

Self-assembly route from a bis-aminal derivative to a new cyclam based macropentacycle†

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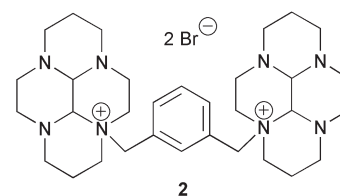
A new powerful two-step synthesis of a cyclam-based macropentacycle ligand is reported. In this procedure, the starting material is the bis-aminal derived from the condensation of cyclam with glyoxal. The tetrameric polyammonium intermediate issued from the self-assembly process and the free ligand were fully characterized by conventional methods and a tetranuclear Cu(II) complex was prepared.

Polyazacycloalkanes are versatile ligands well-known for their high binding affinity towards transition metals;^{1,2} their synthesis and their selective *N*-alkylation have both been very popular objectives of research groups over the last thirty years.³ Recently, tetraazacycloalkane bis-aminal building blocks were successfully used for macrocycle alkylation, especially for macropolycycle synthesis of compounds such as bis-macrocycles or macrotricycles.^{4–12} Indeed, macropolycyclic ligands present a great interest because of their ability to behave as multi-site receptors in the trapping of various substrates or in metal coordination.^{13–20} They are formed by linking macrocyclic rings with spacer bridges, which define multiple cavities. The consequence of such a construction is that metal coordination can result from the macrocyclic sub-units (with possible metal-metal interactions) while the delineated central cavity can constitute an excellent host for bulky anionic species.

Structures exhibiting more than three host receptors in their edifice are often a self-assembly of complementary ligands and ions assembled by coordination polymerization, hydrogen bonding or π - π interactions.^{18–22} To our knowledge, cyclic polymers involving a great number of tetraazacycloalkane ligands linked by covalent bonds have not been reported. In the continuation of our work on bis-aminal tools for macropolycycle synthesis,^{9,12} we report here a new route to a cyclic cyclam tetramer involving a self-assembly process of a cyclam-glyoxal synthon.

Cyclam (1,4,8,11-tetraazacyclotetradecane) reacts with glyoxal in methanolic solution at room temperature to give quantitatively the cyclam-glyoxal (decahydro-3a,5a,8a,10a-tetraazapyrene; **1**) in a *cis* configuration.⁴ In previous works, it was shown that the reaction of *cis*-cyclam-glyoxal with 2 equiv. of an electrophile leads to the selective *N*₁,*N*₈ dialkylation of the macrocycle *via* a diammonium salt;^{4,8,9,12} furthermore, it is established that the two consecutive attacks take place on

the same side of the mean plane of the molecule, which contains the two aminal hydrogen atoms, leading to *cis*-*N*₁,*N*₈-dialkylated adducts. As a consequence of the alkylation, the four nitrogen atoms and the aminal carbon atoms become chiral centers (Fig. 1) and a *RR* or *SS* configuration of the aminal carbon atoms results from the nitrogen atom dialkylation (the all-*cis* disalt presents a C₂ axis as the unique symmetry element). We have recently demonstrated that this *cis* product is favorable to a [2+2] reaction and have taken advantage of this property to synthesize cylindrical macrotricycles.¹² So, compound **3a** (Scheme 1) is easily obtained when 1,3-bis(bromomethyl)benzene is added to the *cis*-cyclam-glyoxal **1** in acetonitrile at room temperature. We have established that the reaction occurs *via* the bis-macrocyclic diammonium salt **2**.



However, in more concentrated solutions, in addition to compound **3a**, a secondary product was detected and identified by mass spectrometry as the [4+4] adduct (Scheme 1). The synthesis of this new compound was optimized under the best conditions of concentration to obtain a 40:60 ratio of the tetramer **3b** to the dimer **3a**. The two compounds were easily separated by crystallization of **3b** in water. The deprotection of the polyammonium salt was performed in hydrazine monohydrate, leading quantitatively to the free cyclic cyclam tetramer **4**, which could be called a macropentacycle in relation to its four macrocycles added to the central cavity (Scheme 2).

The macropolycycles **3b** and **4** have been fully characterized by spectroscopic methods, including 2D NMR experiments, and satisfactory elemental analyses have been obtained. Temperature dependent ¹H and ¹³C NMR studies on **3b** showed at

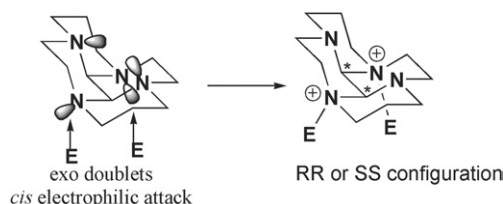
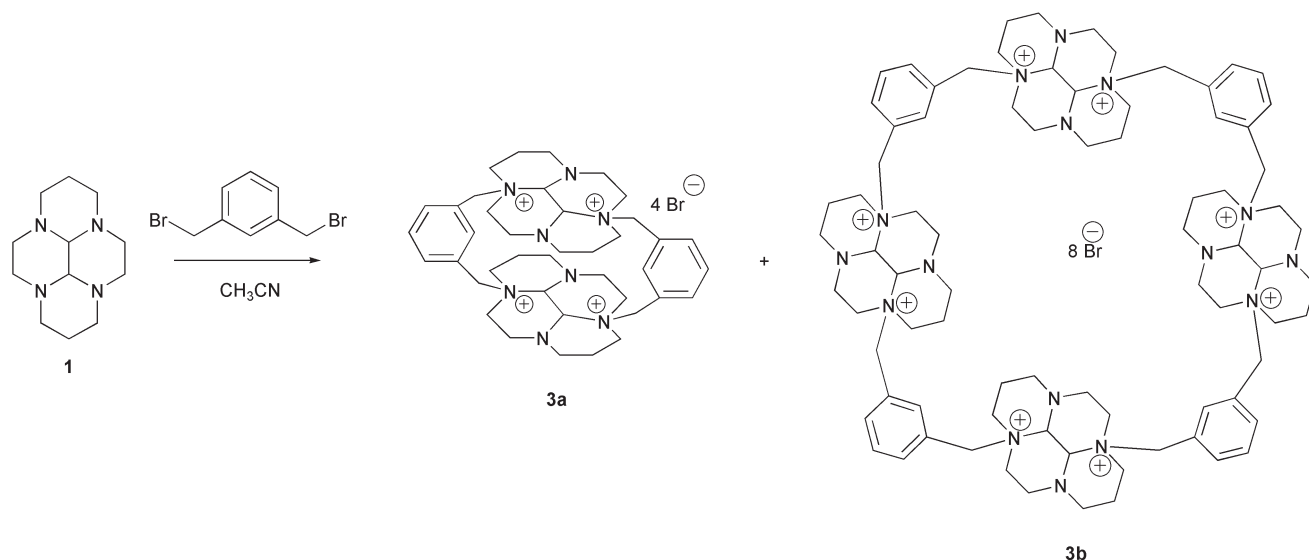


Fig. 1 *Cis* attack of a bis-electrophile on the cyclam-glyoxal **1**.

† Electronic supplementary information (ESI) available: ¹H NMR spectrum of **2a** and X-ray study of **3b**, including views of the asymmetric unit, space-filling models and molecular packing. See <http://www.rsc.org/suppdata/nj/b3/b310074j/>



Scheme 1 Tetramer formation.

284 K an exchange phenomenon between nonsymmetric conformations. At higher temperature, the spectra became more simple, because of a high degree of symmetry and a unique configuration of the tetrameric structure. The final free tetramer **4** exhibited simple NMR spectra corresponding to a symmetric edifice.

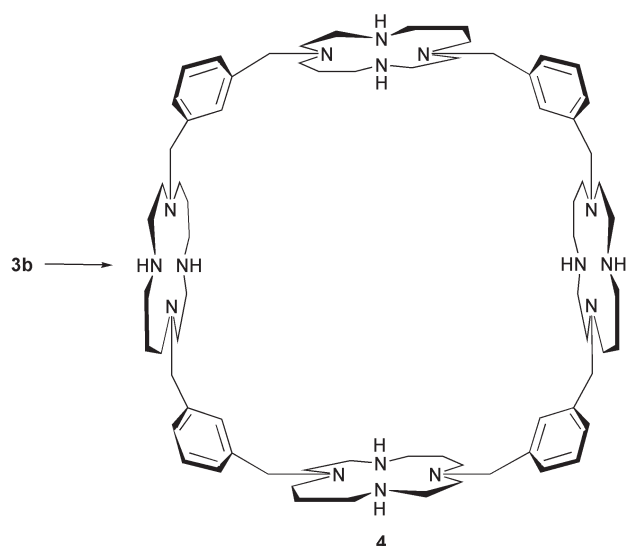
The structure of **3b** was established unequivocally by single-crystal X-ray analyses proving the formation of the [4 + 4] adduct (Fig. 2). This tetramer is constituted of a sequence of alternating *RR* and *SS* cyclam-glyoxal subunits linked with 1,3-dimethylbenzene spacers, resulting in an achiral meso structure. Moreover, the molecule presents a secondary saddle-shaped structure. One bromide atom lies in the central cavity and four others are situated at the center of each face of the edifice.

In solution, the high symmetry of **3b** observed in NMR spectroscopy, a consequence of the two sigma planes of the unique meso structure, emphasizes a highly selective self-assembly process. We have previously observed that for the diammonium salt **2** and macrotricyclic **3a**, the alkylation reaction is stereospecific, since these compounds have been obtained as unique but unidentified configurations.^{9,12} Supplementary information about these configurations was provided by the following experiment: when the bis-macrocycle diammonium salt **2** was allowed to react with 1,3-bis(bromomethyl)benzene

in concentrated solution, the former cyclic dimer **3a** and tetramer **3b** were obtained, in a 60:40 ratio as described earlier. The following conclusions can be formulated from these observations: (i) the polyammonium salts of the bis-macrocycle⁹ **2** and of the macrotricyclic¹² **3a** are the meso diastereoisomers; (ii) the [4 + 4] reaction proceeds in reality *via* the initial formation of the meso bis-macrocycle building block, which evolve to the cyclic dimer **3a** and, partially in concentrated solution, to the tetramer **3b**.

The copper (II) complex [Cu₄(**4**)](ClO₄)₈·13H₂O was synthesized using the corresponding perchlorate salt and characterized by elemental analyses, mass spectrometry, UV-visible and IR spectroscopy. A typical band for Cu-cyclam at 530 nm in the UV-vis spectrum and a shifting of the NH band in the IR ($\delta\nu_{\text{NH}} = -54 \text{ cm}^{-1}$) after complexation highlight the copper coordination. EPR measurements were investigated (solid state, CH₃CN at 120 K, RT) but no intermetallic interaction was evidenced, certainly due to the too long distances between the different coordination sites, unlike the corresponding cylindrical dimer copper (II) complexes.¹⁷ However molecular modelling indicated that in the complex, the charged cavity is favorable to the trapping of large anionic species.

In conclusion, we describe here a new macropentacyclic ligand obtained in reasonable yields in a two-step synthesis. The availability of the starting materials, cyclam, glyoxal and α,α' -dibromo-*meta*-xylene allows the synthesis of large quantities of this compound. The configurations of the tetrameric polyammonium salt and, subsequently, the dimeric and the bis-macrocylic ones have been elucidated. We are now extending the scope of the methodology to other tetrameric derivatives and studying the polyammonium intermediates, which constitute a class of very attractive crown ligands for host-guest processes involving anions.



Scheme 2 Tetramer deprotection with hydrazine monohydrate.

Experimental

General

All reagents were of commercial quality and solvents were dried using standard procedures. Elemental analyses were performed at the Service de Microanalyse of the CNRS (Gif sur Yvette, France). Mass spectrometry analyses were performed at the Centre Régional de Mesures Physiques de l'Ouest (Rennes, France). The single-crystal X-ray diffraction data were measured at the Centre de Ddiffractométrie X (University of Rennes 1, France).

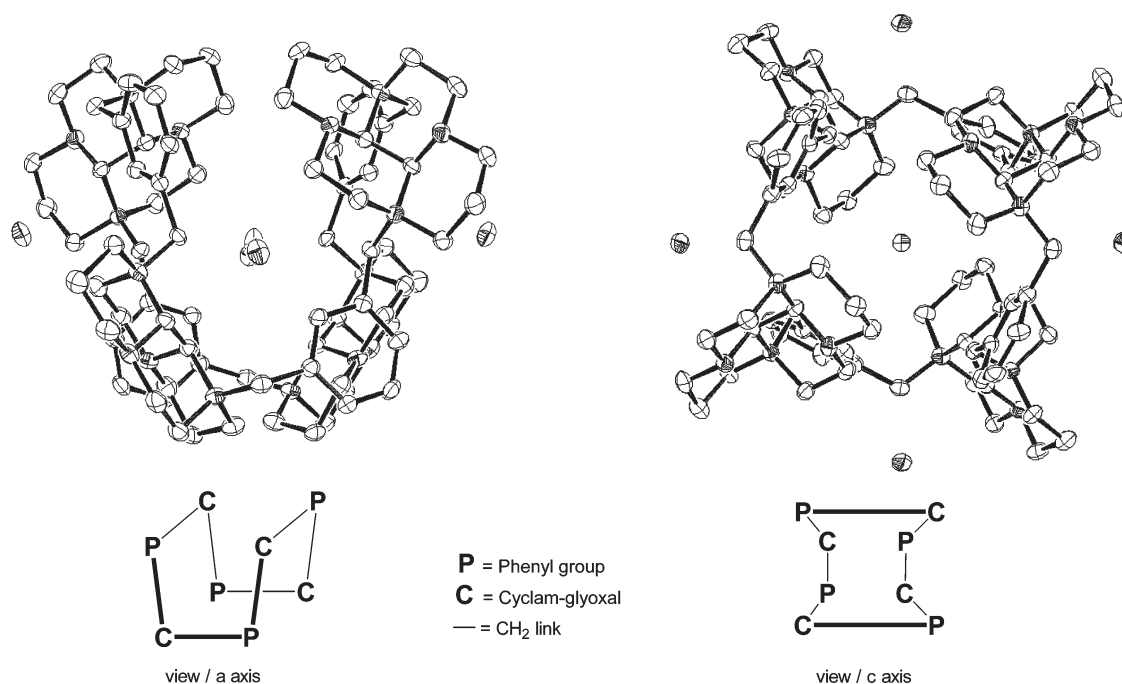


Fig. 2 ORTEP views of **3b** along two axes, with 50% probability ellipsoids.

X-Ray diffraction

Colorless rod-shaped crystals of **3b** were obtained from evaporation of an aqueous solution. The data collection was performed at room temperature on a Nonius Kappa CCD diffractometer with graphite monochromated MoK α radiation. Unit-cell determination, Lorentz, polarization data reduction were carried out using Scalepack and Denzo software.²³ The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 with, respectively, the SIR97²⁴ and SHELXL97²⁵ suites of programs. The hydrogen atoms were introduced in the last step and refined isotropically. Crystallographic data are summarized in Table 1. The organic moiety of the assembled molecule appeared to be the tetramer $\{[C_{20}H_{30}N_4Br]^{8+}\}$ with symmetry $\bar{4}$. Five Br[−] anions per tetramer were found unambiguously, one in the center $\bar{4}$ position and four symmetrically related about this center, in front of each open lateral side of the tetramer. Each side of a tetramer is also closed by the homologous Br[−] anion of a neighboring tetramer unit (see Electronic supplementary information). This leads to a cell content of four $\{[C_{20}H_{30}N_4Br]_4Br\}^{3+}$. Three other Br[−] anions are expected per tetramer but could not be located. Substitutional disorder is definitely present. At this step, surrounding the tetramer, six residual Fourier peaks remained per asymmetry unit (among which one is on another $\bar{4}$ center; *i.e.*, there are 21 peaks per tetramer). All are virtually assignable to oxygen atoms (electronic charge around 8 e[−]), except one, equivalent to half an oxygen. We suppose the last three Br[−] anions are randomly located over these sites. Taking into account the bulk of the Br[−] anions, a satisfactory solution is reached giving them a statistical occupation factor of 0.25 (effective charge becomes $0.25 \times 36 = 9$, close to 8) and placing them instead of the Fourier peaks having the (similarly) lowest displacement parameters. These three sites are in general positions. Two of them are too close to be occupied simultaneously in the same symmetry unit. The other 9 peaks attached to the tetramer are ascribable to O atoms generated from three unique atoms. Among these atoms, one is on a $\bar{4}$ center, one is in general position with an occupation factor of 1 and the last is also in a general position but with an occupation factor of 0.5 ($1 + 4 \times 1 + 4 \times 0.5 = 7$ O per tetramer). They are assumed to belong to water molecules (the corresponding hydrogen

Table 1 Crystal data, data collection parameters and refinement^a results for **3b**

Empirical formula	[C ₂₀ H ₃₀ N ₄ Br] ₄ Br ₄ O ₇
Formula weight	2057.2
Molecular symmetry	$\bar{4}$
Crystal system	Tetragonal
Space group	$I-4$ d
<i>Z</i>	4
<i>a</i> /Å	24.976(7)
<i>b</i> /Å	24.976(7)
<i>c</i> /Å	16.258(3)
<i>U</i> /Å ³	10 142(5)
$\alpha = \beta = \gamma/^\circ$	90.000(5)
<i>T</i> /K	293(2)
λ /Å	0.7107
μ /mm ^{−1}	3.216
Measured reflections	8450
Unique reflections	4326
Obs. reflect. [$I > 2\sigma(I)$]	3054
<i>R</i> _{int}	0.0356
<i>R</i> ₁ [$I > 2\sigma(I)$]	0.070 [0.102]
<i>wR</i> ₂ ^b [$I > 2\sigma(I)$]	0.235 [0.195]

^a Refinement on all 4309 F^2 , 261 parameters, 0 restraints, 4326 data, 17 rejected, 3054 with $I > 2\sigma(I)$. ^b $w = 1/[\sigma^2 + (0.128P)^2 + 22.17P]$ with $P = (F_o^2 + 2F_c^2)/3$

atoms were disregarded in the refinement). This solution, assuming 8 Br atoms and 7 O atoms per tetramer, is in good agreement with the microanalysis results.†

Syntheses

Cyclam-glyoxal **1** and the diammonium salt **2** were synthesized as previously described.⁹

Macropolycycles 3a and 3b. A solution of 1,3-bis(bromo-methyl)benzene (1.18 g, 4.5 mmol) in CH₃CN (5 mol l^{−1})

‡ CCDC reference number 223768. See <http://www.rsc.org/suppdata/nj/b3/b310074j/> for crystallographic data in .cif or other electronic format.

was added to a solution of cyclam-glyoxal (1 g, 4.5 mmol) in CH₃CN (5 mol l⁻¹) at room temperature under vigorous stirring. After 3 days, filtration of the white precipitate formed gave a mixture of macropolycyclic polyammonium salts **3a** and **3b**. The smallest amount of distilled water at 80 °C was added to solubilize the white powder and the mixture was placed at 5 °C overnight. The colorless crystals formed were then filtered, washed with cold distilled water, recrystallized a second time in distilled water and dried to give **3b** in 20% yield (0.43 g). In parallel, ethanol was added to the filtrate under vigorous stirring. The white precipitate formed was filtered, washed with ethanol and ether and finally dried to give **3a** in 50% yield (1.09 g).

3a. Described in previous work.¹²

3b. ¹H NMR (D₂O, 400 MHz, 284 K): δ = 1.04 (d, 1H, CHβ), 1.33 (t, 1H, CHα), 1.90 (d, 1H, CHβ), 2.22 (t, 1H, CHα), 2.32 (m, 2H, CHβ), 2.43 (d, 1H, CHα), 2.96 (t, 1H, CHα), 3.25 (m, 2H, CHα), 3.32 (d, 1H, CHα), 3.41 (m, 3H, CHα), 3.57 (m, 2H, CHα), 3.70 (d, 1H, CHα), 4.00 (t, 1H, CHα), 4.45 (t, 1H, CHα), 4.63 (d, 1H, CHPh), 4.69 (s, 1H, CHAm), 4.77 (t, 1H, CHα), 4.99 (d, 1H, CHPh), 5.71 (d, 1H, CHPh), 6.26 (d, 1H, CHPh), 6.32 (s, 1H, CHAm), 7.41 (s, 1H, CHAr), 7.83 (m, 2H, CHAr), 8.06 (d, 1H, CHAr). ¹³C NMR (D₂O, 100 MHz, 284 K): δ = 20.1 (Cβ), 48.4, 49.3, 50.1, 53.6, 54.3, 56.1 (Cα), 63.1 (CPh), 63.3, 64.0 (Cα), 66.4 (CPh), 76.1, 80.5 (Cam), 129.4, 130.6 (quatCAR), 134.3, 137.7, 140.9, 141.1 (tertCAR). ¹H NMR (D₂O, 400 MHz, 353 K): δ = 1.70 (m, 1H), 1.86 (m, 1H), 2.51 (m, 1H), 2.90 (m, 2H), 3.57 (m, 1H), 3.70–4.45 (m, 10H), 4.96–5.87 (m, 5H), 6.28 (m, 1H), 6.80 (m, 2H), 7.88–8.5 (m, 4H). ¹³C NMR (D₂O, 100 MHz, 353 K): δ = 21.1 (Cβ), 49.1, 49.7, 54.0, 63.9 (Cα), 64.3 (CPh), 80.1 (Cam), 129.4 (quatCAR), 133.8, 139.2, 140.7 (tertCAR). FAB-MS: *m/z* 1937.4 [M + H]⁺. Anal. calcd for C₈₀H₁₂₀N₁₆Br₈·7H₂O: C, 46.39; H, 6.52; N, 10.82%; found C, 46.45; H, 6.79; N, 10.84%.

Polyammonium salt 3b deprotection. The octa-salt **3b** was refluxed in hydrazine monohydrate as previously described⁹ to give, after purification by recrystallization in acetone, the cyclic tetramer **4** in 96% yield. ¹H NMR (CDCl₃, 400 MHz): δ = 1.68 (qt, 4H, CH₂β), 2.35 (t, 8H, CH₂α), 2.44 (t, 8H, CH₂α), 2.63 (t, 8H, CH₂α), 2.66 (t, 8H, CH₂α), 3.59 (s, 4H, CH₂Ph), 3.85 (s, 4H, NH), 7.01–7.41 (m, 4H, CHAr). ¹³C NMR (CDCl₃, 100 MHz): δ = 25.4 (Cβ), 47.4, 49.1, 50.8, 53.0 (Cα), 58.0 (CPh), 128.1 (quatCAR), 130.9, 137.4, 137.1 (tertCAR). FAB-MS (MeOH): *m/z* 1211.01 [M + H]⁺. Anal. calcd for C₇₂H₁₂₀N₁₆: C, 71.48; H, 10.00; N, 18.52%; found C, 71.41; H, 10.10; N, 18.63%. IR (KBr): ν_{NH} = 3285 cm⁻¹.

Preparation of complex [Cu₄(4)][ClO₄]₈·13H₂O. *Caution! Perchlorate salts combined with organic ligands are potentially explosive and should be handled in small quantities and with necessary precautions.*

The perchlorate salt Cu(ClO₄)₂·6H₂O was prepared from the corresponding oxides.

A 0.36 mmol amount of Cu(ClO₄)₂·6H₂O in distilled water (3 mL) was slowly added to a refluxing solution of **4** (0.083 mmol) in acetonitrile (3 mL) and stirred for 5 h. After cooling, methanol was added (5 mL) and the blue powder that precipitated was filtered and re-dissolved in boiling distilled water (4 mL). After cooling, the resulting pale brown microcrystalline aggregates that appeared were collected by filtration and dried to give the complex [Cu₄(4)][ClO₄]₈·13H₂O in 98% yield. ESI-MS (CH₃CN): *m/z* 2253.33 [M + H]⁺. Anal. calcd for

C₇₂H₁₂₀N₁₆O₃₂Cl₈Cu₄·13H₂O: C 34.68, H 5.90, N 8.99; found C 34.73, H 5.70, N 8.92. IR (KBr): ν_{NH} = 3231 cm⁻¹. UV-vis (CH₃CN): λ/nm (ε/M⁻¹ cm⁻¹) 345–350 (1640), 530 (803). EPR (CH₃CN, 295 K and 120 K): *g* = 2.065 (powder, 295 K) and *g* = 2.075 (powder, 120 K).

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References

- 1 R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901–927.
- 2 R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, 1995, **95**, 2529–2586.
- 3 F. Denat, S. Brandès and R. Guillard, *Synlett*, 2000, **5**, 561–574 (review).
- 4 G. R. Weisman, M. E. Rogers, E. H. Wong, J. P. Jasinski and E. S. Paight, *J. Am. Chem. Soc.*, 1990, **112**, 8604–8605.
- 5 J. Rohovec, R. Gyepes, I. Cisarova, J. Rudovsky and I. Lukes, *Tetrahedron Lett.*, 2000, **41**, 1249–1253.
- 6 T. J. Hubin, J. M. McCormick, N. Alcock and D. H. Busch, *Inorg. Chem.*, 1998, **37**, 6549–6551.
- 7 E. H. Wong, G. R. Weisman, D. C. Hill, D. P. Reed, M. E. Rogers, J. S. Condon, M. A. Fagan, J. C. Calabrese, K.-C. Lam, I. A. Guzei and A. L. Rheingold, *J. Am. Chem. Soc.*, 2000, **122**, 10 561–10 572.
- 8 J. Kotek, P. Hermann, P. Vojtisek, J. Rohovec and I. Lukes, *Collect. Czech. Chem. Commun.*, 2000, **65**, 243–266.
- 9 M. Le Baccon, F. Chuburu, L. Toupet, H. Handel, M. Soibinet, I. Déschamps-Olivier, J.-P. Barbier and M. Aplincourt, *New J. Chem.*, 2001, **25**, 1168–1174.
- 10 F. Boschetti, F. Denat, E. Espinosa and R. Guillard, *Chem. Commun.*, 2002, 312–313.
- 11 F. Chuburu, R. Tripiet, M. Le Baccon and H. Handel, *Eur. J. Org. Chem.*, 2003, **6**, 1050–1055.
- 12 S. Develay, R. Tripiet, F. Chuburu, M. Le Baccon and H. Handel, *Eur. J. Org. Chem.*, 2003, 3047–3050.
- 13 H. An, J. S. Bradshaw and R. M. Izatt, *Chem. Rev.*, 1992, **92**, 543–572.
- 14 J.-M. Lehn, *Pure Appl. Chem.*, 1980, **52**, 2441–2459.
- 15 K. E. Krakowiack, J. S. Bradshaw, X. Kou and N. K. Dalley, *J. Heterocycl. Chem.*, 1995, **32**(3), 931–935.
- 16 S. Quici, A. Manfredi, L. Raimondi and A. Sironi, *J. Org. Chem.*, 1995, **60**, 6379–6388.
- 17 M. Lachkar, R. Guillard, A. Atmani, A. De Cian, J. Fisher and R. Weiss, *Inorg. Chem.*, 1998, **37**, 1575–1584.
- 18 A. McAuley and S. Subramanian, *Coord. Chem. Rev.*, 2000, **200–202**, 75–103.
- 19 J. D. Chartres, L. F. Lindoy and G. V. Meehan, *Coord. Chem. Rev.*, 2001, **216–217**, 249–286.
- 20 A. Ingham, M. Rodopoulos, K. Coulter, T. Rodopoulos, S. Subramanian and A. McAuley, *Coord. Chem. Rev.*, 2002, **233–234**, 255–271.
- 21 V. C. Lau, L. A. Berben and J. R. Long, *J. Am. Chem. Soc.*, 2002, **124**, 9042–9043.
- 22 S. Aoki, M. Shiro and E. Kimura, *Chem.-Eur. J.*, 2002, **8**, 929–939.
- 23 Z. Otwinowski and W. Minor, in *Methods of Enzymology, Macromolecular Crystallography*, part. A, eds. C. W. Carter and R. M. Sweet, Academic Press, New York, 1997, vol. 276, pp. 307–326.
- 24 A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.
- 25 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.