Journal of Inclusion Phenomena and Macrocyclic Chemistry **50**: 187–191, 2004.

A New Tetraaza Macrotricycle and Its Inclusion Compound with Chloroform. Synthesis and Crystal Structures*

T. SCHÖNHERR, E. WEBER** and W. SEICHTER
Institut für Organische Chemie der Technischen Universität Bergakademie Freiberg, Leipziger Strasse 29, D-09596 Freiberg/Sachsen, Germany

(Received: 1 November 2003; in final form: 14 February 2004)

Key words: chloroform complex, crystalline inclusion compound, tetraaza macrotricycle, X-ray structure determination

Abstract

A new tetrasubstituted tetraaza macrotricycle **1** was prepared and shown to form a crystalline inclusion compound with chloroform, **1** · chloroform (1:2). Crystal structures of the two compounds are reported. In the unsolvated **1**, tightly interlocked packing of the molecules involving π-stacking interactions of the aromatic groups is determined while in the inclusion compound with chloroform the solvent molecules are accommodated into channels possessing C—H···N contact to **1**.

Introduction

Macrocyclic oligoaza compounds have been prepared in a variety of structural modifications [1] and studied widely with regard to their metal ion complexation [2]. Oligoaza macrocycles have also been found to be good receptor molecules for ammonium cations [3], and in its protonated or quaternary form they are a doorway to the formation of complexes with anionic guests [4]. On the other hand, oligoaza macrocycles are not very often described as acting as a host compound for the complexation or inclusion of uncharged molecular guests [5], though the structural requirements considering geometry and binding parameters of nitrogen atoms in themselves are promising [6]. However, in the course of our study on cyclam derivatives [7], we met the tricyclic tetraaza compound **1** (Scheme 1) which is a doubly bridged aminal type and laterally substituted cyclam [8] that proved to be a host molecule forming a lattice inclusion compound with chloroform.

Here we report on the synthesis and X-ray crystal structures of the new compound **1** and its inclusion complex with chloroform.

Experimental

Synthesis

General

Melting points (uncorrected) were taken on a heating stage microscope (Rapido, Dresden). The IR spectrum (υ in cm^{-1}) was recorded on a Perkin Elmer 1600 FT-IR instrument. NMR spectra (δ in ppm, J in Hz, Me_4Si as internal standard) were obtained with Bruker Avance DPX 400 (^1H: 400 MHz, ^{13}C: 100.61 MHz). The mass spectrum (ESI) was determined on a Hewlett-Packard HP 59987 A instrument.

Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica gel 60 F254 coated plates. All reagents were commercial products and were utilized without further purification. The solvents used were purified or dried by common literature procedures.

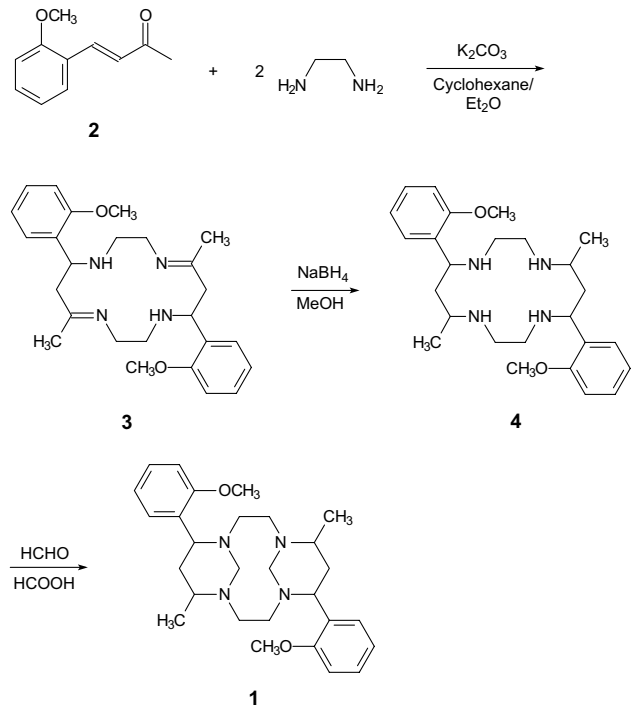
Starting compounds and intermediates

2-Methoxybenzylideneacetone (**2**) was obtained from 2-methoxybenzaldehyde and acetone according to the literature [9].

7,14-Bis(2-methoxyphenyl)-5,12-dimethyl-1,4,8,11-tetraazacyclotetradeca-5,12-diene (**3**) was prepared from **2** and ethylenediamine with anhydrous potassium carbonate in cyclohexane-diethyl ether (1:2) following the literature procedure [10]. Recrystallization from chloroform-diethyl ether yielded 80% yellowish crystals; m.p. 144–145 °C (lit. [10] m.p. 143–145 °C).

* *Supplementary Data* relevant to this publication have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 221992 and 221993.

** Author for correspondence. E-mail: edwin.weber@chemie.tu-freiberg.de



Scheme 1. Synthesis of the host compound.

7,14-Bis(2-methoxyphenyl)-5,12-dimethyl-1,4,8,11-tetra-azacyclotetradecane (**4**) was synthesized by treatment of **3** with $NaBH_4$ in dry ethanol and workup according to the literature [10] which yielded 92% colourless crystals; m.p. 197–198 °C (lit. [10] m.p. 198–199 °C).

7,14-Bis(2-methoxyphenyl)-5,12-dimethyl-1,4,8,11-tetraazacyclo[9.3.1.1^{4,8}]hexadecane (**1**)

To a refluxing solution of **4** (1.76 g, 4 mmol) in methanol (50 mL) was added dropwise a solution of formaldehyde (2.5 mL, aqueous, 40 p.c.) and formic acid (2.5 mL, 98 p.c.) in methanol (50 mL). Refluxing was continued for 5 h. The mixture was made slightly alkaline by addition of NaOH in methanol. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride. Evaporation of the solvent and recrystallization form 2-butanone yielded 87% colourless crystals; m.p. 146 °C; IR (KBr) υ 2956, 2929, 2874, 2831, 1634, 1602, 1585, 1488 (s), 1460 (s), 1439, 1281, 1241 (s), 1205, 1161 (s), 1091, 1042, 1020, 786, 748 (s); ^{1}H-NMR ($CDCl_3$) δ 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.60–1.66 (m, 2H, CHMe), 1.93 (s, 2H, CH_2), 2.29–2.90 (m, 12H, CH_2CH_2, CH_2), 3.81 (s, 6H, OCH_3), 3.83 (m, 2H, CHAr), 4.05 (s, 2H, CH_2), 6.87 (d, $J = 8$, 2H, Ar-H), 7.00 (t, $J = 14.4$, 2H, Ar-H), 7.19 (t, $J = 14.8$, 2H, Ar-H), 7.41 (d, $J = 6.8$, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 19.7 (CH_3), 35.8, 38.3, 49.1 (NCH,CH_2), 55.4 (OCH_3), 57.2, 70.8 (NCH_2N), 110.8, 121.3, 127.4, 128.6, 131.3, 156.8 (Ar); MS(ESI) $m/z = 465$ ($M + H^+$); calculated for $C_{28}H_{40}N_4O_2$: $M = 464.65$.

Crystallography

The crystals used for data collection were obtained by slow evaporation of compound **1** in 2-butanone or chloroform for the free host and the chloroform complex, respectively. The study was performed with an Enraf-Nonius CAD 4 diffractometer with graphite-monochromated CuKα radiation at reduced temperature. Unit cell constants were obtained from the least-squares fit to the settings for 25 reflections centered on the diffractometer. Three standard reflections for intensity control were measured every hour showing no decay in the crystal during the data collection. Intensity data were collected in the ω–2θ scan mode and corrected for background, Lorentz, and polarization effects. The structures were solved using direct methods (SHELXS 93 [11]) and the difference Fourier techniques, and refined by a full-matrix least squares procedure on F_0^2 values (SHELXL 93 [12]). Anisotropic displacement parameters were used to refine the positions of the non-hydrogen atoms. Hydrogen atoms were included at calculated sites with group isotropic temperature factors. The CH_3 groups were treated as rigid and freely rotating.

Crystal data and further details of the refinement calculations are summarized in Table 1. The terminal reliability index ωR in Table 1 is defined as $\left[\sum \omega(F_o^2 - F_c^2)^2 / \sum \omega(F_o^2)^2\right]^{1/2}$.

Results and discussion

Synthesis

Host compound **1** (Scheme 1), constitutionally a doubly bridged and laterally substituted cyclam [8], was synthesized *via* the cyclocondensation route [1a, 13], starting from 2-methoxybenzylideneacetone (**2**) and ethylenediamine to produce the macrocyclic Schiff base **3** [10] which was subjected to a sodium borohydride reduction yielding the substituted cyclam **4** [10]. Reaction of **4** with formaldehyde in the presence of formic acid gave the target compound **1** in 64% overall yield.

The crystalline inclusion compound **1**·chloroform (1:2) has been obtained by simple recrystallization of **1** from chloroform.

Structural studies

The molecular and crystal structures of the free host compound **1** and the solvent inclusion compound **1**·chloroform (1:2) have been determined. Perspective views of the molecular structures including the numbering scheme are displayed in Figures 1 and 2, while Figure 3 illustrates distinguishable docking sites of the host molecule. Crystal packings are presented in Figures 4 and 5. The parameters of hydrogen bond interactions are given in Table 2.

Table 1. Crystal data, experimental parameters and selected details of refinement calculations for **1** and its inclusion compound with chloroform

Compound	**1**	**1** · chloroform (1:2)
Formula	$C_{28}H_{40}N_4O_2$	$C_{30}H_{42}N_4O_2Cl_6$
Molar mass	464.64	703.41
Crystal system, space group	Triclinic, *P*-1	Monoclinic, $P2_1/c$
Unit cell dimensions		
a, Å	7.260(3)	10.567(3)
b, Å	8.458(1)	6.116(1)
c, Å	10.587(2)	26.676(3)
α, deg.	105.98(2)	90.0
β, deg.	91.10(3)	97.01(1)
γ, deg.	93.78(3)	90.0
V, Å^3	623.1(3)	1711.1(6)
Z	1	2
D_{calc} (g cm^{-3})	1.238	1.361
μ (mm^{-1})	0.0617	0.4846
F (0 0 0)	252	732
Data collection		
Radiation (Å)	1.5418	1.5418
Temperature (K)	183(2)	188(2)
Approximate crystal size (mm)	0.30 × 0.30 × 0.30	0.40 × 0.40 × 0.20
No. of collected reflections	2779	3574
within the θ-limit (deg)	4.35–74.80	3.34–74.99
No. of unique reflections	2567	3378
Refinement calculations full-matrix least-squares based on all F^2 values		
No. of refined parameters	155	199
R_1 indices $\sum\|\Delta F\|/\sum\|F_0\|$	0.0426	0.0875
No. of *F* values used [$I > 2\sigma(I)$]	2126	2912
w*R* on F^2	0.1207	0.2324
S (=Goodness of fit on F^2)	1.023	1.090
Min./max. residual electron Density (e Å^{-3})	0.20/−0.18	1.15/−0.70

Both in the unsolvated host compound **1** and its inclusion compound with chloroform (1:2) the asymmetric units contain half of the molecules (Figures 1 and 2). Owing to the double bridging of the macrocycle, the framework of **1** shows a largely rigid conformation which is reflected in almost identical bond lengths and

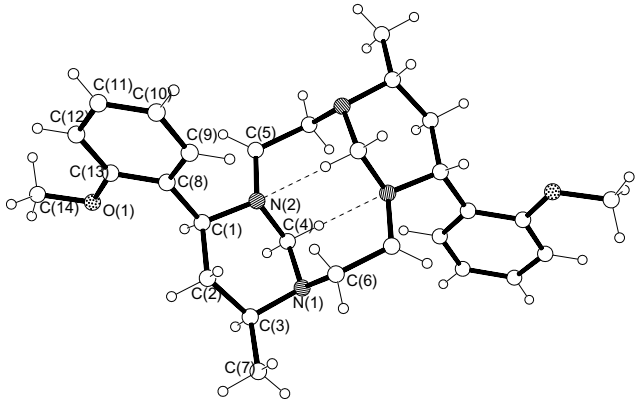


Figure 1. View of the molecular structure of **1** including crystallographic numbering scheme. The nitrogen atoms are hatched, oxygen atoms are dotted, and hydrogen bond type interactions are indicated by dashed lines.

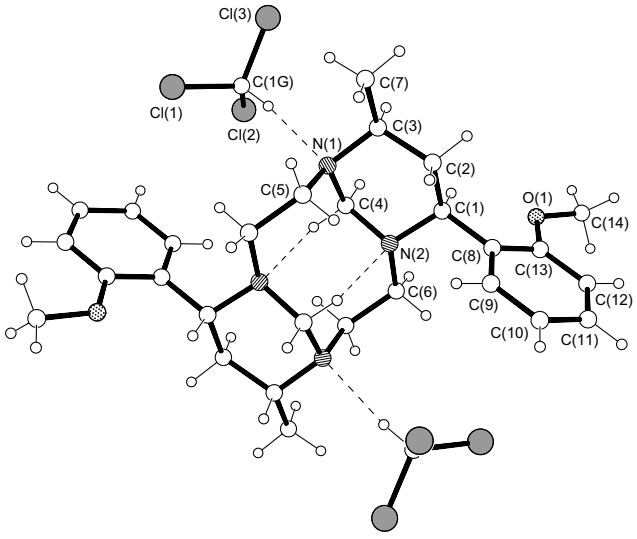


Figure 2. View of the molecular structure of **1** · chloroform (1:2) including crystallographic numbering scheme. The nitrogen atoms are hatched, oxygen atoms are dotted, and chloro atoms are represented by bold circles. Hydrogen bond type interactions are indicated by dashed lines.

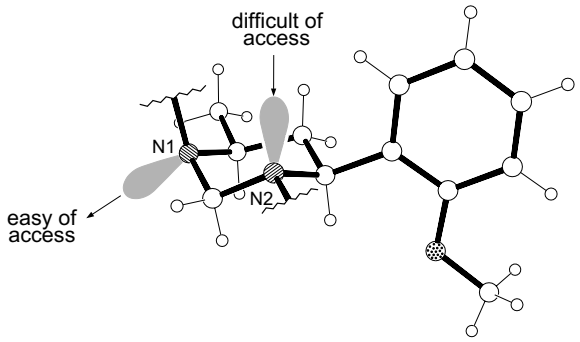


Figure 3. Molecular fragment of **1** relevant to host–guest interaction, showing the steric environment of the n-orbitals at N1 and N2 of the host molecule.

angles in the two structures. A further contribution to this property may also come from the transanular C—H···N interactions formed between hydrogens of the aminal bridges (C4), naturally adopting a trans conformation, and facing nitrogens (N2) (Table 2). Dependent on these interactions and the substituents, the six-membered rings of the tricyclic moiety are in a slightly distorted chair conformation with aryl-to-aryl and methyl-to-methyl substituents both being in thermodynamically favorable trans diequatorial positions to each other. Hence follows the same configuration of the asymmetric carbon atoms at C1 and C3 (e.g., RRSS or the enantiomer). The central ten-membered ring (with an internal centre of symmetry) achieves reasonable staggered conformations about each bond, which is a situation similar to previous reports [8a, b, 14]. Thus, the only conformational freedom being effective to **1** is confined to the rotation of the aryl groups which is different in the structures of free host and inclusion compound. This is shown by the torsion angles of N2—C1—C8—C9, being 42.9° and 56.7° in the unsolvated host and chloroform inclusion, respectively.

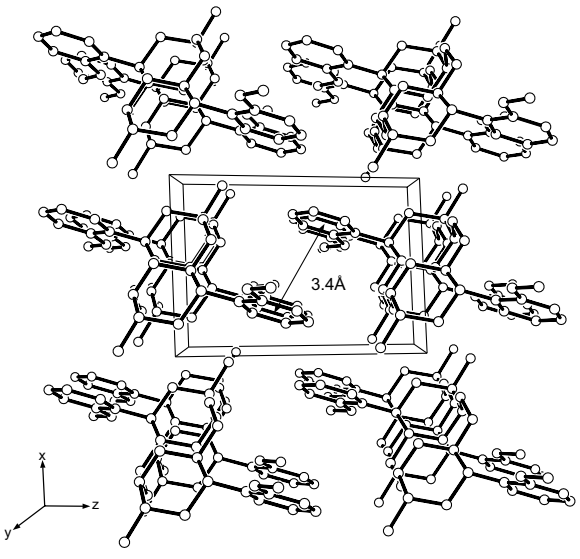


Figure 4. Packing diagram of **1**. The hydrogen atoms are omitted for clarity. π-Stacking interaction is indicated by a double-sided arrow.

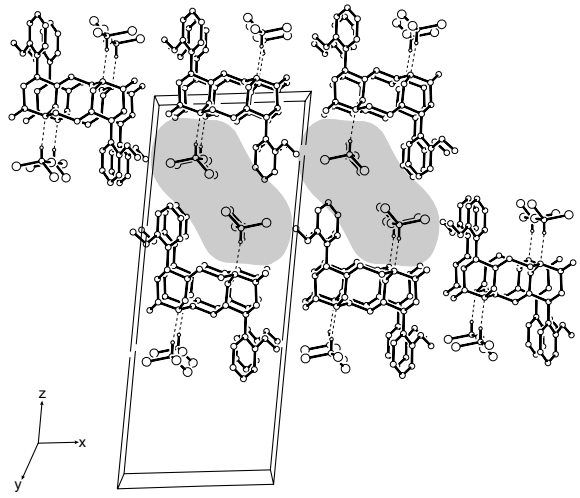


Figure 5. Packing diagram of **1**·chloroform (1:2). The hydrogens, except for the chloroform molecules, are omitted for clarity. The channel area accommodating the guest molecules is indicated by shading.

In the inclusion compound (Figure 2), the chloroform molecules interact *via* the C—H groups to the N1 atoms of the host macrocycle (Table 2) while the N2 atoms due to steric shielding of the neighboring aryl units remain unbound. Looking at the facts more closely (Figure 3), it is seen that the *n*-orbitals of N1 are in relatively open ee-*trans* position to CH_3 but those of N2 are ae-*cis* to aryl and thus difficult to approach from outside.

The packing of **1** is typical of molecular columns along the crystallographic *y*-axis. They are involved in π-stacking interactions that include the aryl units, with face-to-face distance of 3.4 Å, giving rise to a tightly interlocked packing of the molecules (Figure 4). By way of contrast, in the packing of the inclusion compound interlocking of the host molecules is raised and channels along the *y*-axis of the crystal are created that accommodate the solvent molecules (Figure 5). As a result, intermolecular π-stacking interactions between the aryl groups, which is a typical feature of the free host packing is not found here. Instead, weak van der Waals contacts dominate packing of the associated host guest units.

In conclusion, cyclams which are traditional complexants for binding of metal ions [15] may also be used for solid state inclusion of uncharged molecules [16], provided their structures are suitably modified, including conformational rigidity and lateral substitution. With regard to that, compound **1** can be considered a prototype that promises developmental possibilities for new host design.

Acknowledgements

We gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft (FOR 335), the firms of Hoechst and Clariant, as well as the Fonds der Chemischen Industrie.

Table 2. Distances (Å) and angles (deg) of hydrogen bond interactions

Atoms involved D—H···A	Symmetry	Distances		Angle
		D···A	H···A	D—H···A
1				
C(4)—H(4)···N(2)	$1-x, -y, -z$	2.922(5)	2.29	121
1·$CHCl_3$				
C(1G)—H(1G)···N(1)	x, y, z	3.201(1)	2.26	173
C(4)—H(4)···N(2)	$1-x, 2-y, -z$	2.925(4)	2.28	122

References

1. (a) J.S. Bradshaw, K.E. Krakowiak, and R.M. Izatt: *Aza-Crown Macrocycles*, Wiley, New York (1993); (b) S.R. Cooper (ed.): *Crown Compounds: Toward Future Applications*, VCH, Weinheim (1992); (c) N.V. Gerbeleu, V.B. Arion, and J. Burgess: *Template Synthesis of Macrocyclic Compounds*, Wiley-VCH, Weinheim (1999).
2. (a) L.F. Lindoy: *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge (1989); (b) B. Dietrich, P. Viout, and J.-M. Lehn: *Macrocyclic Chemistry*, VCH, Weinheim (1993).
3. (a) P.G. Potvin and J.M. Lehn: 'Design of Cation, and Anion Receptors, Catalysts, and Carriers'. In R.M. Izatt and J.J. Christensen (eds.), *Synthesis of Macrocycles – The Design of Selective Complexing Agents* (Progress in Macrocyclic Chemistry, Vol. 3), Wiley, New York (1987), p. 167; (b) J.L. Atwood, J.E.D. Davies, D.D. MacNicol, and F. Vögtle (eds.): *Comprehensive Supramolecular Chemistry*, Vol. 1, Elsevier, Oxford (1996).
4. (a) A. Bianchi, K. Bowman-James, and E. Garcia-Espana (eds.): *Supramolecular Chemistry of Anions*, Wiley-VCH, Weinheim (1997); (b) F.P. Schmidtchen and M. Berger: *Chem. Rev.* **97**, 1609 (1997); (c) K.T. Holman, J.L. Atwood, and J.W. Steed: 'Supramolecular Anion Receptors'. In G.W. Gokel (ed.), *Advances in Supramolecular Chemistry*, Vol. 4, JAI Press, New York (1997), p. 287; (d) C. Seel, A. Galán, and J. de Mendoza: 'Molecular Recognition of Organic Acids and Anions – Receptor Models for Carboxylates, Amino Acids, and Nucleotides', In E. Weber (ed.), *Supramolecular Chemistry II – Host Design and Molecular Recognition* (Topics in Current Chemistry, Vol. 175), Springer-Verlag, Berlin-Heidelberg (1995), p. 101.
5. (a) J.L. Atwood, J.E.D. Davies, D.D. MacNicol, and F. Vögtle (eds.): *Comprehensive Supramolecular Chemistry*, Vol. 2, Elsevier, Oxford (1996); (b) H. Takemura, T. Shinmyozu, and T. Inazu: *Coord. Chem. Rev.*, **156**, 183 (1996).
6. (a) J.-M. Lehn: *Supramolecular Chemistry*, VCH, Weinheim (1995); (b) J.W. Steed and J.L. Atwood: *Supramolecular Chemistry*, Wiley, Chichester (2000); (c) H.-J. Schneider and A. Yatsimirsky: *Principles and Methods in Supramolecular Chemistry*, Wiley, Chichester (2000).
7. T. Schönherr, E. Weber, and W. Seichter: *Z. Anorg. Allg. Chem.* **627**, 2420 (2001).
8. (a) N.W. Alcock, P. Moore, and K.F. Mok: *J. Chem. Soc. Perkin Trans. 2*, 1186 (1980); (b) R. Tripier, J.-M. Lagrange, E. Espinosa, F. Denat, and R. Guilard: *J. Chem. Soc. Chem. Commun.* 2728 (2001); (c) S. Develay, R. Tripier, F. Chuburu, M. Le Baccon, and H. Handel: *Eur. J. Org. Chem.* 3047 (2003).
9. I.M. Heilbron and J.S. Buck: *J. Chem. Soc.* 1509 (1921).
10. K. Hideg and D. Lloydt: *J. Chem. Soc. Sect. C* 3441 (1971).
11. G.M. Sheldrick: *SHELXS 93*, *Program for Crystal Structure Solution*, Göttingen, Germany (1993).
12. G.M. Sheldrick: *SHELXL 93*, *Program for Crystal Structure Refinement*, Göttingen, Germany (1993).
13. N.F. Curtis: *Coord. Chem. Rev.* **3**, 3 (1968).
14. See also: (a) E.J. Gabe, Y. Le Page, L. Prasad, and G.R. Weisman: *Acta Crystallogr. Sect. B* **38**, 2752 (1982); (b) J.-L. Wang, M. Sun, F.-M. Miao, S.Y. Wu, F.-S. Gong, and X.-H. Duan: *Acta Crystallogr. Sect. C* **47**, 2203 (1991); (c) W.F. de Souza, N. Kambe, Z.J. Jin, N. Kanehisa, Y. Kai, and N. Sonoda: *J. Org. Chem.* **60**, 7058 (1995); (d) G. Royal, V. Dahaoui-Gindrey, S. Dahaoui, A. Tabard, R. Guilard, P. Pullumbi, and C. Lecomte: *Eur. J. Org. Chem.* 1971 (1998); (e) R.W. Alder, T.M.G. Carniero, R.W. Mowlam, A.G. Orpen, P.A. Petillo, D.J. Vachon, G.R. Weisman, and J.M. White: *J. Chem. Soc. Perkin Trans 2*, 589 (1999).
15. (a) E.K. Barefield: *Inorg. Chem.* **11**, 2273 (1972). (b) E.K. Barefield, F. Wagner, A.W. Herlinger, and A.R. Dahl: *Inorg. Synth.* **16**, 220 (1976); (c) G. De Santis, L. Fabbrizzi, M. Licchelli, and P. Pallavicini: in ref. 1 (b), p. 147.
16. (a) J.L. Atwood, J.E.D. Davies, D.D. MacNicol, and F. Vögtle (eds.): *Comprehensive Supramolecular Chemistry*, Vol. 6, Elsevier, Oxford (1996); (b) J.L. Atwood, J.E.D. Davies, and D.D. MacNicol (eds.): *Inclusion Compounds*, Vol. 4, Oxford University Press, Oxford (1991); (c) E. Weber (ed.): *Molecular Inclusion and Molecular Recognition-Clathrates I and II* (Topics in Current Chemistry, Vols. 140 and 149), Springer-Verlag, Berlin-Heidelberg (1987 and 1988).