JOC Article

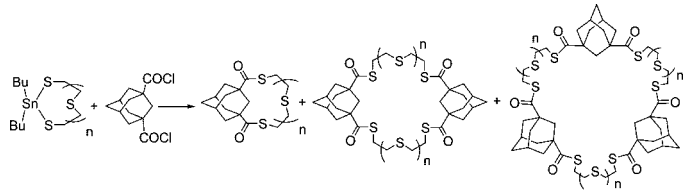
Thiamacrocyclic Lactones: New Ag(I)-Ionophores

Ines Vujasinović,[†,§] Jelena Veljković,[†] Krešimir Molčanov,[‡] Biserka Kojić-Prodić,[‡] and Kata Mlinarić-Majerski*,[†]

Department of Organic Chemistry and Biochemistry, and Department of Physical Chemistry, Ruđer Bošković Institute, Bijenička cesta 54, P.O. Box 180, 10002 Zagreb, Croatia

majerski@irb.hr

Received May 26, 2008



1 n = 0 **2** n = 1 **3** n = 2 **4** n = 3 — **21** — **-** **-** **9** n = 2 **11** n = 3 — **5** n = 0 **7** n = 1 **10** n = 2 **12** n = 3 — **6** n = 0 **8** n = 1 - -

The syntheses of novel adamantane thialactones **5**−**12** are reported, and the results of the heavy- and transition-metal cation extraction experiments are described. The results are compared with those obtained with similar thiamacrocyclic ligands that have flexible chains of methylene groups incorporated into the macrocyclic framework as in **13**−**20**. The results show that most of the hosts studied are very good in complexing the Ag^+ ion. The formation of complexes has also been demonstrated using NMR titration experiments for macrocycles **13** and **14** with AgTFA. Introduction of a single polycyclic molecule into the 15- to 18-membered rings increases the rigidity and preorganizes the ligand for complexation. However, two adamantane molecules embedded in the ring usually diminish the complexing ability of the ligand, primarily due to sterical effects of the bulky adamantane moiety that obstructs formation of an optimal geometry for binding the desired metal ion. The structures of macrocycles **5**, **7**, **9**, **11**, and **19** were determined by X-ray structure analysis, and their conformational properties are discussed. In the solid state, **7**, **11**, and **19** are organized into tubular fashion using C−H···O interactions. Also, two silver complexes with thialactone **13**, **Ag13** and **Ag(13)$_2$**, were prepared and characterized. The structure analysis of **Ag13** and **Ag(13)$_2$** reveals the formation of mononuclear and binuclear species with silver in ambivalent, tetrahedral coordination via sulfur and oxygen from trifluoroacetate anion.

Introduction

Macrocyclic polyethers have widespread use in various areas of science and technology ever since the first preparation of the macrocyclic ligands by Pedersen.[1] The most important characteristic of thiamacrocyclic ligands is their ability to form stable complexes with cations of heavy and transition metals, as well as their ability to selectively bind just one cation from the mixture of cations.[2] For that very reason, interest for the design, synthesis, and application of these synthetic receptors as selective complexing agents has received much attention in the last few decades. Thiamacrocyclic ligands are used in industrial chemistry (selective extractants of metal ions from the waste waters[3,4] and catalytic precursors in the process of direct transformation of coal into oil and gas[5]), analytical chemistry (sensors in ion-selective membrane electrodes),[6,7] synthetic chemistry ("phase-transfer" catalysts and anion activa-

* To whom correspondence should be addressed. Phone: ++385-1-4680196. Fax: ++385-1-4680195.
§ Current address: GlaxoSmithKline Research Centre Zagreb, Prilaz baruna Filipovića 29, 10000 Zagreb, Croatia.
† Department of Organic Chemistry and Biochemistry.
‡ Department of Physical Chemistry.

(1) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
(2) (a) Cooper, S. R.; Rawle, S. C. *Struct. Bonding (Berlin, Ger.)* **1990**, *72*, 1–72. (b) Melson, G. A. *Coordination Chemistry of Macrocyclic Compounds*; Plenum Press: New York, 1979.
(3) Baumann, T. F.; Reynolds, J. G.; Fox, G. A. *Chem. Commun.* **1998**, 1637–1638.
(4) Shamsipur, M.; Hashemi, O. R.; Lippolis, V. *J. Membr. Sci.* **2006**, *282*, 322–327.
(5) Hayward, N.; Schobert, H. H. *Energy Fuels* **1993**, *7*, 326–327.
(6) Fakhari, A. R.; Ganjali, M. R.; Shamsipur, M. *Anal. Chem.* **1997**, *69*, 3693–3696.
(7) Singh, A. K.; Saxena, P. *Talanta* **2005**, *66*, 993–998.

10.1021/jo801143s CCC: $40.75
Published on Web 10/29/2008

tors),[8] and biochemistry (transfer of ions through a membrane).[9,10] Furthermore, they have proved to be efficient models in the study of electron transfer within the Cu(II/I) redox system of "blue proteins" such as azurine.[11] The design of thiamacrocycles as ligands for silver complexes is of interest for radioactive labeling of biological systems with the radioisotope ^{111}Ag that is used, due to convenient radiation properties.[12] For such applications, relatively stable silver complexes are required to prevent transmetalations in the human body.

Up to date, numerous structural modifications of macrocyclic ligands have been performed, where the size of the macrocyclic ring and the type of donor atoms have been changed; various substituents have been introduced, and the structural influence on the complexing properties of ligands has been examined.[13] Today we can accurately define some of the key factors that influence the affinity of a ligand toward a specific cation, effectively controlling its selectivity.[13] Even though a large number of unfunctionalized thiamacrocyclic ligands have been prepared so far,[14] only a relatively small number of thiamacrocyclic ligands with a rigid molecule within their structure are known. In the literature, there are some examples of embedded xylene,[15] keto group,[16] isoalkene,[17] $-CH_2$ group,[18] or polycyclic molecules like pinan,[19] PCU,[20] and adamantane.[21]

In the context of our work on the synthesis of different macrocyclic ligands with adamantane functionality,[22] we turned our attention to thiamacrocyclic ligands with adamantane units embedded into a macrocyclic framework, such as **5**−**12**. An adamantane molecule should function as a rigid spacer that reduces the conformational mobility of the ligand, defining the shape and size of the cavity of the macrocyclic ring, and therefore, improve the selectivity of complexing cations. Furthermore, the adamantane moiety enhances the lipophilicity of the prepared macrocyclic ligand, lowering its solubility in protic solvents such as water and methanol, which is an important property in selective ion extraction.

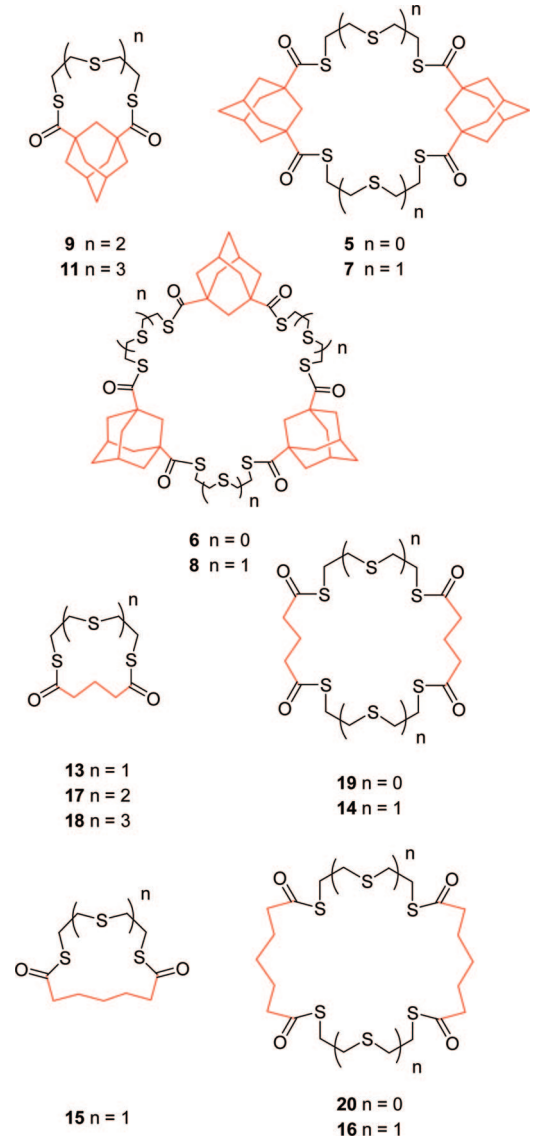


FIGURE 1. Thiamacrocyclic lactones with adamantane and chainlike units embedded into a macrocyclic framework.

In this paper, we report the synthesis of a series of novel adamantane-embedded, thiamacrocyclic ligands **5**−**12**, their characterization by spectroscopic methods, and the investigation of their ability to complex metal ions. The results are compared with those obtained with thiamacrocyclic ligands that have flexible chains of three (**13**, **14**, and **17**−**19**) or five (**15**, **16**, and **20**) methylene groups incorporated into the macrocyclic framework (Figure 1). In addition, we isolated and characterized two silver complexes with macrocyclic ligand **13**, **Ag13** and **Ag(13)$_2$**.

Results and Discussion

Adamantane thiamacrocyclic ligands **5**−**12** were prepared via ring-opening condensation of corresponding stannapolythianes[23] with adamantane-1,3-dicarbonyl dichloride (**21**), applying the same coupling strategy and conditions as we used in the

(8) (a) Shan, N.; Adams, H.; Thomas, J. A. *Inorg. Chim. Acta* **2006**, *359*, 759–765. (b) Fujihara, H.; Imaoka, K.; Furukawa, N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 465–470.
(9) Stephenson, M. J.; Holmes, S. M.; Dryfe, R. A. W. *Electrochem. Commun.* **2004**, *6*, 294–298.
(10) Shamsipur, M.; Azimi, G.; Mashhadizadeh, M. H.; Madaeni, S. S. *Anal. Sci.* **2001**, *17*, 491–494.
(11) Rorabacher, D. B. *Chem. Rev.* **2004**, *104*, 651–697.
(12) Gyr, T.; Mäcke, H. R.; Hennig, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2786–2788.
(13) (a) Schneider, H. J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley & Sons: New York, 2000. (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley & Sons: New York, 2000. (c) Vögtle, F. *Supramolecular Chemistry*; Wiley & Sons: New York, 1991. (d) Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley-VCH: Weinheim, Germany, 1995.
(14) (a) Blake, J.; Schröder, M. *Adv. Inorg. Chem.* **1990**, *35*, 1–80. (b) Cooper, S. R. *Acc. Chem. Rev.* **1988**, *21*, 141–146. (c) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev.* **1985**, *85*, 271–339.
(15) de Groot, B.; Jenkins, H. A.; Loeb, S. J. *Inorg. Chem.* **1992**, *31*, 203–208.
(16) Edema, J. J. H.; Buter, J.; Kellogg, R. M.; Spek, A. L.; van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1992**, 1558–1560.
(17) Buter, J.; Kellogg, R. M.; van Bolhius, F. *J. Chem. Soc., Chem. Commun.* **1990**, 282–284.
(18) de Groot, B.; Loeb, S. J. *Inorg. Chem.* **1989**, *28*, 3573–3578.
(19) Siswanta, D.; Nagatsuka, K.; Yamada, H.; Kumakura, K.; Hisamoto, H.; Shichi, Y.; Toshima, K.; Suzuki, K. *Anal. Chem.* **1996**, *68*, 4166–4172.
(20) (a) Williams, S. M.; Brodbelt, J. S.; Marchand, A. P.; Cal, D.; Mlinarić-Majerski, K. *Anal. Chem.* **2002**, *74*, 4423–4433. (b) Marchand, A. P.; Cal, D.; Mlinarić-Majerski, K.; Ejsmont, K.; Watson, W. H. *J. Chem. Crystallogr.* **2002**, *32*, 447–463.
(21) (a) Mlinarić-Majerski, K.; Pavlović, D.; Luić, M.; Kojić-Prodić, B. *Chem Ber.* **1994**, *127*, 1327–1329. (b) Mlinarić-Majerski, K.; Pavlović, D.; Milinković, V.; Kojić-Prodić, B. *Eur. J. Org. Chem.* **1998**, 1231–1236. (c) Mlinarić-Majerski, K.; Vinković, M.; Škare, D.; Marchand, A. P. *ARKIVOC* **2002**, *IV*, 30–37. (d) Višnjevac, A.; Kojić-Prodić, B.; Vinković, M.; Mlinarić-Majerski, K. *Acta Crystallogr.* **2003**, *C59*, 314–316. (e) Mlinarić-Majerski, K.; Vujasinović, I. *Kem. Ind.* **2007**, *56*, 145–150.

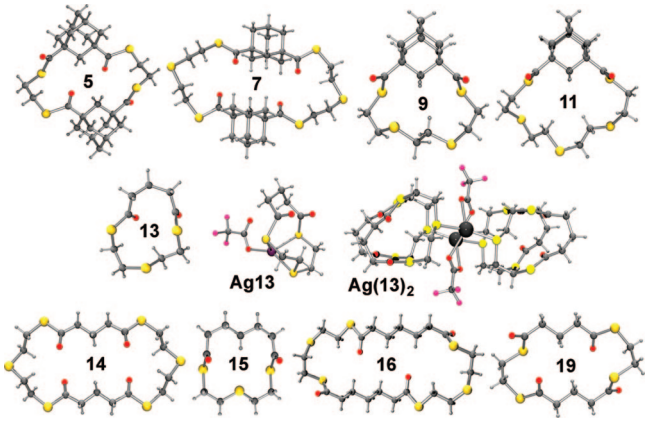


FIGURE 2. Ball-and-stick representation of thialactone structures and silver complexes with ligand **13** determined by X-ray structure analysis. Structures of **5**, **7**, **9**, **11**, and **19** and complexes **Ag13** and **Ag(13)$_2$** are described in this paper, and ligands **13**, **14**, **15**, and **16** are in ref 24.

synthesis of the flexible cyclic polythialactones **13**−**20**, by reaction with glutaryl dichloride or pimeloyl dichloride.[23,24]

Reaction yields, as well as the ratio of the obtained products, depend on the size of the macrocyclic ring and on the number and type of spacer molecules. Thus, the dithialactones with one adamantane unit in the 9- to 12-membered ring (n = 0 or 1) have not been obtained. The best yield (>60%) was achieved in reactions where monomeric ligands with 15−18 atoms in their rings were prepared (ligands **9** and **11**). However, incorporation of two polycyclic molecules, as in **5** and **7**, lowers the product yield to 30−35%. The low yield (5−20%) has also been obtained for the 24-membered rings, as in ligands **6** and **8**.[25]

All new compounds were characterized by analysis of their respective IR, ^{1}H NMR, and ^{13}C NMR spectra, elemental microanalysis, and/or HRMS (see Experimental Section and Supporting Information). The structures of prepared ligands **5**, **7**, **9**, **11**, and **19** and metal complexes of silver with macrocycle **13** were characterized by X-ray structural analysis (Figure 2 and Supporting Information, Figures S1−S7).

In the solid state, thialactones **5**, **7**, and **19** exhibit C_i molecular symmetry, whereas monomers **9** and **11** reveal no ring symmetry. Furthermore, as it was noticed earlier for the thialactones **14** and **15**,[24] thialactones **9** and **11** comprise two crystallographically independent molecules in the unit cells (Table 1 and Supporting Information, Figures S3 and S4, respectively).

The complexation of silver with ligand **13**, with the molar ratios of reactants 1:1 and 1:2, was performed using trifluoroacetate; the ambivalent, tetrahedral silver coordination in mono- and binuclear complexes was obtained. In the mononuclear complex, which is less stable than the binuclear one, silver is coordinated by three sulfur atoms from one macrocyclic ligand and one oxygen atom of trifluoroacetate anion. In the crystal, two crystallographically independent molecules are present, but their geometries are not different. The binuclear complex is of C_i molecular symmetry, and silver is coordinated by two sulfur atoms from two macrocyclic ligands and two oxygen atoms of trifluoroacetate anion acting as a bidentate bridging ligand between two metal cations (separated by 3.785 Å). In both complexes, the metal coordination has no impact on the conformation of macrocycle **13** (Figure 3). The stable ring conformation involves sulfur atoms positioned somewhere between *endo*- and *exo*-orientation, which are easily accessible for coordination.

In the compounds investigated by X-ray structure analysis, there are no strong proton donors available, and the crystal packing is governed by C−H···O and C−H···S hydrogen bonds (Supporting Information, Table S2).

Thialactones **7**, **11**, and **19** form tubular arrays similar to those of ligands **13** and **16**, reported earlier.[24] Adamantane thialactones **7** and **11** form discrete tubules (Figures 4 and 5, respectively), whereas molecules **19** are organized as partially overlapping tubules (Figure 6).

Molecules of **9** crystallized with two conformers, **9a** and **9b**, which alternate generating hydrogen-bonded columns extended in the [100] direction. However, the bulky adamantane moieties of two neighboring molecules are arranged according to pseudoinversion symmetry, leaving no empty space typical of tubular formation (Figure 7).

Compound **5** forms a layered structure linked by a single C−H···O bond, and instead of tubules, the molecules form a herringbone pattern (Figure 8).

The crystal packing of two silver complexes revealed different organizations of macrocylic ligands. The macrocycle ligands in **Ag13** do not form tubules as in the structure of **Ag(13)$_2$**. In the structure of **Ag13**, molecules are oriented in a head-to-tail fashion, generating close packing (Figure 9), whereas in **Ag(13)$_2$** there is a dominant motif of closely packed, double rows of macrocyclic tubules, similar to the packing of the free ligand **13**,[24] alternating by cation−anion layers (Figure 10).

The cation affinity was assessed by extraction experiments of corresponding metal picrate (Ag^+, Cd^{2+}, Cu^{2+}, Pb^{2+}, and Zn^{2+}) within a two-phase system (dichloromethane−water) and by subsequent measurement of the spectrophotometric absorbance of the picrate anion. As the water phase, a mixture of picric acid ($c = 3, 0 \times 10^{-5}$ M) and corresponding metal nitrate was used, whereas a dichloromethane solution of thiamacrocyclic ligand (1.0×10^{-4} M)[26] was used as the organic phase. Results are given in Table 2.

As shown in Table 2, the examined ligands showed the best extracting ability toward silver ions. One possible explanation of good Ag^+ complexation is that hard, divalent cations possessing high hydration energies cannot strongly interact with sulfur atoms in macrocycles, whereas less heavily hydrated soft cations, such as Ag^+, coordinate to soft sulfur donors.[27] Adamantane-derived thiamacrocyclic ligand **11** quantitatively

(22) (a) Marchand, A. P.; Kumar, K. A.; McKim, A. S.; Mlinarić-Majerski, K.; Kragol, G. *Tetrahedron* **1997**, *53*, 3467–3474. (b) Marchand, A. P.; Alihodžić, S.; McKim, A. S.; Kumar, K. A.; Mlinarić-Majerski, K.; Šumanovac, T.; Bott, S. G. *Tetrahedron Lett.* **1998**, *39*, 1861–1864. (c) Mlinarić-Majerski, K.; Višnjevac, A.; Kragol, G.; Kojić-Prodić, B. *J. Mol. Struct.* **2000**, *554*, 279–287. (d) Bryan, J. C.; Mlinarić-Majerski, K.; Kragol, G.; Marchand, A. P. *Z. Kristallogr.−New Cryst. Struct.* **2001**, *216*, 277–279. (e) Mlinarić-Majerski, K.; Kragol, G. *Tetrahedron* **2001**, *57*, 449–457. (f) Mlinarić-Majerski, K.; Šumanovac-Ramljak, T. *Tetrahedron* **2002**, *58*, 4893–4898. (g) Marchand, A. P.; Hazlewood, A.; Huang, Z.; Vadlakonda, S. K.; Rocha, J.-D. R.; Power, T. D.; Mlinarić-Majerski, K.; Klaić, L.; Kragol, G.; Bryan, J. C. *Struct. Chem.* **2003**, *14*, 279–288.

(23) Vujasinović, I.; Veljković, J.; Mlinarić-Majerski, K. *J. Org. Chem.* **2004**, *69*, 8550–8553.

(24) Vujasinović, I.; Veljković, J.; Mlinarić-Majerski, K.; Molčanov, K.; Kojić-Prodić, B. *Tetrahedron* **2006**, *62*, 2868–2876.

(25) In the reactions of stannapolythianes **3** and **4** with dichloride **21**, besides **9** and **11**, traces of dimers **10** and **12** were obtained, respectively. Detailed study of the influence of rigid spacer on macrocyclization, supported by computational analysis, is under investigation.

(26) Nabeshima, T.; Tsukada, N.; Nishijima, K.; Ohshiro, H.; Yano, Y. *J. Org. Chem.* **1996**, *61*, 4342–4350.

TABLE 1. Conformations of S−C−C−S Fragments in Thialactones 5, 7, 9, 11, 13, 14, 15, 16, and 19

compound[a]	molecular symmetry	ring[b]	torsion angle (°)[c] S1−C−C−S2	S2−C−C−S3	S3−C−C−S4	S4−C−C−S5
5	C_i	18	61.3 (2)			
7	C_i	24	−169.2 (2)	−177.9 (2)		
9a	C_1	15	62.0 (4)	174.5 (3)	64.0 (4)	
9b	C_1	15	63.4 (4)	170.6 (2)	64.1 (3)	
11a	C_1	18	58.5 (3)	172.8 (1)	−164.8 (2)	51.2 (3)
11b	C_1	18	163.6 (1)	−177.6 (1)	−178.9 (2)	64.8 (3)
13[d]	C_1	12	−50.4 (5)	−63.9 (4)		
14a[d]	C_i	24	−174.8 (3)	168.3 (3)		
14b[d]	C_i	24	−172.0 (3)	175.9 (3)		
15a[d]	C_1	14	73.6 (5)	−68.1 (5)		
15b[d]	C_1	14	65.2 (5)	−69.5 (5)		
16	C_i	28	−175.5 (4)	69.3 (3)		
19	C_i	18	−57.9 (2)			

[a] Labels **a** and **b** for **9**, **11**, **14**, and **15** denote two crystallographically independent molecules. [b] Number of atoms in the macrocyclic ring. [c] Numbering of atoms is in agreement with the atom numbering given in the ORTEP drawings (Supporting Information, Figures S1−S5). [d] Taken from ref 24.

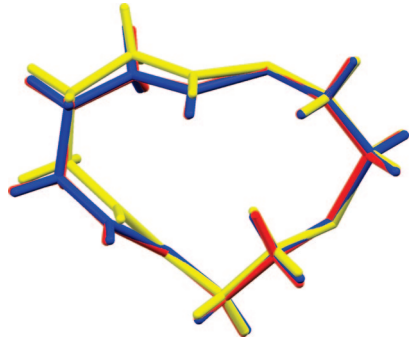


FIGURE 3. An overlap of the macrocycle in the crystal structures of a free ligand **13**[24] (red), **Ag13** complex (yellow), and **Ag(13)$_2$** complex (blue). The 12-membered ring of **13** is conformationally rigid where sulfur atoms stick out of the ring, making them accessible for coordination to the silver cation.

binds Ag^+ ions (>99%). Ligand **11** contains an 18-membered ring, five sulfur atoms, and one adamantane molecule. Its flexible analogue **18**, having an 18-membered ring and five sulfur atoms, showed somewhat weaker, but still very good, complexing ability (93%). Ligand **14**, which contains a 24-membered ring with six sulfur atoms, also showed a very good binding ability to Ag^+ ions (88%). However, its analogue **7**, which has two adamantane molecules embedded in a macrocyclic ring, extracts only 42% of Ag^+ ions. If we compare the molecular structures of ligands **7** and **14** (Figure 2), we see that two adamantane molecules shadow the inner portion of the macrocyclic ring of **7** and also reduce the ring mobility for the most appropriate conformation, which makes the coordination of Ag^+ ions difficult. Such an effect is not present in ligand **14** (Figure 2). In **14**, the macrocyclic ring is not blocked by bulky substituents, and sulfur atoms are prone to metal coordination. The ring flexibility of **14** results in two conformers in the solid state.

However, increasing the flexibility of the structure by increasing the number of atoms in the ring, as in ligand **16**, reduces the complexing power of the ligand as compared to ligand **14**. If the rings are too flexible and too large, they require additional energy for "freezing" the conformation that the ligand occupies in the complex. Ligands **9** and **17**, which contain a 15-membered ring and four sulfur atoms, reduce the extraction of Ag^+ ions to 72−74%. Furthermore, whereas rigid ligand **9** is selective toward the Ag^+ ions, flexible ligand **17** shows

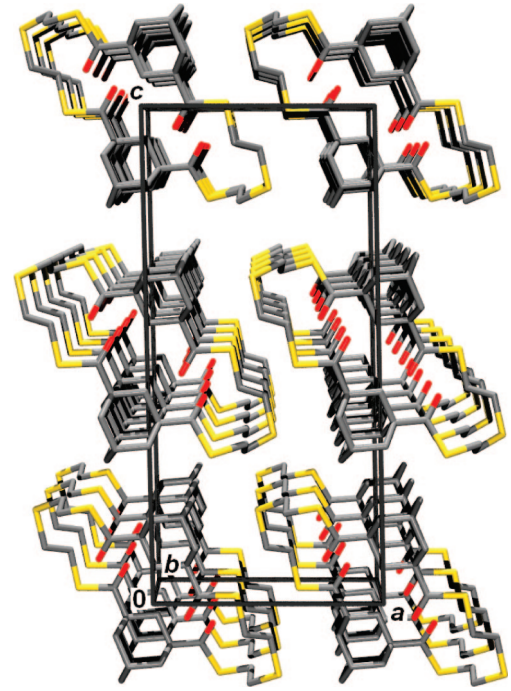


FIGURE 4. Tubules formed in the crystal structure of **7** are extended in the direction [010]. The C−H···O hydrogen bond (between adamantane methylene group and macrocyclic carbonyl group) connects molecules within tubules. The C−H···S interaction connects tubules into layers parallel to the (100) plane.

affinity toward Cu^{2+} ions (19%). Although rings with less than 18 atoms are not complementary in size to the ionic radius of the Ag^+ ion,[28] ligand **13**, with a 12 atom ring containing three sulfur atoms, extracted as much as 64% Ag^+ ions. By analyzing the molecular structure of ligand **13** (Figure 2 and Table 1) it was found that the presence of two carbonyl groups and three sulfur atoms, directed between *endo*- and *exo*-orientation, allows the ambidentate coordination of Ag^+ ions. The binding of Ag^+ in an ambidentate tetracoordination of three sulfur atoms and

(27) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539. (b) Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structures*, 5th ed.; Wiley & Sons: New York, 2001; Chapter 8 and references cited therein.

(28) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751–767.

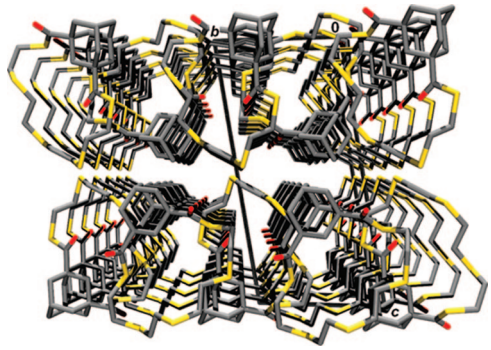


FIGURE 5. Crystal packing of **11** with tubules extended in the [100] direction.

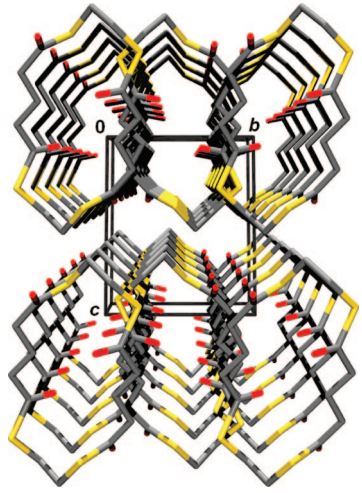


FIGURE 6. Macrocycles of **19** are arranged into partially overlapping tubules running in the [100] direction. The C−H···O hydrogen bonds are formed between methylene and carbonyl groups of symmetry-related molecules.

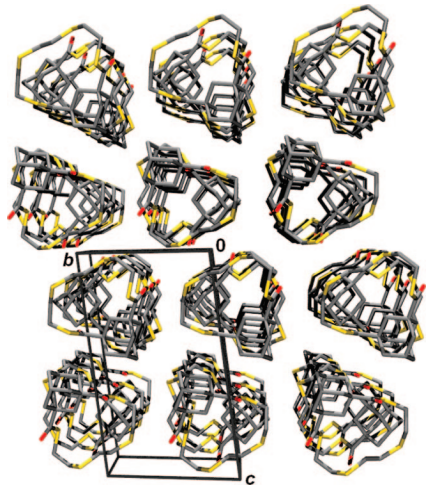


FIGURE 7. Crystal packing of **9a** and **9b** generating hydrogen-bonded columns in the [100] direction. The columns are interconnected by C−H···O hydrogen bonds.

one oxygen atom has been observed in the literature.[29] Also, complexes in which the ligand acts to bridge metal ions by binding to exodentate sulfur are known.[14b,30]

Contrary to ligand **13**, ligand **15**, which contains a seven-membered aliphatic chain and a ring composed of 14 atoms, extracted only 30% of Ag^+ ions. The diminished ability of **15**

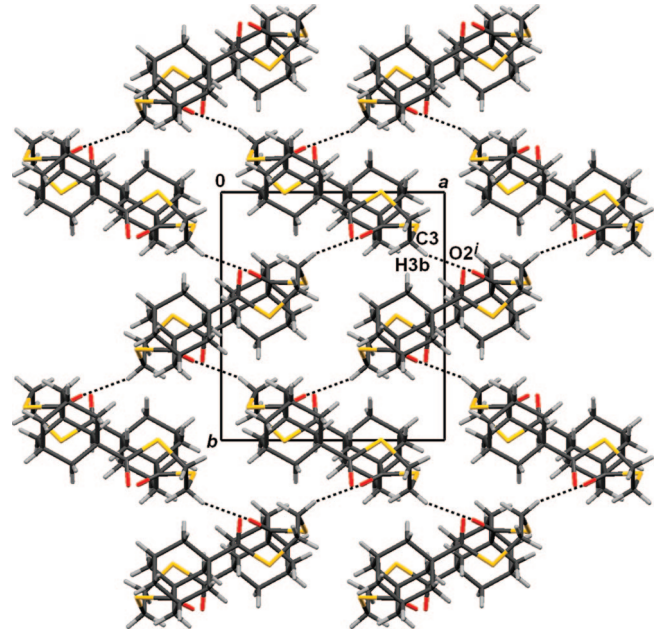


FIGURE 8. Herringbone pattern in the crystal packing of **5** is generated by a single C−H···O hydrogen bond and van der Waals interactions. Symmetry code: (*i*) 1/2 + *x*; 1/2 − *y*; *z*.

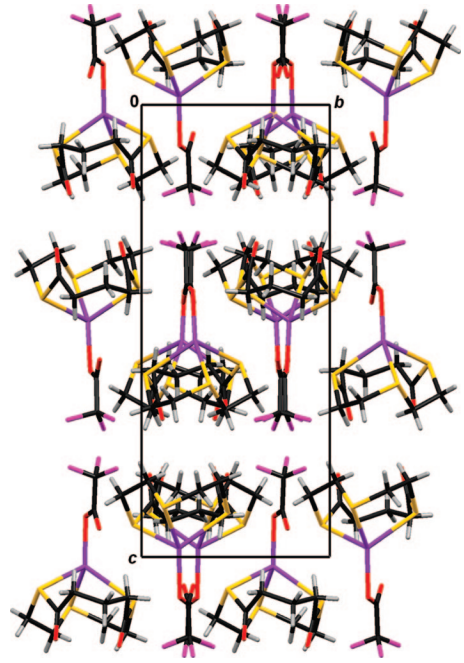


FIGURE 9. Crystal packing of complex **Ag13** resembles closely packed fragile calyxes.

to complex Ag^+ ions is most probably related to increased flexibility of the macrocyclic ring, which makes orientation of sulfur atoms unfavorable for coordination. Ligands with the rigid sequence −CO−S−CH_2−CH_2−S−CO−, as in **5**, **6**, **19**, and **20**, showed negligible complexing ability. By analyzing the molecular structures of ligands **5** and **19** (Figure 2), it can be seen that sulfur atoms adopt an exodentate orientation in both

(29) (a) Blake, A. J.; Champness, N. R.; Howdle, S. M.; Morley, K. S.; Webb, P. B.; Wilson, C. *CrystEngComm* **2002**, *4*, 1–5. (b) Tsuchiya, T.; Shimizu, T.; Kamigata, N. *J. Am. Chem. Soc.* **2001**, *123*, 11534–11538. (c) de Groot, B.; Hanan, G. S.; Loeb, S. J. *Inorg. Chem.* **1991**, *30*, 4644–4647.

(30) (a) de Groot, B.; Leob, S. J. *Inorg. Chem.* **1990**, *29*, 4084–4090.

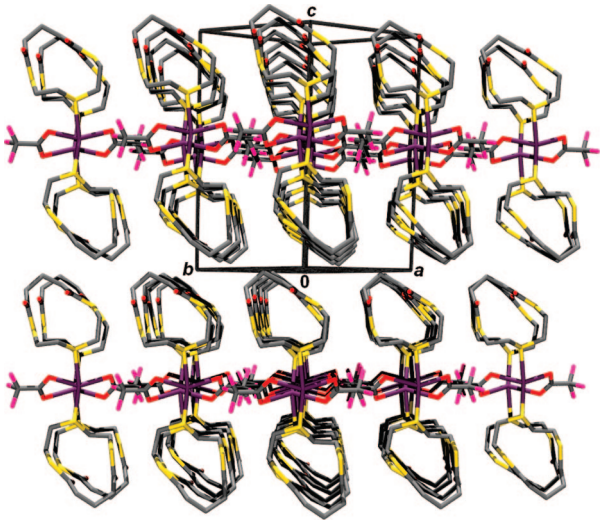


FIGURE 10. Crystal packing of **Ag(13)$_2$** with tubules parallel to [110] is similar to the crystal packing of the free ligand **13**.[24] Cation−anion layers fit into channels among the macrocyclic tubules.

structures. It is obvious that the presence of four carbonyl groups in the mid-size rings (18−22 atoms) causes a significant structure lockup and an unfavorable exodentate orientation of the sulfur atoms, which makes complexation of M^+ ions with ligands less likely. Moreover, in ligand **5**, the presence of two adamantane moieties sterically interferes with ion binding.

To get more insight, establish the binding affinity, and detect complex formation in solution, as well as the stoichiometry of the resulting assemblies, we performed the NMR titrations for corresponding monomer and dimer congeners **13** and **14**, respectively. The titration involved the incremental addition of AgTFA, dissolved in acetone-d_6, to macrocycle **13** and **14** in $CDCl_3$/acetone-d_6 contained in an NMR tube. After each addition of AgTFA, the NMR spectrum was recorded. Clear formation of host−guest assemblies was observed for both ligands (Supporting Information, Figures S8 and S9). Although we observed induced shifts for practically all CH_2 protons in **13**, during the titration of **14** the largest induced shift was observed for the CH_2 signal of carbon atom 5. We used the EQNMR program to estimate the association constant of the formed complex with Ag^+.[31] The fitting clearly indicated formation of a 1:1 complex of **14**/Ag^+ with an association constant $K_{11} = 109 \pm 16\ M^{-1}$ (Supporting Information, Figure S10a). However, we were not able to obtain good fittings for the complex formed with ligand **13** (Supporting Information, Figure S10b). ^1H NMR spectra recorded after dissolving pure crystals of **Ag13** or **Ag(13)$_2$** are identical (Supporting Information, Figures S19 and S20), matching those obtained in a solution during the titration of **13** at a ratio of AgTFA/**13** = 0.75:1 (Supporting Information, Figure S8, line g). These results indicate that in a solution there is fast interconversion between the noncomplexed macrocycle **13** and two types of complexed species, most probably complexes **Ag13** and **Ag(13)$_2$**.

In conclusion, we have prepared new adamantane macrocyclic hosts **5**−**12** that vary in the size of the macrocyclic ring, number of adamantane moieties, and number of donor atoms. We studied their complexing ability toward transition- and heavy-metal cations (Ag^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}).

In picrate extraction surveys, it was possible to show that most of the hosts studied are good in complexing the Ag^+ ion.

(31) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311–312.

TABLE 2. Solvent Extraction of Metal Ions with Selected Hosts

Host	Ring size	Extractability (%)[a] Ag^+	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
13	12	64	BLD[b]	BLD[b]	BLD[b]	BLD[b]
15	14	30	1	BLD[b]	1	2
9	15	72	8	BLD[b]	6	8
17	15	74	19	6	6	3
11	18	99	2	5	2	BLD[b]
18	18	93	4	BLD[b]	5	6
5	18	4	1	5	3	2
19	18	BLD[b]	6	BLD[b]	BLD[b]	BLD[b]
20	22	4	9	BLD[b]	BLD[b]	1
7	24	42	7	6	5	2
14	24	88	BLD[b]	BLD[b]	BLD[b]	2
16	28	70	BLD[b]	BLD[b]	BLD[b]	1
6	27	7	BLD[b]	BLD[b]	5	4
8	33	20	8	1	12	5

[a] Organic phase = dichloromethane: [host] = 1.0×10^{-4} M. Aqueous phase: [picric acid] = 3.0×10^{-5} M and [metal nitrate] = 1.0×10^{-2} M. Errors estimated to be ±0.5%. [b] BLD = below limit of detection.

Introduction of a single polycyclic molecule into the 15- to 18-membered rings increases the rigidity and preorganizes the ligand for complexation (ligand **11**). However, two adamantane molecules embedded in the ring usually diminish the complexing ability of the ligand, primarily due to sterical effects that obstruct formation of an optimal geometry for binding of the desired ion (ligand **7**).

The extraction results obtained for the studied ligands, the NMR titration experiments for macrocyclic congeners **13** and **14**, and the structural analysis of complexes **Ag13** and **Ag(13)$_2$** suggest that preferred ambidentate tetracoordination of Ag^+ ions is favorable with molecules with flexible rings that allow proper accommodation of sulfur atoms and polar anion and also with rigid macrocycle rings, such as in **13**, having sulfur atoms

disposed somewhere between *endo*- and *exo*-orientation that are accessible for coordination to metal.

Experimental Section

General. The NMR spectra were recorded on a 300 or 600 MHz spectrometer. All NMR spectra were measured in $CDCl_3$ using tetramethylsilane as a reference. The assignment of the signals is based on 2D, homonuclear (correlated spectroscopy, COSY) and heteronuclear multiple quantum coherence (HMQC). Infrared spectra were recorded in KBr disks. High-resolution mass values were obtained with a high-resolution mass spectrometer using chemical ionization Q3MS mode. Melting points were obtained using a Kofler apparatus and are uncorrected. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Kieselgel 60 F254) were used, and column chromatography was done by using Kieselgel 60 (70−230 mesh) as the stationary phase. Adamantane-1,3-dicarbonyl dichloride (**21**),[32] tin templates **1**−**4**,[23] as well as the macrocyclic lactones **13**−**18**[23,24] and **19**−**20**,[33] were prepared according to the procedure described in literature. Solvents were purified by distillation. Glutaryl dichloride and pimeloyl dichloride are commercially available.

General Procedure for the Synthesis of Thiamacrocyclic Lactones 5−12. To a solution of corresponding stannathiane **1**−**4**[23] (1 mmol) in dry $CHCl_3$ (80 mL) heated at reflux temperature was added dropwise a solution of adamantane-1,3-dicarbonyl dichloride (**21**, 1 mmol) in dry $CHCl_3$ (20 mL) for 2 h. After being stirred at reflux temperature for 1−4 h, the solution was cooled to rt and treated with 2,2′-bipyridyl (1 mmol). Next, the solution was filtered through a small pad of silica to remove the complex, and the filtrate was concentrated in vacuo. A gross mixture of products was thereby obtained as thick, colorless oil. The crude reaction product was purified by repeated column chromatography on silica gel using a 0→20% of EtOAc−CH_2Cl_2 gradient elution scheme. In this way, pure thiamacrocyclic lactones **5**−**9** and **11** were obtained in 30, 21, 39, 15, 61, and 69% yield, respectively.

3,6,10,13-Tetrathia-1,8(1,3)-diadamantanacyclotetradecaphane-2,7,9,14-tetraone (5). Colorless crystalline solid: mp 284−287 °C; IR (KBr) 2905 (m), 2852 (w), 1676 (s), 1064 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (br s, 4H), 1.83 (d, 8H, $J = 11.7$ Hz), 1.98 (d, 8H, $J = 11.7$ Hz), 1.99 (br s, 4H), 2.21 (br s, 4H), 3.16 (br s, 8H); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.2, 35.2, 37.7, 42.0, 48.7, 204.2; HRMS for $C_{28}H_{36}O_4S_4$ (M^+) calcd 565.157472, found 565.156674. Anal. Calcd for $C_{28}H_{36}O_4S_4$ (565.15): C, 59.54; H, 6.42. Found: C, 59.17; H, 6.03.

3,6,10,13,17,20-Hexathia-1,8,15(1,3)-triadamantanacycloheni-cosaphane-2,7,9,14,16,21-hexaone (6). Colorless crystalline solid: mp 239−240 °C; IR (KBr) 2927 (m), 2905 (m), 2853 (m), 1678 (s), 1449 (m), 1268 (m), 1195 (m), 1062) (m), 923 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (br s, 6H), 1.82−1.94 (m, 24H), 2.09 (br s, 6H), 2.23 (br s, 6H), 3.10 (br s, 12H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.3, 35.1, 38.1, 40.5, 48.8, 204.4; HRMS for $C_{42}H_{54}O_6S_6$ (M^+) calcd 847.2326556, found 847.232296.

3,6,9,13,16,19-Hexathia-1,11(1,3)-diadamantanacycloicosaphane-2,10,12,20-tetraone (7). Colorless crystalline solid: mp 250−253 °C; IR (KBr) 2921 (s), 2906 (s), 2853 (m), 1686 (s), 1424 (m), 1136 (w), 1116 (m), 1073 (s), 947 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (br s, 4H), 1.84−1.93 (m, 16H), 2.10 (br s, 4H), 2.18−2.28 (m, 4H), 2.70−2.82 (m, 8H), 3.02−3.13 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 28.2, 28.7, 32.0, 35.2, 38.1, 40.5, 48.7, 204.4. Anal. Calcd for $C_{32}H_{44}O_4S_6$ (685.08): C, 56.10; H, 6.47. Found: C, 55.94; H, 6.19.

3,6,9,13,16,19,23,26,29-Nonathia-1,11,21(1,3)-triadamantana-cyclotriacontaphane-2,10,12,20,22,30-hexaone (8). Colorless crystalline solid: mp 197−198 °C; IR (KBr) 2921 (m), 2904 (m), 2851 (m), 1670 (s), 1115 (m), 1065 (s) 949 (m); cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (br s, 6H), 1.86−1.91 (m, 24H), 2.06 (br s, 6H), 2.23 (br s, 6H), 2.69−2.75 (m, 12H), 3.03−3.10 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.2, 31.6, 35.1, 38.1, 40.5, 48.7, 204.4. Anal. Calcd for $C_{48}H_{66}O_6S_9$ (1027.62): C, 56.10; H, 6.47. Found: C, 56.28; H, 6.01.

3,6,9,12-Tetrathia-1(1,3)-adamantanacyclotridecaphane-2,13-dione (9). Colorless crystalline solid: mp 157−159 °C; IR (KBr) 2918 (m), 2903 (m), 1666 (s), 1164 (m), 1117 (m), 1067 (m), 917 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (br s, 2H), 1.76 (d, 4H, $J = 12.28$ Hz), 2.14 (s, 2H), 2.18 (d, 4H, $J = 12.28$ Hz), 2.30 (br s, 2H), 2.72−2.79 (m, 8H), 3.10−3.16 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 28.2, 29.8, 33.9, 34.7, 35.4, 36.3, 47.4, 49.1, 204.1. Anal. Calcd for $C_{18}H_{26}O_2S_4$ (402.66): C, 53.69; H, 6.51. Found: C, 53.45; H, 6.23.

3,6,9,12,15-Pentathia-1(1,3)-adamantanacyclohexadecaphane-2,16-dione (11). Colorless crystalline solid: mp 92−95 °C; IR (KBr) 2920 (m), 2907 (m), 2851 (w), 1677 (s), 1663 (s) 1061 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (br s, 2H), 1.81 (d, 4H $J = 12.28$ Hz), 2.05 (d, 6H, $J = 12.28$ Hz), 2.20−2.32 (m, 2H), 2.66−2.87 (m, 12H), 3.07−3.20 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 28.1, 29.5, 32.4, 32.5, 33.3, 35.2, 37.3, 43.1, 48.7, 204.6. Anal. Calcd for $C_{20}H_{30}O_2S_5$ (462.78): C, 51.91; H, 6.53. Found: C, 51.72; H, 6.46.

Solvent Extraction Experiments. The extraction of metal ions from aqueous solution into dichlorometane was performed in capped vials. After the biphasic mixture (the volumes of the aqueous and organic phases were 3 mL each) was stirred vigorously for 3 h at rt, the amount of picrate anion in the aqueous phase was determined by UV−vis spectroscopy monitoring at 356 nm. The extractability was calculated according to eq 1, where $[Pic^-]_{bp}$ is the concentration of picrate in the blank probe (no host in organic phase) and $[Pic^-]$ is the concentration of picrate in the aqueous phase after extraction.

$$\text{extractibility}(\%) = ([Pic^-]_{bp}[Pic^-]/[Pic^-]_{bp} \times 100) \quad (1)$$

All experiments were carried out in triplicate, and the respective results were averaged.

X-ray Diffraction Analysis. The single crystals of macrocyclic thialactones **5**, **7**, **9**, **11**, and **19** were obtained by crystallization from a mixture of $CHCl_3$/MeOH in a 1:1 ratio. The single crystals of complexes **Ag13** and **Ag(13)$_2$** were obtained by slow evaporation from acetone. For the preparation of complexes **Ag13** and **Ag(13)$_2$** and the data collection, see Supporting Information data. CCDC-688438−688452, 695070, and 695071 contain supplementary crystallographic data for this paper at www.CCDC.CAM.UK/DATA_REQUEST/CIF.

Acknowledgment. We thank the Ministry of Science, Education and Sport of the Republic of Croatia for financial support of this study (Grant Nos. 098-0982933-2911 and 098-1191344-2943). We also thank Mrs. M. Alešković for help in performing the EQNMR program.

Supporting Information Available: Crystallographic data and ORTEP drawings for compounds **5**, **7**, **9**, **11**, **19**, **Ag13**, **Ag(13)$_2$**, and copies of the ^1H and ^{13}C (APT) NMR spectra for adamantane thialactones **5**−**9**, **11**, **19**, **20**, **Ag13**, and **Ag(13)$_2$**, as well as the NMR titration data for macrocycles **13** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801143S

(32) Landa, S.; Kamyćek, Z. *Collect. Czech. Chem. Commun.* **1959**, *24*, 1320–1326.

(33) Cort, A. D.; Ercolani, G.; Iamiceli, A. L.; Mandolini, L.; Mencarelli, P. *J. Am. Chem. Soc.* **1994**, *116*, 7081–7087.