Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

"Three-in-one" Complexes Formed by Anionic Guests and Monosubstituted Cationic Alkyldiamino β-Cyclodextrin Derivatives

Emilio Alvarez-Parrilla[a]; Pedro Ramos Cabrer[b]; Laura A. de la Rosa[a]; Wajih Al-soufi[b]; F. Meijide[b]; Jose Vázquez Tato[b]
[a] Depto. de Ciencias Básicas, Universidad Autónoma de Ciudad Juárez, Instituto de Ciencias Biomédicas, Juárez, Mexico [b] Depto. de Química Física, Facultad de Ciencias de Lugo, Alfonso X O sabio s/n, Universidad de Santiago de Compostela, Lugo, Spain

Online publication date: 13 May 2010

To cite this Article Alvarez-Parrilla, Emilio , Cabrer, Pedro Ramos , de la Rosa, Laura A. , Al-soufi, Wajih , Meijide, F. and Tato, Jose Vázquez(2003) '"Three-in-one" Complexes Formed by Anionic Guests and Monosubstituted Cationic Alkyldiamino β-Cyclodextrin Derivatives', Supramolecular Chemistry, 15: 3, 207 — 211
To link to this Article: DOI: 10.1080/1061027031000078211
URL: http://dx.doi.org/10.1080/1061027031000078211

Supramolecular Chemistry, 2003 Vol. 15 (3), pp. 207–211

"Three-in-one" Complexes Formed by Anionic Guests and Monosubstituted Cationic Alkyldiamino β-Cyclodextrin Derivatives

EMILIO ALVAREZ-PARRILLA[a,*], PEDRO RAMOS CABRER[b], LAURA A. DE LA ROSA[a], WAJIH AL-SOUFI[b], F. MEIJIDE[b] and JOSE VÁZQUEZ TATO[b]

[a]*Universidad Autónoma de Ciudad Juárez, Instituto de Ciencias Biomédicas, Depto. de Ciencias Básicas, Anillo envolvente del Pronaf y Estocolmo, s/n. Zona Pronaf, Cd. Juárez, C. P. 32300, Mexico;* [b]*Universidad de Santiago de Compostela, Depto. de Química Física, Facultad de Ciencias de Lugo, Alfonso X O sabio s/n Lugo 27002, Spain*

Received (in Southampton, UK) 1 July 2002; Accepted 2 December 2002

The effect of electrostatic interactions on the complexation of ionic guests by charged β-cyclodextrin (βCD) derivatives is reviewed. Special attention is paid to the numerous studies concerning the effect of electrostatic interactions on (i) the complexation of fluorescent and UV probes; (ii) the catalytic and chiral recognition properties of βCD derivatives; and (iii) the complexation of two bile salts (sodium cholate, NaC, and sodium deoxycholate, NaDC). The formation of three-in-one complexes between NaC and alkyldiamino βCD derivatives is also presented.

Keywords: β-Cyclodextrin; Amino β-cyclodextrin derivatives; Electrostatic interactions; Ionic guests; Inclusion complexes

INTRODUCTION

Native cyclodextrins (Fig. 1) are cyclic, torus-shaped oligomers built up from 6, 7 or 8 glucopyranose units (named α-, β- and γ-CD, respectively) linked by α-(1–4)-glycosidic bonds. Owing to the hydrophobic environment inside the cavity, a variety of organic molecules can be trapped in it to form inclusion complexes. This phenomenon has been used to increase the bioavailability of poorly soluble drugs [1–4], among other applications. Most of these complexes have a 1:1 (cyclodextrin:guest) stoichiometry [5], although higher stoichiometries such as 2:1, 2:2, 1:2 or *n*:*n* [6,7] are not uncommon.

The binding process of guests by cyclodextrins involves the introduction, either on their primary or secondary rim, of the most hydrophobic part of the guest into the cyclodextrin cavity, the less hydrophobic part remaining outside. During this process, there is loss of high-energy water from the cyclodextrin cavity, as well as relief of conformational strain in the cyclodextrin–water adduct. The complexation process is regulated by several intermolecular interactions occurring inside the cavity, which may be considered as short-range forces, or intracavity attractive forces, as recently defined by Rekharsky and Inoue [8]. These forces are hydrophobic interactions, van der Waals interactions, dipole–dipole, dipole–induced-dipole, hydrogen bonding, etc.

When cyclodextrin derivatives are used as hosts, new factors, such as electrostatic interactions or steric hindrance, can also play an important role in the stability, topology and stoichiometry of the complexes formed. The aim of this short review is mainly to describe the influence of the electrostatic interaction on the complexation of anionic guests by cationic mono-substituted amino cyclodextrin derivatives, paying special attention to the results previously obtained by our research group.

It is widely accepted that electrostatic interactions play an important role in biological systems. For this reason, several studies have been carried out in which cationic cyclodextrin derivatives have been used as hosts. These studies have shown that the equilibrium constants of complexes formed between cationic cyclodextrin derivatives and anionic

*Corresponding author. E-mail: ealvarez@uacj.mx

ISSN 1061-0278 print/ISSN 1029-0478 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/1061027031000078211

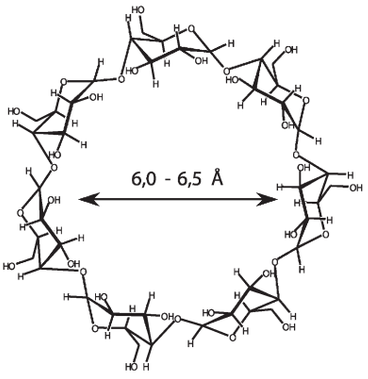


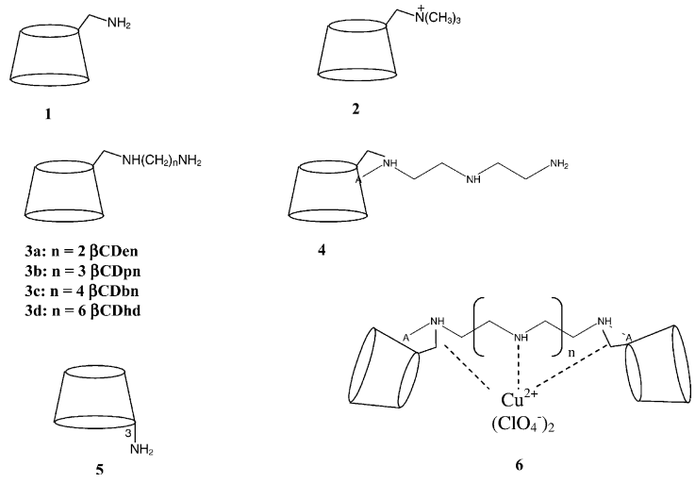
FIGURE 1 Schematic structure of β-cyclodextrin.

guests increase in comparison to those of complexes formed with neutral cyclodextrins [6,9–19]. The opposite effect has been observed when cationic or neutral hosts are complexed by cationic cyclodextrin derivatives [16,17,20]. For instance Noto *et al.* observed a reduction in the stability of the complexes formed when cationic or neutral aromatic guests were complexed by a protonated monoamino β-cyclodextrin derivative **1** (mono-6-amino-6-deoxy-β-cyclodextrin, $\beta CDNH_2$). This effect was attributed to the reduction in the hydrophobic nature of the cyclodextrin cavity due to the lack of desolvation induced by the positively charged amino group, as well as the repulsion between groups with the same charge. Indeed, at pH 11, where the amino group is deprotonated, the stability constants for these hosts were always higher [20].

In 1978 Matsui and Okimoto studied the catalytic properties of a positively charged β-cyclodextrin derivative **2** (mono-6-trimethylammonio-6-deoxy-β-cyclodextrin, βCDtma) on the alkaline hydrolysis of *o*-, *m*- and *p*-acetoxybenzoic acids, observing that the stability and geometry of the complexes formed, as well as the catalytic capacity of the host, depend on the electrostatic interactions between the positively charged amino group of βCDtma and the negative carboxylate group of the host [12]. Similar results were obtained by Park *et al.* when studying the cleavage of *m*-nitrophenyl acetate by mono-6-aminoethylamino-6-deoxy-β-cyclodextrin (βCDen, **3a**) and mono-6-diethyltriamino-6-deoxy-β-cyclodextrin (βCDdien, **4**) [13].

Extensive studies have been carried out in order to determine the influence of Coulombic interactions on chiral recognition/discrimination [3,8,21–24]. Recently Rekharsky and Inoue [8] have reported a systematic study of the thermodynamic parameters involved in the complexation and chiral recognition behavior of $\beta CDNH_2$ with anionic, cationic and neutral chiral guests, from which they reached the following conclusions: i) negatively charged guests exhibit larger affinities toward $\beta CDNH_2$, observing that this positive effect was more pronounced with flexible guests when compared to bulky or rigid guests; ii) the electrostatic attraction between the opposite charges of the host and guests enhanced the chiral discrimination process as a consequence of a difference in the geometry of the complexes formed with the amino derivative and the native cyclodextrin. Lincoln *et al.* have studied the electrostatic effect on the chiral discrimination of anionic amino acids and aromatic molecules by monosubstituted polyamino β-cyclodextrin derivatives alone and in the presence of coordination metals, observing a positive effect of electrostatic interactions on the complexation of the anionic guests, which is increased by the presence of metals [16–19,21].

Several studies have been carried out in which the complexation behavior of β-cyclodextrin monoamino derivatives with anionic fluorescent and UV probes, used as guests, has been studied [10,12,14]. Matsui and Okimoto observed that when the UV probe 4-(4-hydroxy-1-naphthylazo)-1-naphthalenesulfonate was complexed by βCDtma at pH 4 (at which the sulfonate group is fully protonated), its stability constant was smaller than the one for βCD,



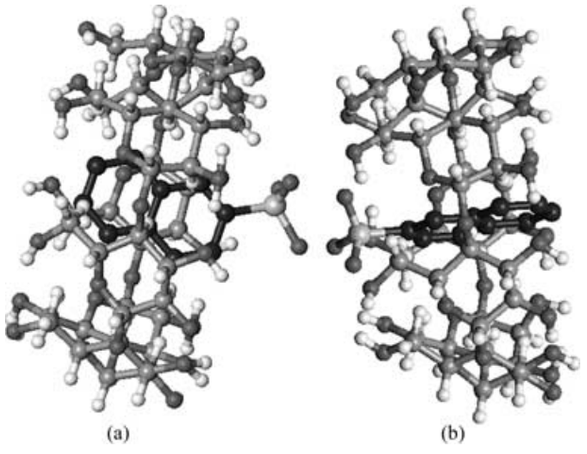


FIGURE 2 Schematic representation of the 1:1 (a) βCD:2NS and (b) $\beta CDNH_2$:2NS complexes, from ref. [11].

while at pH 10.5, in which the sulfonate group is deprotonated, the stability constant was much larger than that for βCD at the same pH. These results were interpreted as a positive effect of the electrostatic interactions over the complexation process [12].

An interesting example of the effect of the electrostatic interactions over the stability and geometry of the complexes formed is observed in the complexation of 2-naphthalenesulfonate (2NS) by $\beta CDNH_2$ and the monoamino derivative in position 3 (mono-3-amino-3-deoxy-β-cyclodextrin, $\beta CD3NH_2$, **5**) [11]. In this study, it was observed that 2NS enters the cavity of βCD and its amino derivative by the side of the secondary hydroxy rim, in agreement with previously reported studies of Nishijo *et al.* for βCD [25]. However, the inclusion degree of 2NS, and the orientation of the sulfonate group are different due to the electrostatic interactions: (i) with βCD the complexation process was regulated by short-range forces, the more hydrophilic sulfonate group staying outside the cavity and orientated toward the secondary rim (Fig. 2a). ii) However, when 2NS was complexed by $\beta CDNH_2$ (Fig. 2b) the electrostatic interactions changed the geometry of the complex, since the sulfonate group faces the primary rim approaching to the protonated amino group. In the case of the complex formed with $\beta CD3NH_2$, the sulfonate group is orientated toward the amino group in the secondary rim, which results in a lower inclusion degree inside the cavity, and consequently a lower stability [25].

Recently, a systematic study of the complexation of the fluorescent probe [6-(*p*-toluidino)naphthalene-2-sulfonate, TNS] by βCD and $\beta CDNH_2$ has been carried out [10]. From the analysis of steady-state and time-resolved fluorescence, ^{13}C NMR and ROESY results, it was proposed that TNS forms two distinct 1:1 and one 2:1 complexes with both hosts. The two 1:1 complexes resulted from the complexation of either toluidine or naphthalenesulfonate moieties (with two microscopic equilibrium constants K_{1a} and K_{1b}). The 2:1 complex (with the microscopic equilibrium constants K_{2a} and K_{2b}) is formed from the complexation of the free moiety in each 1:1 complex by a second cyclodextrin, as shown schematically in Fig. 3. From ROESY data and the estimation of the microscopic constants, it was concluded that the complexation behavior of TNS with βCD was regulated by polarity factors (short-range forces), while both polarity and electrostatic interactions (between the positively charged amino group and the negatively charged sulfonate moiety) regulated it in the case of $\beta CDNH_2$. Similar results were obtained by Yoshida *et al.* for the complexation of TNS and two analogues (*N*-methyl-2-anilinonaphthalene-6-sulfonate, MANS and 1-anilinonaphthalene-8-sulfonate, 1,8-ANS) by monosubstituted diamino-β-cyclodextrin derivatives [15].

In other studies, Liu *et al.* observed that the stability of the complexation of TNS and 1,8-ANS by a polyamine β-cyclodextrin head-to-head dimer **6** was increased by 4–6 and 10–13 times, respectively, when compared with βCD. They also observed a larger enhancement in the stability of the complexes in the presence of Cu(II). They finally concluded that this cyclodextrin dimer acts as a ternary recognition host,

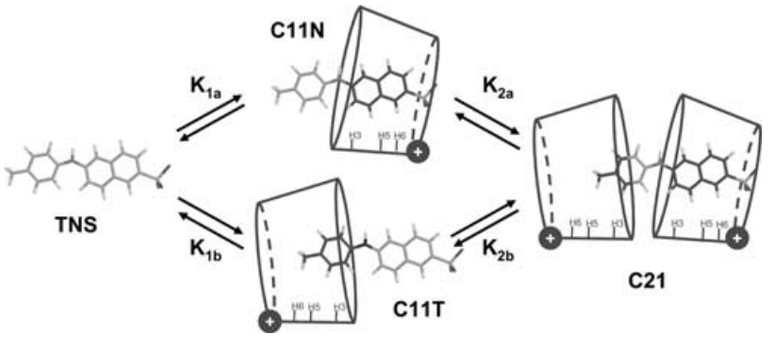


FIGURE 3 Schematic representation of the complexation of the anionic guest TNS by $\beta CDNH_2$, reproduced with permission from ref. [10]: *J. Phys. Chem. B* **2001**, *105*, 5994–6003. Copyright 2001 American Chemical Society.

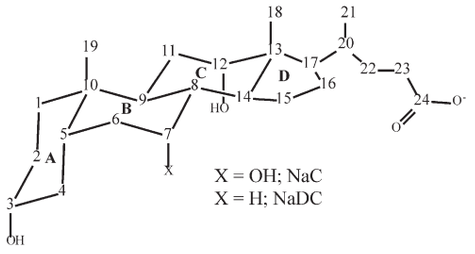


FIGURE 4 Structure of NaC and NaDC.

in which two hydrophobic and one electrostatic/coordination sites are responsible for the stability of the supramolecular structure obtained [26,27].

Recently, Hamai and Ishikawa described the complexation behavior of βCDen with monosulfonate and disulfonate probes. For disulfonate guests, a remarkable effect of pH on the stability of the complexes was observed, with the equilibrium constants at pH 5.5 (where the amino groups are protonated) more than twice those at pH 10.3 [14].

Lincoln *et al.* have carried out several studies on the complexation of amino acids and aromatic carboxylic acids by monosubstituted di- and triamino β-cyclodextrin derivatives of different size. They have concluded that the complexes' stabilities are regulated by several factors such as electrostatic interactions, hydrophobicity and the stereochemistry of both host and guest [19].

THREE-IN-ONE INCLUSION COMPLEXES FROM NaC AND ALKYLDIAMINO βCD DERIVATIVES

Bile salts are natural biological surfactants that play an important role in the digestive process, interacting with food lipids, allowing their solubilization and absorption by the body. Common bile salts have two or three hydroxy groups at the C3, C7 or C12 positions of the characteristic tetracyclic skeleton of steroids [6]. Bile salts also possess a mobile side-chain at the C17 position, which ends with a carboxylic group that can be conjugated with taurine or glycine. Typical examples of bile salts are sodium cholate (NaC) and sodium deoxycholate (NaDC), the only difference between them being the presence or absence of a hydroxy group at position 7 (Fig. 4). This structural difference is responsible for their different behavior in the complexation by βCD and $\beta CDNH_2$, since NaC and NaDC form 1:1 and 2:1 inclusion complexes, respectively, with these cyclodextrins [6].

In all cases, the steroid body enters into the cavity of the cyclodextrins by the side of the secondary hydroxy groups. The formation equilibrium constants for the complexation of both guests with $\beta CDNH_2$ are larger than with βCD. It can also be noticed that there is a larger increment in the case of NaC than for NaDC. These results can be explained in terms of the structure of the complexes, deduced from ROESY spectra. During the complexation of NaC by $\beta CDNH_2$, the steroid body enters into the cavity of one cyclodextrin unit to a deeper degree; with the side-chain unfolded approaching the amino group, because of the Coulombic interactions between the carboxylate anion and the protonated amino group. This effect produces a higher value of the complexation constant. However, in the case of the NaDC–$\beta CDNH_2$ system, in which a 2:1 complex is formed, the deeper inclusion of the steroid body into the first cyclodextrin cavity reduces the inclusion degree inside the cavity of the second $\beta CDNH_2$ when compared to βCD, and as a consequence the global stability constant is reduced [6].

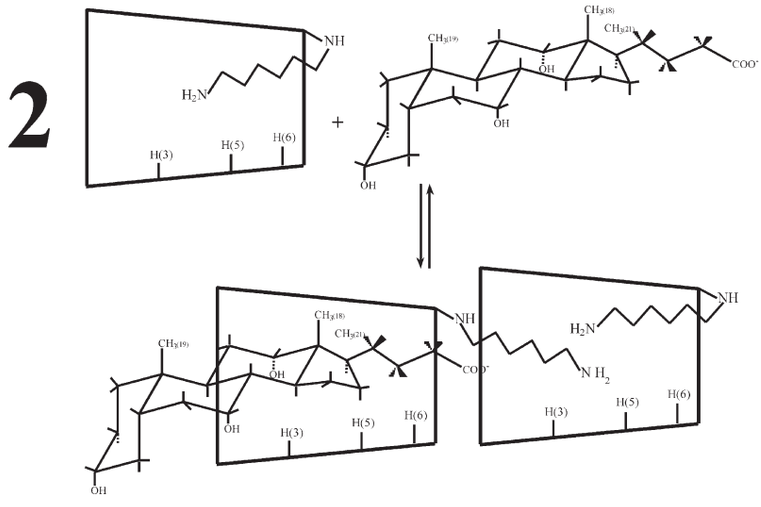


FIGURE 5 Schematic structure of the complex formed between NaC and βCDhd, deduced from ROESY cross-peak interactions, at biological pH (approximately pH 8).

Further studies have demonstrated that the ditopic guest NaDC forms supramolecular linear conglomerates or dendrimer-like supramolecular structures when it is complexed by β-cyclodextrin dimers [6,28] or trimers [29]. In these studies, the effects of electrostatic interactions and steric hindrance were carefully analyzed. Even so, more systematic studies on the influence of these factors in the complexing behavior of bile salts by cyclodextrins are still required. Therefore, the complexation of NaC by monosubstituted polyaminoderivatives of βCD was studied, and the results obtained are discussed.

The equilibrium constant for the 1:1 complex formed between NaC and βCDen (a monosubstituted diaminoderivative of βCD) is comparable to that for $\beta CDNH_2$ [9]. From ROESY data, it was possible to conclude that the mobile side-chain of NaC is unfolded toward the protonated ethylenediamino group located on the primary rim, a conclusion in agreement with previous studies with $\beta CDNH_2$ [6].

Surprisingly, when NaC was complexed by the diamino derivative βCDhd (mono-6-aminohexylamino-6-deoxy-β-cyclodextrin, **3d**), a 2:1 stoichiometry (deduced from NMR measurements) was obtained instead of the usual 1:1 stoichiometry. Further information was obtained from ROESY experiments of the host and the NaC–βCDhd system, from which the complex structure (see Fig. 5 for a schematic representation) can be deduced. Initially, the diamino side-chain is located inside the cyclodextrin cavity forming an intramolecular complex, in agreement with results obtained by Lincoln *et al.* [30]. When the complex is formed, the NaC molecule expels the amino side-chain from the cavity, allowing its complexation by a second βCDhd since the size of the βCD cavity is big enough to accommodate two alkyl chains. Thus, the resulting 2:1 complex has the following features: it is i) a NaC–βCDhd intermolecular complex; ii) a βCDhd–βCDhd intermolecular complex as the amino side chain of a βCDhd is included in the cavity of a second βCDhd; and iii) an intramolecular complex as the amino side chain of a βCDhd is included into its own cavity. This is why we call it a "three-in-one" complex. As far as we know, this is the first example of this type of inclusion complex with cyclodextrins.

The length of the alkyl chain is a key factor in the formation of this new class of complexes. Thus, the common 1:1 stoichiometry was found for the complex formed between NaC and the propylenediamine derivative, βCDpn (mono-6-aminopropylamino-6-deoxy-β-cyclodextrin, **3b**), the value for the equilibrium constant being $4.5 \times 10^3\,M^{-1}$. However, NMR data for the system NaC–βCDbn (the butylenediamine derivative of βCD, mono-6-aminobutylamino-6-deoxy-β-cyclodextrin, **3d**) supported the existence of a mixture of 1:1 and 2:1 stoichiometries.

Acknowledgements

Financial support from Xunta de Galicia (Project XUGA PGIDT99PX126201B) and CYTED (Project VIII.3) is gratefully acknowledged. E. Alvarez-Parrilla and L. A. de la Rosa thank CONACyT (*Repatriación* grant).

References

[1] Szejtli, J. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1988.
[2] Szejtli, J. In *Comprehensive Supramolecular Chemistry*; Szejtli, J., Osa, T., Eds.; Pergamon Press: Oxford, 1996; Chapter 1, pp 5–19.
[3] Easton, C. J.; Lincoln, S. F. *Modified Cyclodextrins*; Imperial College Press: London, 1999.
[4] Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803–822.
[5] Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875–1917.
[6] Ramos Cabrer, P.; Alvarez-Parrilla, E.; Meijide, F.; Seijas, J. A.; Rodríguez Núñez, E.; Vázquez Tato, J. *Langmuir* **1999**, *15*, 5489–5495.
[7] Alvarez-Parrilla, E.; Ramos Cabrer, P.; Meijide, F.; Vázquez Tato, J. *Biol. J. Armenia: Special Issue* **2001**, 136–147.
[8] Rekharsky, M. V.; Inoue, Y. *J. Am. Chem. Soc.* **2002**, *124*, 813–826.
[9] Pal Singh, A.; Ramos Cabrer, P.; Alvarez-Parrilla, E.; Meijide, F.; Vázquez Tato, J. *J. Incl. Phenom. Macrocyclic Chem.* **1999**, *35*, 335–348.
[10] Alvarez-Parrilla, E.; Al-Soufi, W.; Ramos Cabrer, P.; Novo, M.; Vázquez Tato, J. *J. Phys. Chem. B* **2001**, *105*, 5994–6003.
[11] López de las Heras, F., Alvarez-Parrilla, E., Vázquez Tato, J. *Ciencia en la Frontera*, In press.
[12] Matsui, Y.; Okimoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3030–3034.
[13] Park, K. K.; Lee, J. P.; Park, J. W. *Bull. Korean Chem. Soc.* **1994**, *15*, 171–173.
[14] Hamai, S.; Ishikawa, S. *Spectrochim. Acta A* **2001**, *57*, 1–8.
[15] Ito, N.; Yoshida, N.; Ichikawa, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 965–972.
[16] Brown, S. E.; Coates, J. H.; Easton, C. J.; Lincoln, S. F. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 739–743.
[17] Brown, S. E.; Haskard, C. A.; Easton, C. J.; Lincoln, S. F. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 1013–1018.
[18] Haskard, C. A.; Easton, C. J.; May, B. L.; Lincoln, S. F. *Inorg. Chem.* **1996**, *35*, 1059–1064.
[19] Kean, S. D.; May, B. L.; Clements, P.; Easton, C. J.; Lincoln, S. F. *Aust. J. Chem.* **1999**, *52*, 1157–1163.
[20] D'Anna, F.; Meo, P. L.; Riela, S.; Gruttadauria, M.; Noto, R. *Tetrahedron* **2001**, *57*, 6823–6827.
[21] Brown, S. E.; Coates, J. H.; Duckworth, P. A.; Lincoln, S. F.; Easton, C. J.; May, B. L. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1035–1040.
[22] Nair, U. B.; Armstrong, D. W. *Microchem. J.* **1997**, *57*, 199–217.
[23] Kitae, T.; Nakayama, T.; Kano, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 207–212.
[24] Kitae, T.; Nakayama, T.; Kano, K. *J. Inclusion Phenom. Macrocyclic Chem.* **1998**, *33*, 345–359.
[25] Nishijo, J.; Ushiroda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1790–1796.
[26] Liu, Y.; You, C. C.; Wada, T.; Inoue, Y. *Tetrahedron Lett.* **2000**, *41*, 6869–6873.
[27] Liu, Y.; You, C. C.; Li, B. *Chem. Eur. J.* **2001**, *7*, 1281–1288.
[28] Alvarez-Parrilla, E.; Ramos Cabrer, P.; Pal Singh, A.; Al-Soufi, W.; Meijide, F.; Rodríguez Núñez, E.; Vázquez Tato, J. *Supramol. Chem.* **2002**, *14*, 397–404.
[29] Alvarez-Parrilla, E.; Ramos Cabrer, P.; Al-Soufi, W.; Meijide, F.; Rodríguez Núñez, E.; Vázquez Tato, J. *Angew. Chem., Int. Ed.* **2000**, *16*, 2856–2859.
[30] Field, M. J.; May, B. L.; Clements, P.; Tsanaktsidis, J.; Easton, C. J.; Lincoln, S. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1251–1258.