

## Encapsulation of cations and anions by azacrowns: thermodynamic and structural aspects

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*Abstract* - The ligands in the series [3k]aneN<sub>k</sub> (k=6-12), when neutral or partially protonated, can form complexes with many cations, and when extensively protonated they can form adducts with polycharged anions. We shall report some general trends in both cation and anion coordination. In particular thermodynamic and structural parameters obtained for cation and anion complexes will be considered in this paper. The analysis of such parameters enables some characteristics in the molecular recognition of both metal cations and anions to be outlined.

### INTRODUCTION

In the last few years we have synthesized a number of polyazacycloalkanes of the general formula (-CH<sub>2</sub>CH<sub>2</sub>NH-) <sub>k</sub> which contain from 7 to 12 nitrogen atoms separated from each other by -CH<sub>2</sub>CH<sub>2</sub>- groups. Denoting these compounds as [3k]aneN<sub>k</sub> there is now a series available from the small [9]aneN<sub>3</sub> to the large [36]aneN<sub>12</sub>. These macrocycles form complexes with metal ions in which there are many stable 5-membered chelate rings. Variations in structural properties can be studied across the series of [3k]aneN<sub>k</sub> ligands as a function of the number, *k*, of nitrogen atoms. As *k* increases the size of the macrocyclic cavity increases and also the ligand as a whole becomes more flexible. Consequently both mononuclear and polynuclear complexes can be obtained, with a variety of geometrical structures. Furthermore, protonation of one nitrogen atom has a strong influence on the properties of adjacent atoms by virtue of the shortness of the alkyl chain which separates it from them. Protonation of these macrocycles occurs readily, even in water in the absence of added acid, yielding polyprotonated species which are well suited to the study of anion coordination. The polyprotonated macrocycles are particularly useful as models for supramolecular catalysts such as enzymes in such reaction as the dephosphorylation of nucleotides like ATP (ref.1). The polyazacycloalkanes (and even better, some cage-derivatives of them that we will see later) are also able to impose a type of pre-organization on the complexation of metal ions of biological interest and can therefore be used for biomimetic studies.

### COORDINATION OF CATIONS

We have examined a number of complexes of the cations Mn<sup>2+</sup>, Fe<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, Pd<sup>2+</sup> and Pb<sup>2+</sup>. As may be expected the Mn<sup>2+</sup> complexes are the least stable. Structurally, single crystal X-ray analysis of the perchlorate salt of the cation [Mn([21]aneN<sub>7</sub>)]<sup>2+</sup> has revealed a very irregular polyhedron with all 7 nitrogen atoms bound to the metal cation. The Mn-N distances vary between 2.34 and 2.70 Å (ref. 2). With Fe<sup>2+</sup> only a few complexes with the larger polyazacycloalkanes have been

studied so far, but it can be stated that the  $[\text{Fe}\{[21]\text{aneN}_7\}]^{2+}$  cation is about 100 times more stable than the manganese analogue just described (ref. 3).  $\text{Co}^{2+}$  (ref. 4),  $\text{Ni}^{2+}$  (ref. 5),  $\text{Cu}^{2+}$  (ref. 6),  $\text{Zn}^{2+}$  (ref. 7) and  $\text{Cd}^{2+}$  (ref. 8) form both *mono-* and *bis-*metallo-ion complexes with the larger polyazacycloalkanes in aqueous solution. The crystal structures of some *bis-*metallo-ion complexes of  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Cd}^{2+}$  have been determined and described previously. A *tris-*metallo-ion complex of copper(II) has also been identified in aqueous solutions containing the ligand  $[33]\text{aneN}_{11}$  or  $[36]\text{aneN}_{12}$ , but the structures of these complexes have not been determined as yet. The complexes of  $\text{Pd}^{2+}$  are of particular interest as the chemistry and thermodynamics of the formation of polyamine complexes of this cation are not thoroughly well known. Some of the thermodynamic and spectroscopic data which we have obtained for *mono-* and *poly-*metallo-ion complexes with the ligands  $[18]\text{aneN}_6$ ,  $[21]\text{aneN}_7$ ,  $[24]\text{aneN}_8$  are given in Table 1. The *tris-*metallo-ion complex with  $[21]\text{aneN}_7$  has also been shown to be

TABLE 1. Thermodynamic and spectroscopical parameters for some palladium-azamacrocycles complexes.

Reaction	log K	$-\Delta H^\circ$ (kcal mol $^{-1}$ )	$\lambda_{\text{max}}$ ( $\epsilon$ ) (neutral pH)
$\text{Pd}^{2+} + [18]\text{aneN}_6$	29.2		
$\text{Pd}^{2+} + [21]\text{aneN}_7$	24.5		
$2\text{Pd}^{2+} + [18]\text{aneN}_6$	51.8 <sup>a</sup>	49.7 <sup>a</sup>	342(1330)
$2\text{Pd}^{2+} + [21]\text{aneN}_7$		51.7	377(2400)
$2\text{Pd}^{2+} + [24]\text{aneN}_8$		51.6	298(2030)

<sup>a</sup> The corresponding  $\Delta S^\circ$  value is 70 cal. deg $^{-1}$  mol $^{-1}$

present in solution. In the latter complex, one nitrogen atom has been deprotonated and this negatively charged atom acts as a bridge between two palladium atoms, as shown in Fig. 1. The structures of the palladium complexes of  $[18]\text{aneN}_6$  and  $[24]\text{aneN}_8$  are shown in the same figure. In all of these complexes the  $\text{Pd}^{2+}$  cation exhibits square-planar coordination with donor atoms of nitrogen and chlorine (ref. 9).

We are at present continuing our studies of the complexes formed by  $\text{Pb}^{2+}$  with the large polyazacycloalkanes. The formation constants of many complexes have been determined,

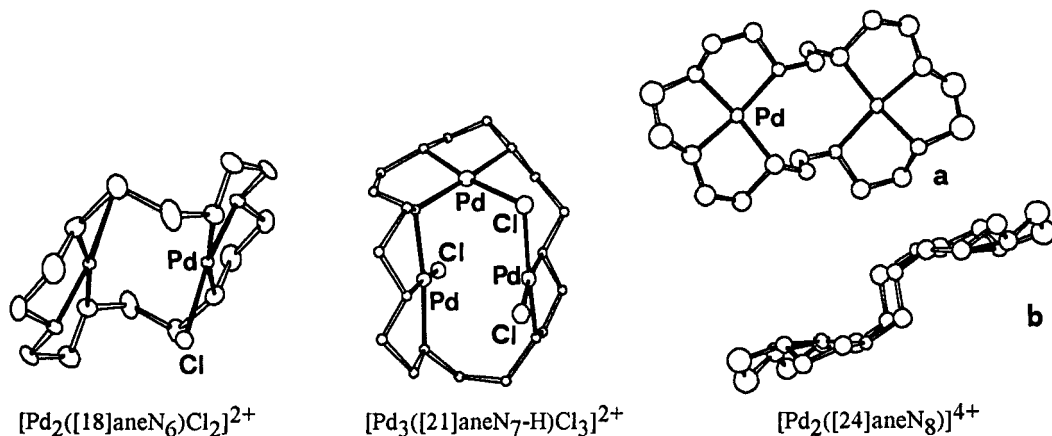


Fig. 1 Crystal structures of some azacrown complexes of palladium(II) - a) top view, b) lateral view.

and we have found that as the ring size increases there is a tendency for the number of lead atoms bound in the complex to increase from 1 to 3. Many lead(II) complexes exist in a protonated form and there are also many complexes containing hydroxo groups. The complex  $[\text{Pb}_2\{[30]\text{aneN}_{10}\}(\text{ClO}_4)_2](\text{ClO}_4)_2$  has been isolated and its structure is shown in Fig. 2; each lead atom is attached to 4 nitrogen atoms from the macrocycle, further interacting at longer distances with the remaining nitrogen atom of the ligand and one oxygen atom from a perchlorate ion, in a rather irregular coordination polyhedron.

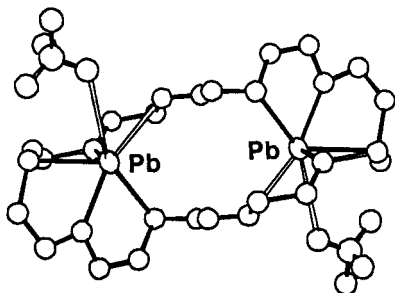


Fig. 2 Crystal structure of the lead(II) complex  $[\text{Pb}_2[30]\text{aneN}_{10}(\text{ClO}_4)_2]^{2+}$

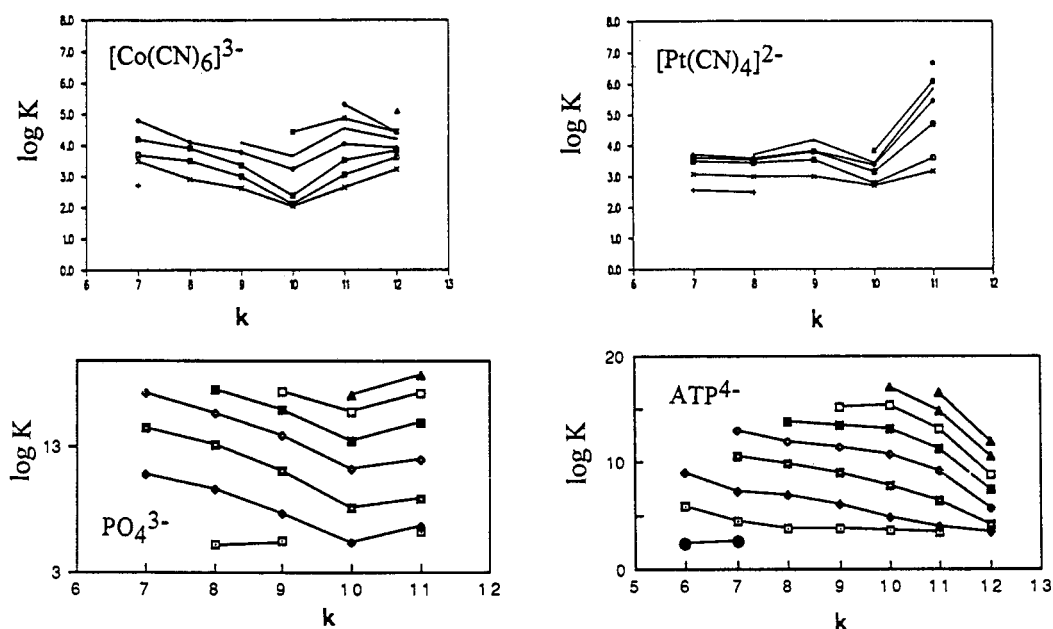
### PROTONATION

As has been mentioned the nitrogen atoms of a polyazacycloalkanes may be protonated one after another. In the oligoprotonated species, the protons tend to be attached to nitrogen atoms which are as far apart from one another as possible. For example, it has been shown by nmr measurements that the 3 protons in  $[\text{H}_3\text{Me}_4[18]\text{aneN}_6]^{3+}$  are located on alternate nitrogen atoms (ref. 10). When more than half of the nitrogen atoms are protonated some of them will have to be adjacent to each other (separated only by one  $\text{C}_2\text{H}_4$  group), producing zones within the macrocycle of different charge density, as in  $[\text{H}_4[21]\text{aneN}_7]^{4+}$  (ref. 1). An interesting example is furnished by the cation  $[\text{H}_8[30]\text{aneN}_{10}]^{8+}$  whose crystal structure reveals that there are two parallel rows of protonated nitrogen atoms, each row containing four  $\text{NH}_2^+$  groups, separated from each other by a non-protonated group (ref. 11).

As the extent of protonation increases, interactions between  $>\text{NH}_2^+$  groups increase and in consequence the molecule tends towards a configuration in which the nitrogen atoms are co-planar; the fully, protonated polyaza-cycloazaalkanes assume a shape close to circular. These conformational changes, together with the establishment of zones of different charge density, enable conditions to be determined for selective anion coordination and other types of molecular recognition.

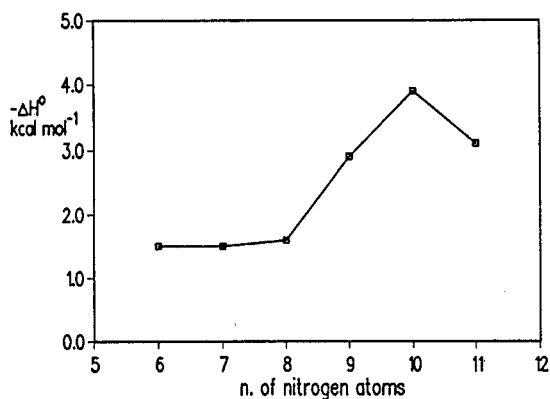
### COORDINATION OF ANIONS

When the macrocycles under discussion are protonated they are able to interact with variously charged anions to give supramolecular complexes. The strength of the interaction and therefore the equilibrium constant for the formation of such species depends on a number of factors. 1) *Charge density*. The interaction between the cation and anion is weaker the lower the charge density in the region of contact. Thus, for a given degree of protonation, the stability of the supercomplex increases with the charge on the anion, and decreases as the macrocyclic ring becomes larger (Fig. 3). 2) *Hydrogen bonding*. The formation of hydrogen bonds evidently plays an important role in the formation of supercomplexes. For example, the macrocyclic quaternized cation  $(\text{Me}_6[12]\text{aneN}_4)^{4+}$ , in which hydrogen bonding is precluded, does not interact at all with the anion  $[\text{Co}(\text{CN})_6]^{3-}$  in aqueous solution, or in the solid state (ref. 12). If the formation of a supercomplex were driven only by the electrostatic force of attraction between the oppositely charged moieties these ions would be expected to interact. 3) *Conformational factors*. Molecular mechanics calculations have shown that the most stable conformation of the fully protonated  $(\text{H}_k[3k]\text{aneN}_k)^{k+}$  isolated ions is close to a circular one.

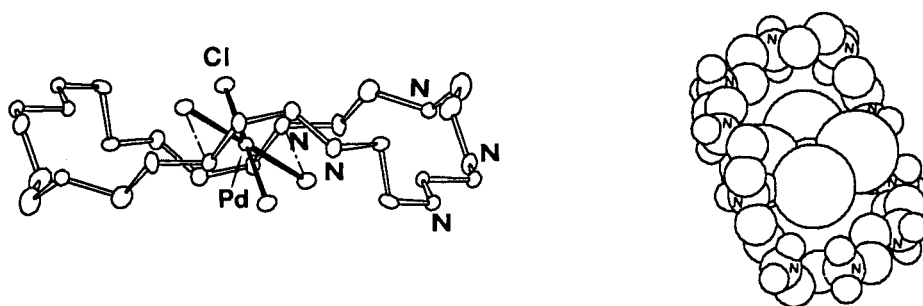


**Fig. 3** Curves of equilibrium constants versus the number of nitrogen atoms  $k$ . The equilibrium is: Anion + Protonated macrocycles. The curves from the bottom to the top are referred to increased degrees of protonation. The lower complete curve is related to tetraprotonated species.

However, the conformation of the cation is strongly affected when it interacts with an anion. We have shown that when the anion can enter into the macrocyclic cavity a more stable complex is formed than when the anion is located external to the cavity. The equilibrium constants for the anion  $[\text{Co}(\text{CN})_6]^{3-}$  are shown as a function of  $k$  in Fig. 3 (ref. 13). The constants decrease slightly with increasing ring size up to the 30-membered ring of  $[\text{30}] \text{aneN}_{10}$ . However, there is an abrupt departure from this tendency as, for a given degree of protonation, the constants for  $[\text{33}] \text{aneN}_{11}$  are larger, not smaller, than those of the previous member of the series. Pina *et al.* (ref. 14) have shown by means of photochemical measurements that this anion enters the central cavity of  $(\text{H}_{11}[\text{33}] \text{aneN}_{11})^{11+}$ , whereas a crystal structure analysis has shown that the same anion is not encapsulated by  $(\text{Hg}[\text{30}] \text{aneN}_{10})^{8+}$  (ref. 11). The extra stability of the compound with a 33-membered ring compared with compounds having smaller rings is therefore to be attributed to an inclusion effect. Analogous behavior was found with  $[\text{Pt}(\text{CN})_4]^{2-}$  (ref. 15) (Fig. 3), but not with  $[\text{Fe}(\text{CN})_6]^{4-}$ . We have also measured the values of  $\Delta H^\circ$  for the reactions between the ion  $[\text{PdCl}_4]^{2-}$  and the series of large cations  $(\text{H}_k[\text{3}k] \text{aneN}_k)^{k+}$ , and the results are shown in Fig. 4. The enthalpy of reaction remains constant from  $k=6$  to  $k=8$



**Fig. 4**  $-\Delta H^\circ$  values for the reaction:  
 $\text{PdCl}_4^{2-} + \text{H}_k[\text{3}k] \text{aneN}_k^{k+}$   
 plotted versus the number  $k$  of nitrogens.

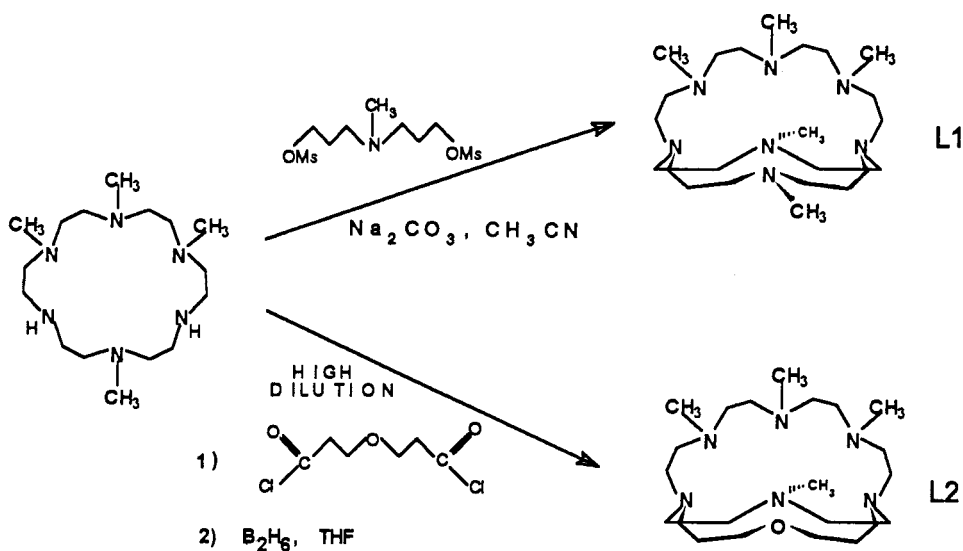


**Fig. 5** ORTEP drawing and space filling representation of the  $[(\text{PdCl}_4)(\text{H}_{10}[30]\text{aneN}_{10})]^{8+}$  cation.

and then rises to a maximum at  $k=10$ . This increase has been attributed to a greater degree of penetration into the cavity until, with  $k=10$  the anion is fully encapsulated as can be seen in the structure (Fig. 5) (ref. 16). With phosphate the formation constants for the adducts formed with protonated forms of  $[33]\text{aneN}_{11}$  are larger than those obtained for the equally protonated forms of  $[30]\text{aneN}_{10}$ , but this effect was not observed with anions derived from diphosphate and ATP (Fig. 3). The catalytic effect brought about by these polyazacycloalkanes on the dephosphorylation reaction of ATP has been followed by NMR and HPLC techniques. The results indicate that the hydrolysis of ATP is not dependent on the strength of the interaction and the ATP entering the macrocyclic cavity. Nevertheless, it has been demonstrated that the cyclic nature of the protonated polyazaalkane is an important factor in the catalytic action (ref. 1). To summarize,  $[\text{PdCl}_4]^{2-}$  forms an inclusion complex with the 30-membered ring, while  $[\text{Co}(\text{CN})_6]^{3-}$  and phosphate require a 33-membered ring to do so. With the other anions which we have examined, namely,  $[\text{Fe}(\text{CN})_6]^{4-}$ ,  $[\text{PtCl}_6]^{2-}$ , and anions derived ATP, ADP, AMP and diphosphate, there is evidence for a strong interaction but not for the formation of an inclusion complex with the rings studied so far.

#### FUTURE PROSPECTS

We have synthesized the compound  $\text{Me}_4[18]\text{aneN}_6$ , in which there are 2 nitrogen atoms not methylated, shown in Fig. 6. This compound can be used as the starting point for



**Fig. 6** Synthetic pathway for the preparation of the novel cage ligands L1 and L2.

the synthesis of derivatives with side-chains or indeed of cage structures. Two cage ligands which have been made are shown in Fig. 6. We are now studying reactions of these ligands with transition and alkali metal ions. The structure of the complex of zinc(II) with L1 was determined. The coordination of the zinc ion is distorted trigonal bipyramidal with one water molecule in the equatorial plane. This water molecule interacts *via* hydrogen bonds with two uncoordinated nitrogen atoms of the ligand.

Many complexes of zinc with ligands in the  $[3k]aneN_k$  series have similar stability to corresponding complexes of cadmium. This is shown in the  $ML^{2+}$  complexes with  $[18]aneN_6$  and  $[24]aneN_8$ , and in the  $M_2L^{4+}$  complexes with  $[3k]aneN_k$ ,  $k=9, 10$  and  $11$ . By contrast, the  $ML^{2+}$  complexes of cadmium with L1 and L2 are more stable than those of zinc by 4.8 and 3.4 log units respectively.

A fascinating perspective, opened up by this kind of complexes, is substitution of the water molecule by different substrate interacting with the metal center and unbound nitrogen atoms.

#### REFERENCES

1. A. Bencini, A. Bianchi, E. Garcia-España, E. C. Scott, L. Morales, B. Wang, T. Deffo, F. Takusagawa, M. P. Mertes, K. B. Mertes, and P. Paoletti, *Bioorg. Chem.*, **20**, 8 (1992).
2. A. Bencini, A. Bianchi, P. Dapporto, E. Garcia-España, V. Marcelino, M. Micheloni, P. Paoletti, and P. Paoli, *Inorg. Chem.*, **29**, 1716 (1990).
3. A. Bencini, A. Bianchi, M. Micheloni, P. Paoletti, E. Garcia-España, and M. A. Nino, *J. Chem. Soc., Dalton Trans.*, 1171 (1991).
4. A. Bencini, A. Bianchi, E. Garcia-España, M. Micheloni, and P. Paoletti, *Inorg. Chem.*, **28**, 2480 (1989).
5. A. Bencini, A. Bianchi, M. Castellò, P. Dapporto, J. Faus, E. Garcia-España, M. Micheloni, P. Paoletti, and P. Paoli, *Inorg. Chem.*, **28**, 3175 (1989).
6. A. Bencini, A. Bianchi, E. Garcia-España, M. Giusti, S. Mangani, M. Micheloni, P. Orioli, and P. Paoletti, *Inorg. Chem.*, **26**, 1243 (1987).
7. A. Bencini, A. Bianchi, P. Dapporto, E. Garcia-España, M. Micheloni, and P. Paoletti, *Inorg. Chem.*, **28**, 1188 (1989).
8. A. Bencini, A. Bianchi, M. Castellò, M. Di Vaira, J. Faus, E. Garcia-España, M. Micheloni, and P. Paoletti, *Inorg. Chem.*, **28**, 347 (1989).
9. A. Bencini, A. Bianchi, E. Garcia-España, P. Paoletti, P. Paoli, T. A. Ramirez, and A. Rodriguez, *Inorg. Chem.*, in press.
10. A. Bencini, A. Bianchi, E. Garcia-España, V. Fusi, M. Micheloni, P. Paoletti, J. A. Ramirez, A. Rodriguez, and B. Valtancoli, *J. Chem. Soc., Perkin*, in press.
11. A. Bencini, A. Bianchi, E. Garcia-España, M. Giusti, S. Mangani, M. Micheloni, P. Orioli, and P. Paoletti, *Inorg. Chem.*, **26**, 3902 (1987).
12. A. Bianchi, M. Micheloni, P. Orioli, P. Paoletti, and S. Mangani, *Inorg. Chim. Acta*, **146**, 153 (1988).
13. A. Bianchi, M. Micheloni, and P. Paoletti, *Coord. Chem. Rev.*, **110**, 17 (1991).
14. F. Pina, L. Moggi, M. F. Manfrin, V. Balzani, M. W. Hosseini, and J. M. Lehn, *Gazz. Chim. Ital.*, 119 (1989).
15. A. Bencini, A. Bianchi, P. Dapporto, E. Garcia-España, M. Micheloni, J. A. Ramirez, P. Paoletti, and P. Paoli, *Inorg. Chem.*, **31**, 1902 (1992).
16. A. Bencini, A. Bianchi, M. Micheloni, P. Paoletti, P. Dapporto, P. Paoli, and E. Garcia-España, *J. Inclusion Phen. Mol. Recognition in Chem.*, **12**, 291 (1992).