 °C for 48 h. The solvent was rotary evaporated and the crude product was recrystallised in water–ethanol to yield a white solid (51%), $\delta_H$ ($D_2O$) 1.94 (2H, m, C$H_2$CH$_2$N), 2.25 (2H, m, C$H_2$CH$_2$N), 2.68 (2H, t, *J* 6.6, C$H_2$CO$_2$H), 2.89 (2H, t, *J* 6.6, NC$H_2$CH$_2$-CO$_2$H), 3.07–3.63 (16H, m, CH$_2$N), 4.11 (2H, s, NC$H_2$Py), 7.97 (1H, t, *J* 6.6, H$_{Py}$), 8.03 (1H, d, *J* 7.9, H$_{Py}$), 8.54 (1H, m, H$_{Py}$), 8.74 (1H, d, *J* 5.1, H$_{Py}$); $\delta_C$ ($D_2O$) 21.1, 23.8 (*C*H$_2$CH$_2$N), 31.5 (*C*H$_2$CO$_2$H), 40.5, 40.7, 43.9, 45.0, 48.3, 51.3, 52.4, 53.3, 53.7 (CH$_2$N), 58.4 (N*C*H$_2$Py), 129.3, 130.4, 144.2, 150.3, 154.9 (C$_{Py}$), 176.3 (CO$_2$H); *ν* (KBr)/cm$^{-1}$ 1720 (CO$_2$H); *m*/*z* (APCI) 364.8 (M + H$^+$).

**1,4-Dibenzyl-1,4,7,10-tetraazacyclododecane 4b′.** This compound was prepared from **4b** following the general procedure (colourless oil, 81%), $\delta_H$ ($CDCl_3$) 2.58 (8H, m, CH$_2$N), 2.76 (4H, m, CH$_2$N), 2.84 (4H, s, CH$_2$N), 3.48 (4H, s, NC$H_2$Ph), 7.23–7.38 (10H, m, Ph); $\delta_C$ ($CDCl_3$) 44.6, 46.2, 50.2, 51.5 (CH$_2$N), 57.8 (N*C*H$_2$Ph), 126.7, 127.9, 129.0, 138.2 (Ph); *m*/*z* HRMS (M + H$^+$) Calc. for $C_{22}H_{33}N_4$: *m*/*z*, 353.2705. Found: *m*/*z*, 353.2726 (Calc. for $C_{22}H_{36}Cl_4N_4 \cdot H_2O$: C, 51.2; H, 7.4; N, 10.8%. Found: C, 51.2; H, 7.6; N, 10.7).

**1,4-Dipicolyl-1,4,7,10-tetraazacyclododecane 5b′.** This compound was prepared from **5b** following the general procedure (brown oil, 79%), $\delta_H$ ($CDCl_3$) 2.67 (8H, m, CH$_2$N), 2.85 (4H, m, CH$_2$N), 2.93 (4H, s, CH$_2$N), 3.64 (4H, s, NC$H_2$Py), 7.10 (2H, m, H$_{Ar}$), 7.32 (2H, d, *J* 7.7, H$_{Ar}$), 7.48 (2H, dt, *J* 7.6, 1.8, H$_{Ar}$), 8.52 (2H, d, *J* 4.2, H$_{Ar}$); $\delta_C$ ($CDCl_3$) 44.5, 45.8, 50.6, 51.4 (CH$_2$N), 58.6 (N*C*H$_2$Py), 121.4, 122.8, 135.8, 148.3, 158.1 (C$_{Ar}$); *m*/*z* (APCI) 355.3 (M + H$^+$).

**1,4-Dipropyl-1,4,7,10-tetraazacyclododecane 6b′.** This compound was prepared from **6b** following the general procedure (colourless oil, 71%), $\delta_H$ ($CDCl_3$) 0.88 (6H, t, *J* 7.3, C$H_3$CH$_2$), 1.45 (4H, m, CH$_3$C$H_2$CH$_2$N), 2.40–2.56 (12H, m, CH$_2$N), 2.71 (4H, m, CH$_2$N), 2.80 (4H, m, CH$_2$N); $\delta_C$ ($CDCl_3$) 11.7 (*C*H$_3$CH$_2$), 18.9 (CH$_3$*C*H$_2$CH$_2$N), 45.2, 46.5, 50.9, 51.5, 55.3 (CH$_2$N); *m*/*z* (FAB) 257.2505 (M + H$^+$; 100%).

**1,4-Bis(2-carboxyethyl)-1,4,7,10-tetraazacyclododecane tetrahydrochloride 8b′.** This compound was prepared from **8b** hydrolysed in 6 M HCl (10 mL). The acidic solution was stirred at 90 °C for 48 h. The solvent was rotary evaporated and the crude product was recrystallised in water–ethanol to yield a white solid (58%),† $\delta_H$ ($D_2O$) 2.75 (4H, m, C$H_2$CO$_2$H), 2.95 (4H, m, NC$H_2$CH$_2$CO$_2$H), 3.06–3.24 (16H, m, CH$_2$N); $\delta_C$ ($D_2O$) 31.0 (NCH$_2$*C*H$_2$CO$_2$H), 44.1, 45.2, 45.9, 50.9, 51.3 (CH$_2$N), 177.3 (CO$_2$H); *ν* (KBr)/cm$^{-1}$ 1720 (CO); *m*/*z* HRMS (M + H$^+$) Calc. for $C_{14}H_{29}N_4O_4$: *m*/*z*, 317.2189. Found: *m*/*z*, 317.2192.

**1-(2-Carboxyethyl)-4-picolyl-1,4,7,10-tetraazacyclododecane tetrahydrochloride 9b″.** This compound was prepared from **9b′** hydrolysed in 6 M HCl (10 mL). The acidic solution was stirred at 90 °C for 24 h. The solvent was rotary evaporated and the crude product was recrystallised in water–ethanol to yield a white solid (49%),† $\delta_H$ ($D_2O$) 2.89–3.51 (20H, m, CH$_2$N and C$H_2$CO$_2$H), 4.17 (2H, s, NC$H_2$Py), 7.97 (1H, t, *J* 6.2, H$_{Py}$), 8.04 (1H, d, *J* 8.0, H$_{Py}$), 8.55 (1H, t, *J* 8.0, H$_{Py}$), 8.72 (1H, d, *J* 5.9, H$_{Py}$); $\delta_C$ ($D_2O$) 30.0 (*C*H$_2$CO$_2$H), 43.3, 44.9, 45.0, 46.9, 50.1, 50.6, 52.5, 53.0, 54.5, 56.4 (CH$_2$N), 129.6, 131.5, 145.0, 150.4, 152.4 (C$_{Py}$), 177.7 (CO$_2$H); *ν* (KBr)/cm$^{-1}$ 1720 (CO$_2$H); *m*/*z* (FAB) 336.2400 (M + H$^+$, 100%).

### Single-crystal X-ray diffraction ‡

**Compound 3a.** $C_{14}H_{20}N_4O_4$, $M = 308.34$, monoclinic, $P2_1/c$, $a = 7.190(8)$, $b = 8.080(4)$, $c = 12.279(12)$ Å, $\beta = 102.40(9)°$, $V = 697(1)$ Å$^3$, $Z = 2$, $\lambda$(Mo-K$\alpha$) = 0.710 73 Å, $\mu = 1.10$ cm$^{-1}$, $F(000) = 328$, $D_{calc} = 1.470$ g cm$^{-3}$, $T = 293$ K. Refinement of 111 variables gave $R = 0.077$, $R_w = 0.181$ and $S_w = 0.973$ (residual $\Delta\rho \leq 0.409$ e Å$^{-3}$) by using 600 reflections with $I > 2\sigma(I)$. The structure is presented in Fig. 1.

**Compound 4b.** $C_{24}H_{30}N_4O_2 \cdot \frac{1}{2}H_2O$, $M = 415.52$, monoclinic, $P2_1/a$, $a = 13.465(3)$, $b = 12.608(4)$, $c = 14.504(3)$ Å, $\beta = 116.85(3)°$, $V = 2197(1)$ Å$^3$, $Z = 4$, $\lambda$(Mo-K$\alpha$) = 0.710 73 Å, $\mu = 0.84$ cm$^{-1}$, $F(000) = 912$, $D_{calc} = 1.257$ g cm$^{-3}$, $T = 293$ K, 5000 reflections measured. Refinement of 272 variables gave $R = 0.049$, $R_w = 0.130$ and $S_w = 1.035$ (residual $\Delta\rho \leq 0.255$ e Å$^{-3}$) by using 2946 reflections with $I > 2.0\sigma(I)$. The structure is presented in Fig. 2.

† Hydrochloride salts decomposed when heated.

‡ CCDC reference number 207/369. See http://www.rsc.org/suppdata/p1/1999/3499 for crystallographic files in .cif format.

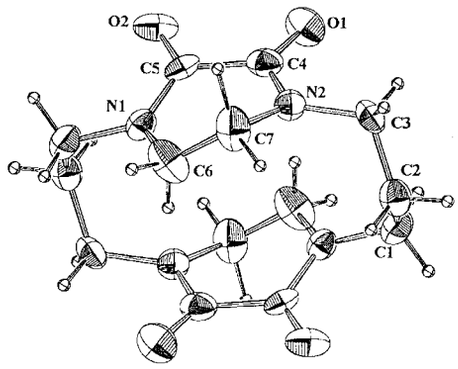



**Fig. 1** ORTEP diagram of the molecular structure of 1,5,8,12-tetraazatricyclo[10.2.2.2$^{5,8}$]octadecane-6,7,13,14-tetraone **3a**, with crystallographic numbering scheme.

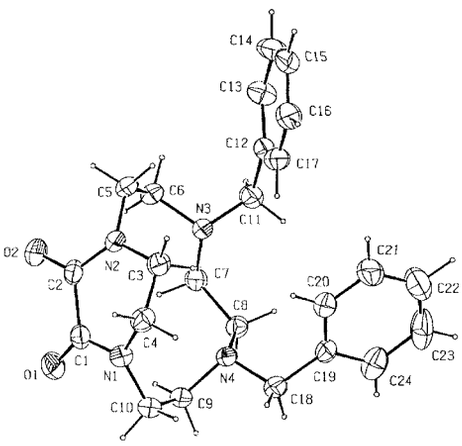



**Fig. 2** ORTEP diagram of the molecular structure of 1,4-dibenzyl-1,4,7,10-tetraazabicyclo[8.2.2]tetradecane-11,12-dione **4b**, with crystallographic numbering scheme.

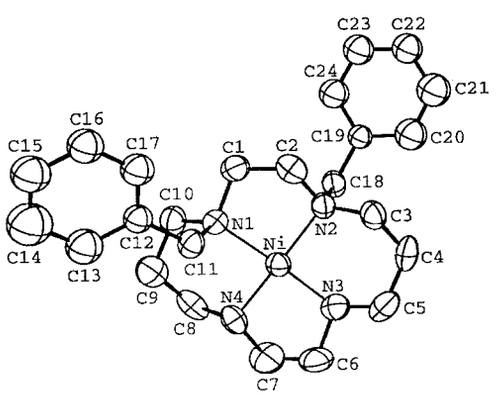



**Fig. 3** ORTEP diagram of the molecular structure of the complex [Ni(**4a′**)](ClO$_4$)$_2$, with crystallographic numbering scheme.

**Complex [Ni(4a′)](ClO$_4$)$_2$.** $C_{24}H_{36}Cl_2N_4NiO_8$, $M = 638.19$, monoclinic, $P2_1/c$, $a = 9.785(1)$, $b = 27.604(3)$, $c = 10.306(1)$ Å, $\beta = 91.55(2)°$, $V = 2783(1)$ Å$^3$, $Z = 4$, $\lambda$(Mo-K$\alpha$) = 0.710 73 Å, $\mu = 9.45$ cm$^{-1}$, $F(000) = 1336$, $D_{calc} = 1.523$ g cm$^{-3}$, $T = 294$ K, 5312 reflections measured. Refinement of 352 variables gave $R = 0.054$, $R_w = 0.061$ and G.O.F = 1.083 (residual $\Delta\rho \leq 0.471$ $e$ Å$^{-3}$) by using 1719 reflections with $I > 1.5\sigma(I)$. The structure is presented in Fig. 3.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