J Incl Phenom Macrocycl Chem (2010) 67:483–487
DOI 10.1007/s10847-009-9725-4

SHORT COMMUNICATION

Solvent induced selectivity switching in aromatic-anion binding molecular receptors

Jozef A. Z. Hodyl · Stephen F. Lincoln · Kevin P. Wainwright

Received: 10 September 2009 / Accepted: 10 December 2009 / Published online: 10 January 2010
© Springer Science+Business Media B.V. 2010

Abstract Selectivity reversal within a series of hydroxy-substituted benzoates can be induced simply by changing from an aqueous to a non-aqueous environment when using a cyclen derived molecular receptor offering two alternative guest binding mechanisms.

Keywords Inclusion complex · Hydroxybenzoates · Cyclen derivatives · Association constants · Solvent effects

Introduction

The availability of selective sensors for the simple and immediate detection of anionic species is of great significance to a number of different areas of human endeavor, for example, in the rapid and accurate diagnosis of various medical and environmental conditions. Because of this there is enormous global effort in pursuit of this objective [1–5]. In earlier work we discovered that a cyclen (cyclen = 1,4,7,10-tetraazacyclododecane) derived molecular receptor for aromatic anions, $[Cd(\mathbf{1})]^{2+}$, shown in Fig. 1, shows significant affinity and selectivity towards *o*-hydroxybenzoate anions [6]. This became evident when anion association constant measurements were made using a series of structurally isomeric hydroxybenzoates, by monitoring fluorescence perturbations during titrations conducted in 20% aqueous 1,4-dioxane. It was found that as the hydroxy substituent moved sequentially from the *para*- to the *ortho*-position of the benzoate the association constant increased markedly and, if the *meta*- and *ortho*-dihydroxybenzoates are considered, by up to three orders of magnitude. $[Cd(\mathbf{1})]^{2+}$ and related receptors are known from X-ray crystallographic studies to bind to benzoate guests primarily through classical hydrogen bonding from the O–H and N–H donors that are convergent into the base of the binding pocket [7, 8]. The remarkable thing about this selectivity pattern is that *o*-hydroxybenzoate (salicylate) is markedly less basic than *p*-hydroxybenzoate and consequently, if this binding mechanism alone were to operate, should form much weaker hydrogen bonds. On the basis of observed fluorescence quenching and geometrical considerations we proposed that the enhanced affinity of the *o*-hydroxybenzoates, and to a lesser extent the *m*-hydroxybenzoates, arises from a second effect whereby O–H…π hydrogen bonding from the guest to one or other of the aromatic rings that collectively define the binding pocket in the host occurs, as shown in Fig. 1b. The sequence of stability *ortho* > *meta* > *para* matches the degree to which the hydroxy group of the guest is directed towards the interior of the binding pocket and hence towards an aromatic ring. A variation of this proposal is that a water molecule may interpose in the O–H…π hydrogen bonding and bridge between the hydroxy group of the guest and an aromatic ring (see, for example, the structure shown as Fig. 1c) in a manner somewhat akin to that seen when aromatic π hydrogen bonding to water was first reported [9].

Electronic supplementary material The online version of this article (doi:10.1007/s10847-009-9725-4) contains supplementary material, which is available to authorized users.

J. A. Z. Hodyl · K. P. Wainwright (✉)
School of Chemistry, Physics and Earth Sciences, Flinders University, GPO Box 2100, Adelaide, SA 5001, Australia
e-mail: Kevin.Wainwright@flinders.edu.au

S. F. Lincoln
School of Chemistry and Physics, University of Adelaide, Adelaide, SA 5005, Australia

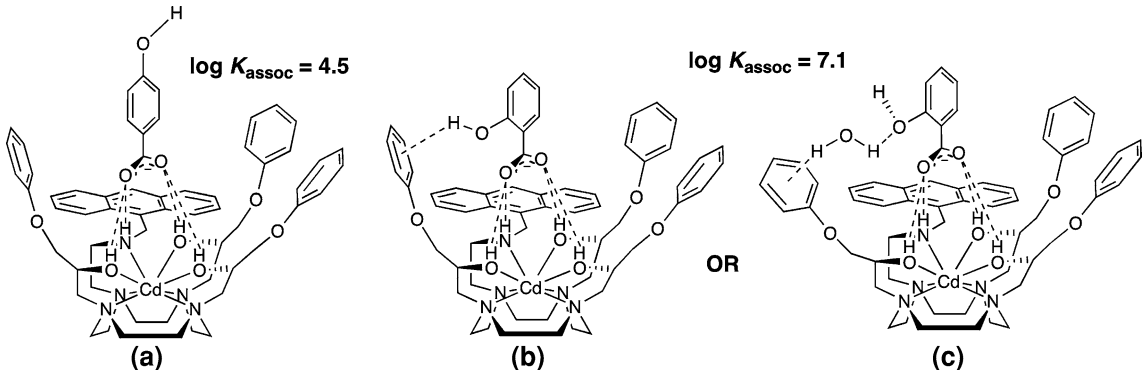


Fig. 1 $[Cd(\mathbf{1})]^{2+}$ binding of **a** *p*-hydroxybenzoate, **b** and **c** *o*-hydroxybenzoate, without and with the interposition of water. Log K_{assoc} values determined in 20% aqueous 1,4-dioxane [6]

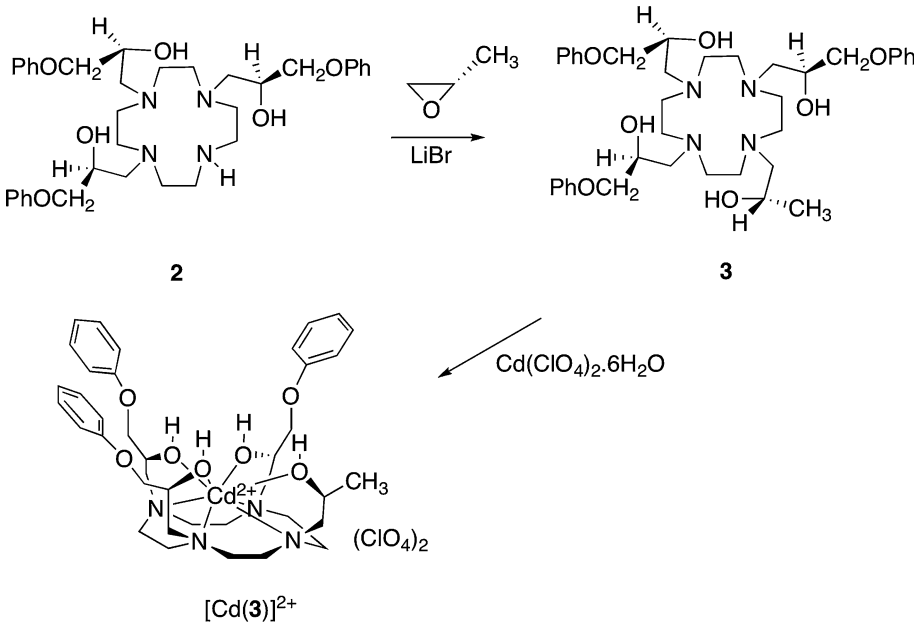
To search for further evidence of O–H…π hydrogen bonding between hydroxybenzoates with favourably positioned hydroxy moieties and this class of receptor we have now synthesised $[Cd(\mathbf{3})]^{2+}$ (Scheme 1) in which the pendant anthracene of $[Cd(\mathbf{1})]^{2+}$ has been replaced by a pendant methyl group. Whilst the main objective of this work was to look for reductions in the association constants of guests suspected of forming O–H…π hydrogen bonds, concomitant with loss of the principal aromatic moiety from $[Cd(\mathbf{1})]^{2+}$, we also took the opportunity to investigate the role of water as a possible stabilizing intermediary in the suspected O–H…π hydrogen bonding. We are now able to report not only further evidence for O–H…π hydrogen bonds in favourable cases, but also that the presence or absence of water has the quite remarkable effect of being able to reverse the ordering of association constants for the series of *o*-, *m*- and *p*-hydroxy-substituted benzoates with these hosts.

Experimental

General

All reactions were performed under an atmosphere of nitrogen. Solvents were pre-dried and purified using known literature methods. 1,4,7-Tris((2*S*)-2-hydroxy-3-phenoxypropyl) cyclen, **2**, was prepared by the literature procedure [6]. Microanalyses were carried out at the University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer. Referencing of the ^{13}C NMR chemical shifts was to the central resonance of the solvent multiplet: δ 77.00 for $CDCl_3$ and δ 49.00 for CD_3OD. ^{1}H NMR chemical shifts were referenced to the central resonance of the residual non-deuterated solvent peak: δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6 and δ 1.94 for CD_3CN. Molar conductivity measurements (Λ) were made in 10^{-3} mol dm^{-3} solutions in anhydrous DMF at ambient

Scheme 1



temperature using a Model Aqua-C Conductivity-TDS-Temp. Meter.

Association constant measurements

NMR monitored titrations, conducted at 298 K, in which the changing chemical shift of the ^{1}H resonance from one of the guest protons was tracked were used. The procedure involved preparation of individual samples containing guest alone or host and guest in 0.7 cm^3 of deuterated solvent in 5 × 180 mm NMR tubes. Samples for NMR titrations were added to the NMR tubes with Gilson Pipetman micropipettes. Concentration of the guest species in each tube was kept constant at 1 mM while varying the host for each sample from 0 to 10 mM. The samples in each tube were prepared by addition of 50 μL of guest from a 14 mM stock solution made up in the appropriate deuterated solvent. A host stock solution of 14 mM was prepared, in the same solvent, from which aliquots of between 5 and 500 μL were added to each sample, each in a different NMR tube, to give a series of samples with host : guest ratios between 0.1 and 10 that were topped up to 0.7 cm^3 with deuterated solvent. A locally written, non-linear regression procedure was used to process the chemical shift data and hence obtain the association constants and theoretical titration curves.

All guest species were used as their sodium salts (although Na(I) can bind to free host ligand, **3**, since **3** already has the much more strongly binding Cd(II) ion coordinated to it when used as the host the possibility of any interference by Na(I) is remote), which were prepared by treatment of an aqueous or ethanolic solution of the conjugate acid with NaOH until the pH of the solution was at least two pH units above the pK_a of the carboxyl moiety. The salt was then isolated either by filtration or removal of the solvent in vacuo and recrystallised from ethanol or methanol.

Syntheses

*1-((2S)-2-hydroxypropyl)-4,7,10-tris-((2S)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane (**3**)*

To a pressure vessel containing a solution of **2** (600 mg, 0.963 mmol) in dry acetonitrile (1 cm^3) and LiBr (26.2 mg, 0.302 mmol), (*S*)-propylene oxide (88 mg, 1.51 mmol) was added. The vessel was sealed and the contents then heated to 80 °C and stirred at that temperature for 3 days. Following this the vessel was cooled, opened and the reaction mixture dissolved in water (20 cm^3). The aqueous solution was then extracted with chloroform (3 × 10 cm^3). The extracts were combined, dried ($MgSO_4$) and the solvent then evaporated leaving spectroscopically pure **3** as a viscous, brown oil, 630 mg, 96%. ^{1}H NMR ($CDCl_3$): δ 7.3 (6H, m, Ar*H*); 6.9 (9H, m, Ar*H*); 4.8–2.8 (38H, br m, –CH_2, –O*H*, –C*H*); 1.3 (3H, s, (–CH_3)). ^{13}C NMR ($CDCl_3$): δ 158.35 (2 C, Ar, *ipso*); 158.32 (1 C, Ar, *ipso*); 129.25 (6 C, Ar); 120.92 (2 C, Ar); 120.73 (1 C, Ar); 114.57 (2 C, Ar); 114.49 (2 C, Ar); 114.39 (2 C, Ar); 70.13 (1 C, O*C*H_2); 70.04 (2 C, O*C*H_2); 67.84 (1 C, *C*H); 65.89 (1 C, *C*H); 65.67 (1 C, *C*H); 65.34 (1 C, *C*H); 63.26 (1 C, –*C*H_2N) 58.04 (1 C, *C*H_2N); 56.92 (2 C, *C*H_2N); 52.33 (2 C, cyclen *C*H_2); 51.04 (2 C, cyclen *C*H_2); 50.36 (2 C, cyclen *C*H_2); 49.71 (2 C, cyclen *C*H_2); 21.87 (1 C, –*C*H_3). To obtain a sample suitable for microanalysis **3** was converted to its tetrahydrochloride by treating a solution of it (534 mg, 0.79 mmol), in ice-cold ethanol (5 cm^3) with 37% aqueous HCl (10 cm^3, 121 mmol). The resultant solution was then evaporated to dryness and redissolved in methanol (0.5 cm^3). Addition of diethyl ether then precipitated the product, which was filtered off, washed with diethyl ether (10 cm^3) and dried in vacuo to give **3**·4HCl·1.5H_2O as an off-white powder, 583 mg, 89%. (Found: C, 53.46; H, 7.23; N, 6.57. $C_{38}H_{63}Cl_4N_4O_{8.5}$ requires C, 53.46; H, 7.44; N, 6.56%).

*(1-((2S)-2-hydroxypropyl)-4,7,10-tris-((2S)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane)cadmium(II) diperchlorate hemihydrate, [Cd(**3**)](ClO_4)$_2$·0.5H_2O*

To a refluxing solution of **3** (248 mg, 0.36 mmol) in dry ethanol (10 cm^3), cadmium perchlorate hexahydrate (168 mg, 0.40 mmol) dissolved in dry ethanol (5 cm^3) was added dropwise over 5 min. A white precipitate formed and redissolved immediately. The reaction was heated at reflux temperature for a further 1 h and then cooled to room temperature. The solvent was evaporated leaving a viscous, light-brown oil which was dissolved in minimal methanol then precipitated and triturated with diethyl ether to yield [Cd(**3**)](ClO_4)$_2$·0.5H_2O as an off-white powder that was dried in vacuo, 281 mg, 79%. $\Lambda_M = 128\ \Omega^{-1}\ cm^2\ mol^{-1}$ (1×10^{-3} mol dm^{-3} in DMF). (Found: C, 45.62; H, 5.54; N, 5.42. $C_{38}H_{59}CdCl_2N_4O_{16.5}$ requires C, 45.59; H, 5.74; N, 5.60%.) ^{13}C NMR (CD_3OD): δ 159.92 (1 C, Ar, *ipso*); 159.86 (1 C, Ar, *ipso*); 159.79 (1 C, Ar, *ipso*); 130.67 (2 C, Ar); 130.63 (2 C, Ar); 130.56 (2 C, Ar); 122.40 (3 C, Ar); 115.81 (2 C, Ar); 115.74 (2 C, Ar); 115.66 (2 C, Ar); 70.66 (1 C, –O*C*H_2); 70.42 (1 C, –O*C*H_2); 70.04 (1 C, –O*C*H_2); 66.65 (2 C, –*C*H); 66.50 (1 C, –*C*H); 65.79 (1 C, –*C*H); 63.26 (1 C, –N*C*H_2); 56.24 (2 C, –N*C*H_2); 56.15 (1 C, –N*C*H_2); 54.56 (2 C, cyclen –*C*H_2); 53.05 (2 C, cyclen –*C*H_2); 51.53 (2 C, cyclen –*C*H_2); 50.49 (2 C, cyclen –*C*H_2); 22.13 (1 C, –*C*H_3).

Results and discussion

The homochiral receptor ligand **3** was prepared in 96% yield from the known compound 1,4,7-tris((2*S*)-2-hydroxy-3-phenoxypropyl)cyclen, **2** [6], by reacting it with (*S*)-propylene oxide for 72 h in acetonitrile at 80 °C in a sealed pressure vessel (to avoid loss of the epoxide), using LiBr as a catalyst. As we have noted previously [6], *N*-alkylation reactions of **2** are exceedingly slow, and in the absence of LiBr, which is a recognized catalyst for epoxide ring openings [10, 11], no reaction could be induced. Complexation with Cd(II) was straightforward leading to the receptor complex $[Cd(\mathbf{3})]^{2+}$, isolated as its diperchlorate salt in 79% yield, that is presumed on the basis of numerous crystal structures of related complexes to have the eight-coordinate structure shown [7, 8, 12]. In DMF $[Cd(\mathbf{3})]^{2+}$ behaves as a 1:2 electrolyte ($\Lambda_M = 128\ \Omega^{-1}$ $cm^2\ mol^{-1}$) indicating [13], as expected [14], little or no retention of ClO_4^- in the aromatic-anion binding pocket.

To establish the relative anion binding ability of $[Cd(\mathbf{3})]^{2+}$ compared to $[Cd(\mathbf{1})]^{2+}$, and the influence of water on the stabilization of hydroxybenzoate guests within the binding pocket, a series of association constant measurements were made using ^{1}H NMR monitored titrations in different solvents. Prior to doing this Job's Method of Continuous Variation [15], was employed, using ^{1}H NMR monitoring in DMSO-d_6 and a variety of different aromatic anions, to deduce the stoichiometry of the host:guest interactions. Through this it was verified that except in the case of *p*-nitrophenolate, which has been shown previously to give 1:2 host:guest inclusion complexes [7], only 1:1 inclusion complexes are formed. The association constants determined are tabulated in Table 1 alongside the previously determined data for $[Cd(\mathbf{1})]^{2+}$ for comparison.

From Table 1 the progressive increase in the association constant for a benzoate with $[Cd(\mathbf{1})]^{2+}$, in 20% aqueous 1,4-dioxane, as a hydroxy group is first introduced to the *para*-position and then moved sequentially to the *meta*- and to the *ortho*-position(s) can be seen. It is also seen that this selectivity pattern is mirrored with $[Cd(\mathbf{3})]^{2+}$, when in the similar solvent mixture, 20% aqueous CD_3CN (deuterated 1,4-dioxane would have been prohibitively expensive, CD_3CN is closer in dielectric constant than DMSO). It is noticeable, however, that the substitution of the anthracene containing arm by a methyl containing arm, lowers the affinity for all the hydroxybenzoates, but not for benzoate itself where O–H…π hydrogen bonding is not possible. Furthermore, the reduced affinity of the hydroxybenzoates is most marked for those having a hydroxy group in an *ortho*-position, where it is best positioned to engage in O–H…π hydrogen bonding, and progressively less so as the hydroxy group moves further towards the upper extremity of the binding pocket. Even more interesting is the total reversal of the association constant ordering for $[Cd(\mathbf{3})]^{2+}$ when non-aqueous conditions (DMSO-d_6) are used, which strongly supports the idea that water molecule interposition between the hydroxy group and the aromatic wall of the pocket, as shown in Fig. 1c, is an essential component of O–H…π hydrogen bonding stabilization. The stability ordering seen in DMSO-d_6 is that which would be expected simply from the trend in the pK_a of the benzoate group, with the most acidic benzoate (2,6-dihydroxybenzoic acid) displaying the weakest binding, suggesting that O–H…π hydrogen bonding is weak or non-existent in the absence of water. The ordering of the two association constants measured in CD_3OD suggests that methanol is not able to act in a similar way to water in facilitating O–H…π hydrogen bonding, although with the limited data available this conclusion should be treated with caution.

Conclusion

Although we have not yet been able to demonstrate by X-ray crystallography the O–H…π hydrogen bonding that we suspect to be stabilising some of these host–guest

Table 1 Association constants expressed as $\log(K/mol^{-1}\ dm^3)$ for the inclusion of hydroxybenzoate anions within the receptor complexes $[Cd(\mathbf{1})]^{2+}$ and $[Cd(\mathbf{3})]^{2+}$ determined by ^{1}H NMR monitored titration, unless otherwise noted, following the previously reported procedure [6]

Guest anion	Receptor complex				pK_a^c
	$[Cd(\mathbf{1})]^{2+a}$	$[Cd(\mathbf{3})]^{2+}$	$[Cd(\mathbf{3})]^{2+}$	$[Cd(\mathbf{3})]^{2+}$	
Solvent:	20% H_2O/dioxane	20% D_2O/CD_3CN^b	DMSO-d_6	CD_3OD	
Benzoate	2.3 ± 0.1	3.10 ± 0.08	4.11 ± 0.06	3.96 ± 0.09	4.19
p-OH	4.5 ± 0.3	3.18 ± 0.28	4.09 ± 0.07		4.54
m-OH	5.3 ± 0.5	3.49 ± 0.17	4.16 ± 0.09		4.30
o-OH	7.1 ± 0.5	3.70 ± 0.15	3.08 ± 0.08	3.23 ± 0.03	2.97
2,6-diOH	7.5 ± 0.9	4.64 ± 0.36	2.05 ± 0.03		1.05

Measured at 298 ± 1 K with [guest anion] = 10^{-3} M. Uncertainties are one SD

[a] Data taken from [6], determined by fluorescence perturbation, buffered at pH 7.0 (0.02 mol dm^{-3} lutidine). [b]Buffered at pH 7.0 (0.01 mol dm^{-3} HEPES). [c]Taken from [16]

complexes, circumstantial evidence for its existence is mounting. Through this work we see manifestation of it not only by the reduction of the *o*-hydroxybenzoate association constants when the aromaticity of the binding cavity is diminished by removal of the anthracene moiety, but also by the effect of added water, which, instead of attracting the water soluble *o*-hydroxybenzoates away from the cavity, actually enhances their association, presumably by facilitating intracavity O–H…π hydrogen bonding.

Acknowledgment We are grateful to the Australian Research Council for the support of this work.

References

1. Kubik, S., Reyheller, C., Stuwe, S.: Recognition of anions by synthetic receptors in aqueous solution. J. Incl. Phenom. Macrocycl. Chem. **52**, 137–187 (2005)
2. Amendola, V., Bonizzoni, M., Esteban-Gómez, D., Fabbrizzi, L., Licchelli, M., Sancenón, F., Taglietti, A.: Some guidelines for the design of anion receptors. Coord. Chem. Rev. **250**, 1451–1470 (2006)
3. Gale, P.A., Quesada, R.: Anion coordination and anion-templated assembly: highlights from 2002 to 2004. Coord. Chem. Rev. **250**, 3219–3244 (2006)
4. Gale, P.A., García-Garrido, S.E., Garric, J.: Anion receptors based on organic frameworks: highlights from 2005 and 2006. Chem. Soc. Rev. **37**, 151–190 (2008)
5. Schneider, H.-J., Yatsimirsky, A.K.: Selectivity in supramolecular host–guest complexes. Chem. Soc. Rev. **37**, 263–277 (2008)
6. Bradbury, A.J., Lincoln, S.F., Wainwright, K.P.: Fluorescent signaling provides deeper insight into aromatic anion uptake by metal-ion activated molecular receptors. New J. Chem. **32**, 1500–1508 (2008)
7. Smith, C.B., Stephens, A.K.W., Wallwork, K.S., Lincoln, S.F., Taylor, M.R., Wainwright, K.P.: Metal ion-dependent molecular inclusion chemistry: inclusion of aromatic anions by coordinated 1, 4, 7, 10-tetrakis((S)-2-hydroxy-3-phenoxypropyl)-1, 4, 7, 10-tetraazacyclododecane. Inorg. Chem. **41**, 1093–1100 (2002)
8. Robinson, T.S., Wyness, O., Lincoln, S.F., Taylor, M.R., Tiekink, E.R.T., Wainwright, K.P.: A structural study of the synergic envelopment of acetonitrile by a Cd(II) activated molecular receptor formed from cyclen with appended 2-hydroxy-3-phenylpropyl moieties. Inorg. Chim. Acta **359**, 1413–1420 (2006)
9. Atwood, J.L., Hamada, F., Robinson, K.D., Orr, G.W., Vincent, R.L.: X-ray diffraction evidence for aromatic π hydrogen bonding to water. Nature **349**, 683–684 (1991)
10. Chakraborti, A.K., Basak, A., Grover, V.: Chemoselective protection of carboxylic acid as methyl ester: a practical alternative to diazomethane protocol. J. Org. Chem. **64**, 8014–8017 (1999)
11. Chakraborti, A.K., Rudrawar, S., Kondaskar, A.: Lithium bromide, an inexpensive and efficient catalyst for opening of epoxide rings by amines at room temperature under solvent-free condition. Eur. J. Org. Chem. 3597–3600 (2004)
12. Wainwright, K.P.: Applications for polyaza macrocycles with nitrogen-attached pendant arms. Adv. Inorg. Chem. **52**, 293–334 (2001)
13. Geary, W.J.: The use of conductivity measurements in organic solvents for the characterization of coordination compounds. Coord. Chem. Rev. **7**, 81–122 (1971)
14. Smith, C.B., Wallwork, K.S., Weeks, J.M., Buntine, M.A., Lincoln, S.F., Taylor, M.R., Wainwright, K.P.: Metal ion dependent molecular inclusion chemistry: inclusion of *p*-toluenesulfonate and *p*-nitrophenolate within the structure of coordinated 1,4,7,10-tetrakis((S)-2-hydroxy-3-phenoxypropyl)-1, 4, 7, 10-tetraazacyclododecane. Inorg. Chem. **38**, 4986–4992 (1999)
15. Hirose, K.: In: Schally, C.A. (ed.) Analytical Methods in Supramolecular Chemistry, pp. 17–54. Weinheim, Wiley-VCH (2007)
16. Howard, P., Meylan, W.: Physical Properties Database. Syracuse Research Corporation, Environmental Science Centre, North Syracuse (1999)