Tetrahedron Letters 50 (2009) 1610–1613

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Inclusion of aromatic and aliphatic anions into a cationic water-soluble calix[4]arene at different pH values

Carmelo Sgarlata [a], Carmela Bonaccorso [a], Fabio Giuseppe Gulino [a], Valeria Zito [b], Giuseppe Arena [a], Domenico Sciotto [a,*]

[a] Dipartimento di Scienze Chimiche, Università degli Studi di Catania—Viale A. Doria 6, 95125 Catania, Italy
[b] IBB, CNR, c/o Dipartimento di Scienze Chimiche, Università degli Studi di Catania—Viale A. Doria 6, 95125 Catania, Italy

ARTICLE INFO

Article history:
Received 14 November 2008
Revised 15 January 2009
Accepted 20 January 2009
Available online 23 January 2009

Keywords:
Calixarenes
Anions
Inclusion
Water

ABSTRACT

A cationic calix[4]arene derivative binds both aliphatic and aromatic, carboxylate and sulfonate anions in aqueous solution thanks to concerted electrostatic and hydrophobic interactions. The sulfonate guest inclusion is affected by the different mobility of the host caused by the pH change.

Supramolecular chemistry in water is a rapidly growing area.[1] New compounds have been developed which mimic natural systems in their ability to bind a given substrate with high affinity and selectivity in water. However, whilst cation recognition is now a well-established area of supramolecular chemistry, the coordination chemistry of anions has not received the same attention with a few exceptions.[2]

The design and synthesis of hosts for anion recognition is a demanding one as anions are sensitive to the pH and the medium; on the other hand, several noncovalent interactions may be exploited for organic anion recognition, and these include electrostatic, and hydrophobic interactions (π–π or CH–π) or a combination of both. Furthermore, if charged hosts are used, counterions may effectively compete for the binding site, as demonstrated by Schmidtchen et al.[3] Thus, owing to the variety of effects that come into play in anion recognition, this field remains challenging[4] and has been extensively reviewed recently.[5]

Synthetic anion hosts may be either positively charged or neutral. In the former case, anion binding is due to electrostatic interactions often in combination with hydrogen-bonding and hydrophobic interactions. N–H groups and/or protonated amines are the functional groups mainly involved in this class of interactions. Calixarenes are among the most widely used molecular scaffolds for the synthesis of artificial receptors,[6] thanks to their easy functionalization and tunable three-dimensional structure. A variety of polar groups, such as sulfonates,[7] carboxylic acids,[8] amines[9], and phosphonates,[10] render calixarenes water-soluble, thus paving the way to the investigation of these hosts in water.[11] Though different amino-calixarene derivatives for anion binding have been reported,[5a,12] to the best of our knowledge there are only few papers concerning molecular recognition in water.[3,13] We have previously investigated the molecular recognition of cationic and neutral species by calix[4]arenes in water;[14] these studies have shed light on the role played by charged groups in the inclusion of guests into the calixarene apolar cavity; guest complexation has been found to occur thanks to the synergy between electrostatic interactions and hydrophobic interactions with the upper rim and the calixarene cavity, respectively.

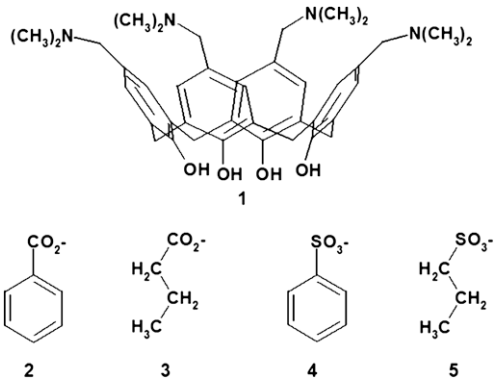
We are now focusing our attention on 5,11,17,23-tetrakis-[(dimethylamino)methyl]-25,26,27,28-tetrahydroxy-calix[4]arene (**1**)[15] (Scheme 1) that lends itself to the recognition of anionic guests in aqueous solution; the anions investigated in the present work are also shown in Scheme 1.

The binding of this host to neutral aromatic guest has been previously studied in aqueous solution under fairly acidic condition (pD 1.4)[16] where the host is believed to be fully protonated. No studies have ever been performed in water at neutral pH, nor has the existence of the zwitterionic form of **1** ever been proved. There is only indirect evidence suggesting that **1** may exist as a zwitterionic form.[15]

The acid–base properties of the host were studied potentiometrically in aqueous solution (t = 25 °C).[17] The results of the potentiometric analysis are shown in Table 1. Host **1** has two titratable

* Corresponding author. Tel.: +39 095 7385001; fax: +39 095 580137.
E-mail address: dsciotto@unict.it (D. Sciotto).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.100



Scheme 1. Host and guests that were investigated.

Table 1
Log K values for the protonation of **1** (L), 25 °C, I = 0.1 mol dm^{-3} ($NaNO_3$)

Reaction	pK_a[a]
$H_2L \rightleftarrows HL + H$	3.29 (2)
$HL \rightleftarrows L + H$	8.15 (2)

Charges are omitted for clarity.
[a] 3σ in parentheses.

protons, the first of which is fully dissociated at pH 5, whereas the second one dissociates appreciably above pH 7.

pK_{a1} is to be ascribed to the dissociation of a phenolic hydroxyl of the lower rim,[18] whereas pK_{a2} is associated to the deprotonation of one of the four ammonium protons of the upper rim. Above pH 8.3–8.5, the emf reading starts drifting slowly and the resulting potentiometric curves curl back indicating the formation of a precipitate that is hardly detectable to the naked eye; the precipitate becomes clearly visible 10–15 min after the onset of the drifting. As pH increases, the percentage of ammonium residue that is protonated becomes increasingly smaller, and this (i.e., the loss of a proton) renders the host insoluble in water.

To further support the potentiometric findings, we performed electrophoretic experiments at pH 2.0 and 6.8 (phosphate buffers).[19] The electrophoretic mobility of **1** was compared to that of a tetracationic calixarene, employed as a standard.[20] The experiments performed at pH 2.0 show that **1** has the same mobility as the standard tetracationic compound, indicating that the host is fully protonated at both the upper and lower rims. At neutral pH the migration of the host decreases, which is indicative of the loss of protons. Both potentiometric and electrophoretic data lead to conclude that only the hydroxyl proton of **1** is lost under neutral conditions in water.

The ^{1}H NMR analysis in D_2O supports both the potentiometric and the electrophoretic data. Preliminarily, we explored the concentration range 5×10^{-4}–1.5×10^{-2} mol dm^{-3} to make sure that micelles did not form; indeed, the proton signals did not change, and this rules out micelle formation within the concentration range of interest. This, in turn, indicates that one of the phenolic oxygens of the lower rim is deprotonated; the decreased flexibility has been shown to result from an effective intramolecular hydrogen bond between the phenolate and the phenolic units of the lower rim.[18] It is worth stressing that at pD 7.1 all the four amino groups are still practically protonated.

^{1}H NMR was also used to determine the stereochemistry of binding and the inclusion constants for the guests shown in Scheme 1.[21] The investigation of the carboxylates was restricted to pD 7.1 where both guests exist in their anionic form.

Compared to the uncomplexed guest, the guest proton signals shift to higher fields with increasing host concentration, indicating that the guest molecule is encapsulated into the calix[4]arene cavity. Guest signals are also detected as a single resonance due to the fast exchange between the free and the complexed species on the ^{1}H NMR timescale. For the benzenesulfonate, and for the propanesulfonate guest, the complexation-induced shifts (CIS) follow the order $H_{para} > H_{meta} > H_{ortho}$ and $H_c > H_b > H_a$, respectively, regardless of the pH (Figs. 1 and 2); this shows that the guest is included in the cavity as illustrated in Figure 3. The chemical shifts of the benzoate and butanoate follow the same order as the benzenesulfonate and propanesulfonate guests, respectively, indicating that they are included in a manner similar to that of the analogous sulfonate derivatives.

All the guests are included thanks to concerted hydrophobic and electrostatic effects. The binding constant values (Table 2) indicate that (i) the aromatic anions form stronger complexes than the aliphatic anions at the same pH; (ii) the inclusion complex of the guest is stronger in the acidic region than at neutral pH, regardless of the nature of the organic group attached to the anionic residue. The tighter binding of the aromatic guests is due to a π–π interaction that is known to be more effective than the CH–π interaction occurring in the aliphatic guest–host complexes.[22] Likely, the tighter binding observed at pH 2 is to be ascribed to the greater

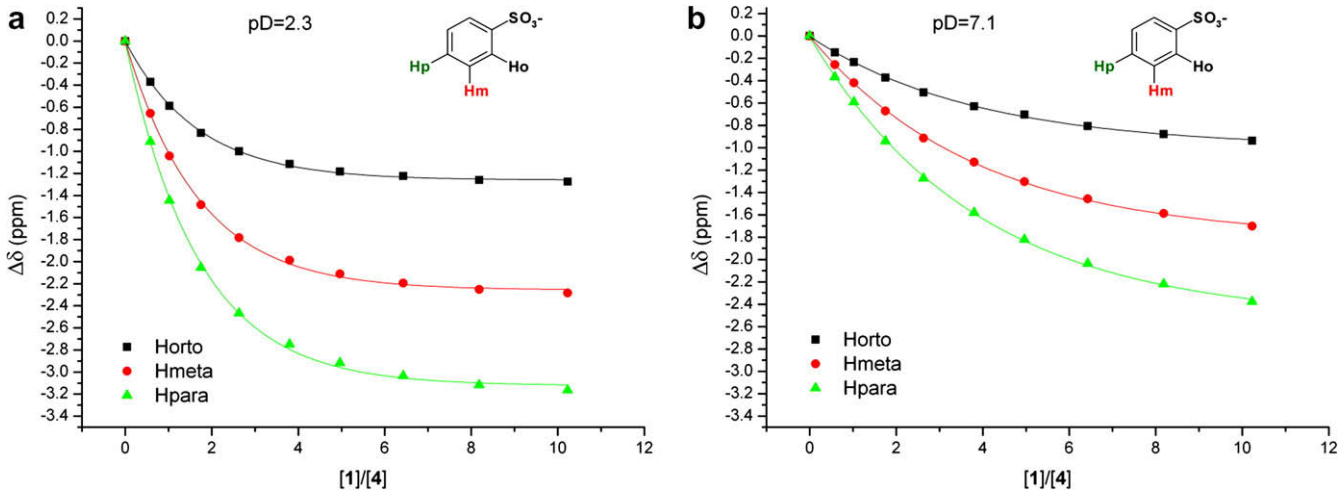


Figure 1. Plots of Δδ observed (ppm) versus (a) [**1**]/[**4**] pD = 2.3 and (b) [**1**]/[**4**] pD = 7.1 in D_2O, 25 °C.

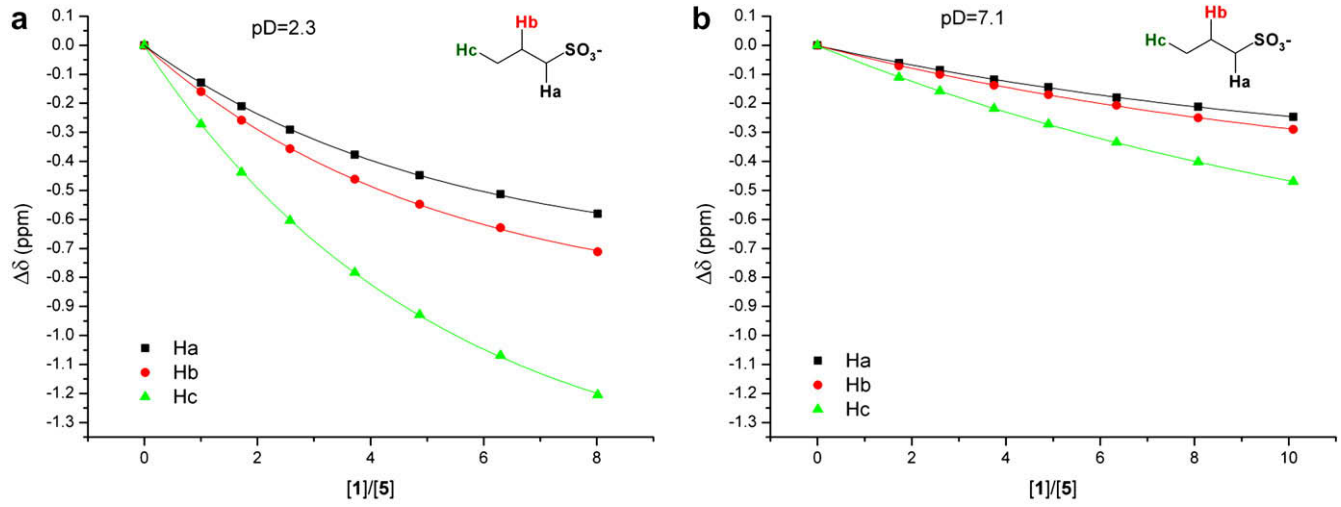


Figure 2. Plots of $\Delta\delta$ observed (ppm) versus (a) [**1**]/[**5**] pD = 2.3 and (b) [**1**]/[**5**] pD = 7.1 in D_2O, 25 °C.

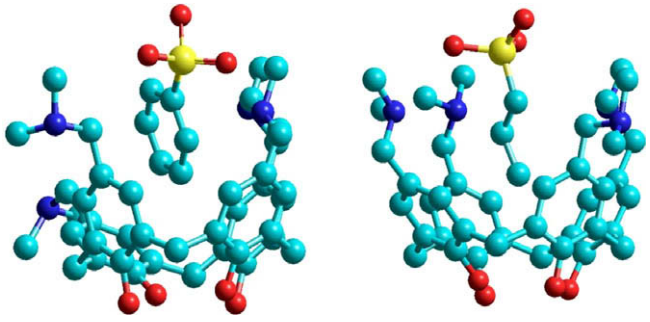


Figure 3. Optimized structure for **1**-benzenesulfonate (left) and **1**-propanesulfonate (right); the optimization was carried out with Molecular Mechanics and Force Field Amber. Explicit water molecules are omitted for clarity.

Table 2
Log*K* values for the complex formation of **1** with the anionic guests shown in Scheme 1 at different pD and 25 °C

Guest	Log*K*[a]	
	pD 2.3	pD 7.1
2	—	2.32 (1)
3	—	1.50 (2)
4	3.09 (1)	2.44 (1)
5	2.24 (2)	1.48 (2)

[a] σ in parentheses.

mobility of the host in acidic region; such a flexibility would allow for a better fit of the guest. ITC measurements, currently underway, indicate that the real situation is more complex than that depicted by the values of the binding constants only. The enthalpy of inclusion is negative for all the guests (though not of the same magnitude)[23], whilst the entropy of inclusion is not favorable for all the guests.

In conclusion we have shown that **1** is able to include both sulfonates and carboxylates having an aliphatic or aromatic moiety in water. The binding strength of the sulfonate guests changes with the pH, and this is to some extent linked to the different flexibility of the host in the two pH regions.

The splitting of the binding constant values into the compounding ΔH and ΔS values should provide a more detailed description of the processes occurring in water.

Acknowledgment

MIUR is gratefully acknowledged for partial support.

Supplementary data

Supplementary data (ESI-MS, ^1H and ^{13}C NMR spectra concerning the tetracationic calixarene employed as reference compound) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.100.

References and notes

1. Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2366–2393.
2. (a) Gale, P. A.; Garcia-Garrido, S. E.; Garric, J. *Chem. Soc. Rev.* **2008**, *37*, 151–190; (b) Plitt, P.; Gross, D. E.; Lynch, V. M.; Sessler, J. L. *Chem. Eur. J.* **2007**, *13*, 1374–1381; (c) Beer, P. D.; Bayly, S. R. *Top. Curr. Chem.* **2005**, *255*, 125–162; (d) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (e) O'Neil, E. J.; Smith, B. D. *Coord. Chem. Rev.* **2006**, *250*, 3068–3080; (f) Martıinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419–4476.
3. (a) Schmidtchen, F. P. *Chem. Ber.* **1981**, *114*, 597–607; (b) Worm, K.; Schmidtchen, F. P.; Schier, A.; Schäfer, A.; Hesse, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 327–329; (c) Worm, K.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 65–66.
4. Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443–448.
5. (a) Kubic, S.; Reyheller, C.; Stuwe, S. *J. Inclusion Phenom. Macrocycl. Chem.* **2005**, *52*, 137–187; (b) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 1–226.
6. (a) Gutsche, C. D. In *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1998; (b) Gutsche, C. D. *Calixarenes: An Introduction*; Royal Society of Chemistry: Cambridge, 2008; (c)*Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001; (d)*Calixarenes in the Nanoworld*; Vicens, J., Harrowfield, J., Eds.; Springer: Dordrecht, 2007.
7. (a) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Mababe, O. *Tetrahedron Lett.* **1984**, *25*, 5315–5318; (b) Shinkai, S. *Pure Appl. Chem.* **1986**, *58*, 1523–1528; (c) Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, R.; Manabe, O. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2297–2299.
8. (a) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981–982; (b) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689–4694.
9. (a) Nagasaki, T.; Sisido, K.; Arimura, T.; Shinkai, S. *Tetrahedron* **1992**, *48*, 797–804; (b) Shimizu, S.; Kito, K.; Sasaki, Y.; Hirai, C. *Chem. Commun.* **1997**, 1629–1630.
10. (a) Almi, A.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177–2182; (b) Arimura, T.; Nagasaki, T.; Shinkai, S.; Matsuda, T. *J. Org. Chem.* **1989**, *54*, 3766–3768.
11. (a) Kimentovà, J.; Vojtìsek, P. *J. Mol. Struct.* **2007**, *826*, 48–63; (b) Ryu, E. H.; Zhao, Y. *Org. Lett.* **2005**, *7*, 1035–1037.
12. Matthews, S. E.; Beer, P. D. *Supramol. Chem.* **2005**, *17*, 411–435.
13. (a) Mchedlov-Petrossyan, N. O.; Vilkova, L. N.; Vodolazkaya, N. A.; Yakubovskaya, A. G.; Rodik, R. V.; Boyko, V. I.; Kalchenko, V. I. *Sensors* **2006**, *6*, 962–977; (b) Dudic, M.; Colombo, A.; Sansone, F.; Casnati, A.; Donofrio, G.; Ungaro, R. *Tetrahedron* **2004**, *60*, 11613–11618; (c) Corbellini, F.; Fiammengo,

R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569–6575; (d) Corbellini, F.; Di Constanzo, L.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946–9947.

14. (a) Arena, G.; Casnati, A.; Contino, A.; Lombardo, G. G.; Sciotto, D.; Ungaro, R. *Chem. Eur. J.* **1999**, *5*, 738–744; (b) Arena, G.; Casnati, A.; Contino, A.; Gulino, F. G.; Sciotto, D.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **2000**, 419–423; (c) Arena, G.; Contino, A.; Gulino, F. G.; Magrì, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **2000**, *41*, 9327–9330; (d) Casnati, A.; Sciotto, D.; Arena, G. Water-Soluble Calixarenes. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001. Chapter 24.
15. Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, *110*, 6153–6162.
16. Baur, M.; Frank, M.; Schatz, J.; Schildbach, F. *Tetrahedron* **2001**, *57*, 6985–6991.
17. All measurements were carried out at 25.0 °C and $I = 0.1$ mol dm^{-3} (sodium nitrate). Solutions of the ligand with concentrations ranging from 2.7 to 3.7×10^{-3} mol dm^{-3} were titrated with standardized sodium hydroxide (ca. 0.1 mol dm^{-3}) within the pH range 2.5–8.5. For further experimental details see Reference 18. Hyperquad (http://www.hyperquad.co.uk/hq2000.htm) was used to calculate the stability constant values.
18. Arena, G.; Calì, R.; Lombardo, G. G.; Rizzarelli, E.; Sciotto, D.; Ungaro, R. *Supramol. Chem.* **1992**, *1*, 19–24.
19. Agarose and polyacrylamide gels were used to obtain information on the charge of **1** under acidic and neutral conditions, respectively. To monitor the progress of separation and to locate the end of the run, we employed *meso*-tetrakis(*N*-methyl-4-pyridyl)porphyrin as dye with a high electrophoretic mobility in conjunction with the tetracationic *cone*-5,11,17,23-tetrakis(trimethylammonium)-25,26,27,28-tetrapropoxy-calix[4]arene that was used as an internal standard. The compounds were detected by spraying with Dragendorff's reagent.
20. *Procedure for the synthesis of cone-5,11,17,23-tetrakis(trimethylammonium)-25,26,27,28-tetrapropoxy-calix[4]arene*: Methyl iodide (4.0 g, 35.8 mmol) was added to a THF suspension (20 ml) containing *cone*-5,11,17,23-tetraamino-25,26,27,28-tetrapropoxy-calix[4]arene[11a] (0.4 g, 0.6 mmol) and K_2CO_3 (1.2 g, 8.7 mmol). The precipitate was filtered out and dissolved in water. The aqueous phase was treated with CH_2Cl_2 and concentrated in vacuo. The amorphous solid was precipitated out of the solution by using NH_4PF_6. Ion exchange chromatography of a solution of this material yielded cone-5,11,17,23-tetrakis(trimethylammonium)-25,26,27,28-tetrapropoxy-calix[4]-arene tetrachloride (352 mg, yield 71%): ^{1}H NMR (ppm, 500 MHz, D_2O, 25 °C): 7.50 (s, ArH, 8H), 4.59 (d, $J = 13.0$ Hz, Ar–CH_2–Ar, 8H), 4.00 (t, $J = 7.5$ Hz, Ar–O–CH_2, 8H), 3.61 (d, $J = 13.0$ Hz, Ar–CH_2–Ar, 8H), 3.43 (s, N(CH_3)$_3$, 36H), 1.98 (m, OCH_2–CH_2–CH_3, 8H), 0.96 (t, $J = 7.5$ Hz, OCH_2–CH_2–CH_3, 12H); ^{13}C NMR (ppm, 125 MHz, D_2O, 25 °C): 157.85 (Ar), 141.45 (Ar), 136.92 (Ar), 119.74 (Ar), 77.81 ($OCH_2CH_2CH_3$), 57.37 (N^+CH_3), 31.25 ($ArCH_2$), 22.97 ($OCH_2CH_2CH_3$), 9.75 ($OCH_2CH_2CH_3$); ESI-MS m/z (rel. int.%) 1001.43 ([M+Cl]$^-$, 100).
21. Fielding, L. J. *Tetrahedron* **2000**, *56*, 6151–6170. the complexation induced shift data (CIS) were treated by using HyperNMR (http://www.hyperquad.co.uk/hypnmr.htm).
22. (a) Muller-Dethlefs, K.; Hobza, P. *Chem. Rev.* **2000**, *100*, 143–168; (b) Nishio, M.; Hirota, M.; Umezawa, Y. In *The CH–π Interaction. Evidence, Nature and Consequences*; Wiley-VCH: New York, 1998; (c) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.
23. Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420–5426.