Pergamon

Tetrahedron Letters 41 (2000) 8311–8315

TETRAHEDRON LETTERS

The cooperative effect of electrostatic and hydrophobic forces in the complexation of cationic molecules by a water-soluble resorcin[4]arene derivative

Seong Jin Park and Jong-In Hong*

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-747, South Korea

Received 21 June 2000; revised 23 August 2000; accepted 25 August 2000

Abstract

A new water-soluble resorcin[4]arene derivative **4** was synthesized and the complexation of cationic guests in D_2O was studied by ^1H NMR spectroscopy. A 1:1 binding mode was elucidated by a Job's plot. The cooperative effect of electrostatic and hydrophobic interactions acts as a binding force for a strong complex formation with appropriate cationic guests in water. The thermodynamic parameters of complexation of guest **I** determined by a van't Hoff plot indicate that the complexation process is both enthalpically and entropically driven.

Keywords: host–guest complex; cooperative effect; water-soluble resorcin[4]arene.

The formation of host–guest complexes in water is a basic chemical process that controls many significant biological events. Numerous attempts to understand biological molecular recognition in water using natural and artificial hosts have been made with cyclodextrines[1] and water-soluble cyclophanes.[2] In addition, the related compounds such as calix[*n*]arenes ($n=4$, 6 and 8), which have relatively well-defined inclusion cavities, have also been studied in more recent years.[3] There are, however, a few examples using resorcin[4]arene units which can offer more rigid hydrophobic pockets for molecular recognition.[4] Recently, we reported water-soluble resorcin[4]arene derivatives which have ammonium units or metal–ligand centers and described their host–guest chemistry with aromatic carboxylates as guests.[4a,b]

The recognition of quaternary ammonium salts by artificial receptors was extensively studied in the last decade. For the complexation of cationic charged molecules, some anionic charged

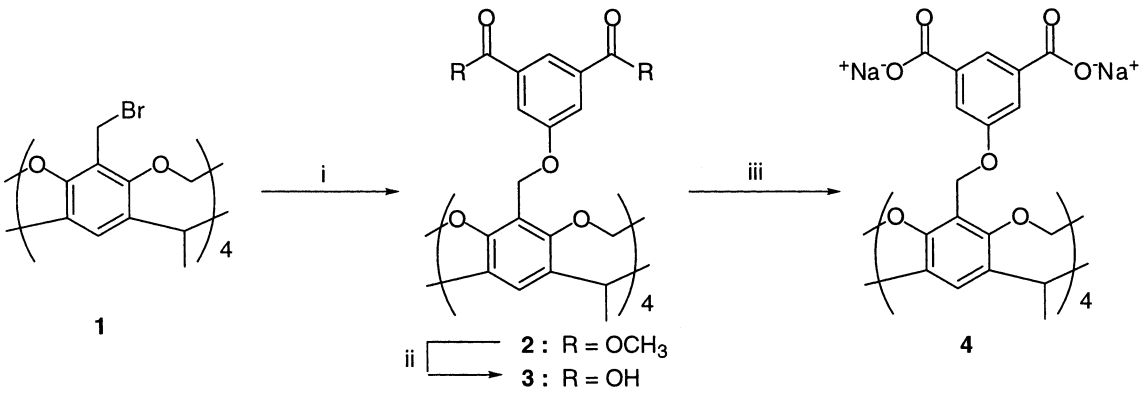
* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01441-6

water-soluble calix[*n*]arene derivatives have been used.[3] Only a few systems, however, have been reported to bind pyridinium or quaternary ammonium salts in water using resorcin[4]arene as a basic skeleton.[4h–j] Moreover, in those cases charged octol systems were used. Herein we report binding phenomena resulting from a new water-soluble, anionic charged resorcin[4]arene derivative for pyridinium and quaternary ammonium salts in water.

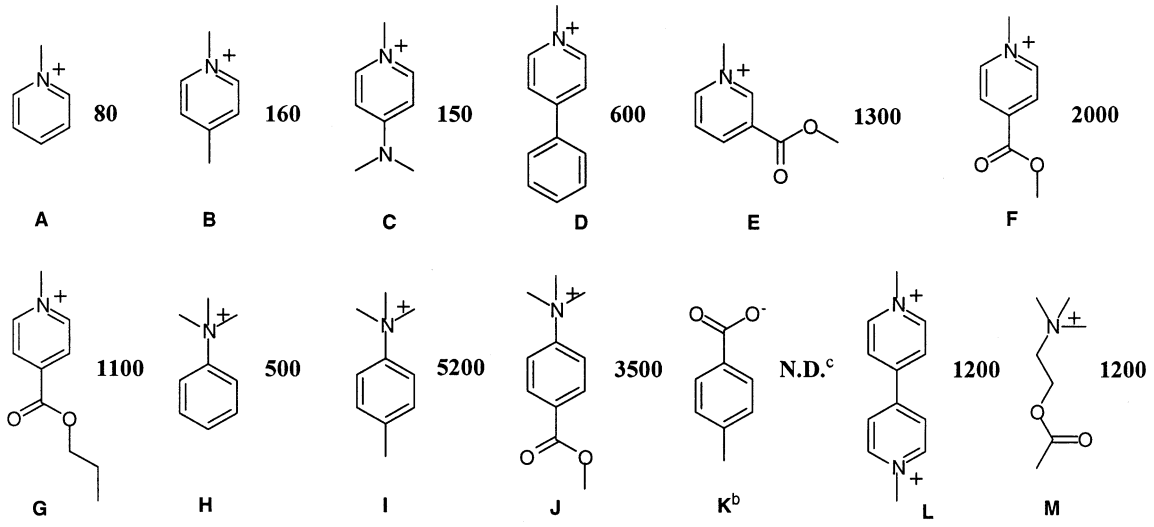
Resorcin[4]arenes having methylene bridges have a more rigid structure than calix[*n*]arenes.[5] As described independently by Shinkai and Ungaro,[3a–c,j,h] this rigidity can give rise to selectivity in the binding of cationic charged molecules, namely, the rigid water-soluble basket-shaped hosts are able to selectively bind the aromatic portion of pyridinium and quaternary ammonium salts in aqueous media.

Compound **4**[6] was synthesized from the known bromomethylcavitand **1**[7] (Scheme 1). Although compound **3** itself is barely soluble in water, compound **4** obtained by the addition of a slight excess amount of NaOH to the suspension of **3** in H_2O was rapidly dissolved. The ^1H NMR chemical shifts of **4** in D_2O were concentration-independent.[8] This means that micelle formation within the experimental concentration range could be ruled out. The inclusion phenomena of several cationic charged molecules were investigated by ^1H NMR titration experiments. Relatively slight upfield shifts were observed for the *N*-methyl protons of pyridinium and ammonium salts, while both the alkyl protons at the *m*- or *p*-position of guests and guest aromatic protons experienced large complexation-induced shifts (CIS). Pendent aromatic groups on the upper rim of **4** showed upfield shifts (0.04–0.5 ppm) with a successive addition of aromatic guests. This tells us that the rigidity of the resorcin[4]arene unit plays a key role in the selective inclusion of guests, and the pendent aromatic groups may be well situated to create a hydrophobic environment around the complexed guests.[3a–c,j,h] The binding constant values (Table 1) were obtained by measuring the host's chemical shift values and refining the CIS values by using nonlinear least-squares fitting methods. The maximum signal change was observed at 0.5 mole fraction from the Job's plot between host **4** and guest **I**, indicating 1:1 binding.



Scheme 1. Reagents and conditions. (i) 5-Hydroxy-dimethylisophthalate, K_2CO_3; (ii) NaOH, THF/MeOH/H_2O, rt, HCl (1N); (iii) NaOH

Table 1
Binding constants (M^{-1}) of the 1:1 host–guest complexes in D_2O[a]



[a] Binding constants were obtained by ^1H NMR titrations on the basis of the 1:1 binding model at 300 K. All counterions are I^-. [b] Counterion is Na^+. [c] No detectable complexation-induced ^1H NMR shift changes were observed.

A negatively charged aromatic carboxylate guest **K** did not show any detectable CIS, meaning that there is a significant electrostatic contribution to the binding. For a reference molecule **7**[9] having no hydrophobic pocket, a little CIS was observed upon addition of guest **J** ($K \sim 8\ M^{-1}$). This implies that a strong complexation is not expected only with electrostatic interaction. Guests having an alkyl, phenyl or an alkoxy carbonyl moiety at the *m*- or *p*-position showed stronger binding than those without an attached side chain, which also indicates that for strong complex formation the hydrophobic interaction is important in aqueous media. In addition, the fact that $-CH_3$ protons of the guest's pendent group experienced large upfield shifts (e.g. $\Delta\delta$ of **E** = 2.9, $\Delta\delta$ of **F** = 3.3, $\Delta\delta$ of **G** = 3.1, $\Delta\delta$ of **J** = 3.9 ppm) indicates that methyl protons reside in the shielding region of the resorcin[4]arene unit. Moreover, comparing the binding constants for guest **F** and guest **G**, it turns out that an alkyl moiety of appropriate length shows a more effective hydrophobic interaction in the apolar cavity. Of special interest is the appreciable binding by **4** of methylviologen (**L**) that has been used as a biological oxidation–reduction indicator and neurotransmitter acetylcholine (**M**). This would provide the modified redox potential of bound methylviologen and a greater understanding of the nature of the interaction which play a role in neurotransmitter-receptor binding.[10]

In order to elucidate the thermodynamic parameters controlling the complexation process, temperature-dependent ^1H NMR titrations were performed to give a van't Hoff plot between **4** and guest **I** (Fig. 1), and it was shown that the complexation process is both enthalpically ($\Delta H° = -3.24$ kcal mol^{-1}) and entropically favored ($\Delta S° = 6.22$ cal K^{-1} mol^{-1}). This indicates that both the enthalpy gain from electrostatic and hydrophobic interactions, and entropy gain from desolvation cooperatively contribute to the binding of cationic charged guests. Although subtle variations in the guest structure are known to lead to the different complexation thermodynamics,[11] this is one of the rare cases in which both enthalpic and entropic gain contribute to the effective binding in water.[11,12]

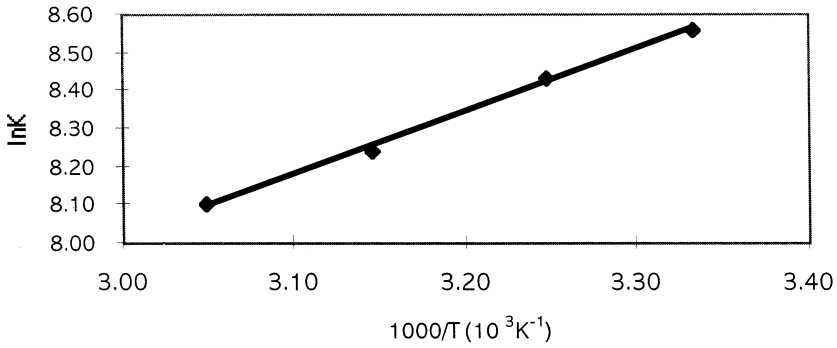


Figure 1. van't Hoff plot between host **4** and guest **I**

In conclusion, we have synthesized a new water-soluble resorcin[4]arene derivative which shows 1:1 binding to cationic charged molecules, i.e. pyridinium and quaternary ammonium salts. The cooperative effect of electrostatic and hydrophobic interactions contributes to strong complex formation in aqueous media.

Acknowledgements

This work was supported by a Korean Research Foundation Grant (KRF-99-042-D00073). S.J.P. thanks the Ministry of Education for the BK 21 fellowship.

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6. Selected spectral data for **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 4H, Ar*H*), 7.80 (s, 8H, Ar*H*), 7.45 (s, 4H, Ar*H*), 5.85 (d, J=7.13 Hz, 4H, ArOCH_{out}H$_{in}$OAr), 5.13 (q, J=7.36 Hz, 4H, C*H*CH$_3$), 5.01 (s, 8H, ArCH_2O), 4.63 (d, J=7.13 Hz, 4H, ArOCH$_{out}$$H_{in}$OAr), 3.87 (s, 24H, ArCO$_2CH_3$), 1.86 (d, J=7.35 Hz, 12H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 158.6, 153.9, 139.1, 132.0, 123.5, 122.0, 120.9, 120.0, 99.8, 61.3, 52.3, 31.2, 16.1; ESI-MS m/z 1480 (M^+). Selected spectral data for **3**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.08 (bs, 8H, ArCOO*H*), 8.06 (s, 4H, Ar*H*), 7.92 (s, 4H, Ar*H*), 7.66 (s, 8H, Ar*H*), 5.89 (d, J=7.50 Hz, 4H, ArOCH_{out}H$_{in}$OAr), 4.91 (m, 12H, ArCH_2O+C*H*CH$_3$), 4.47 (d, J=7.59 Hz, 4H, ArOCH$_{out}$$H_{in}$OAr), 1.91 (d, J=7.31 Hz, 12H, CHCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4, 158.6, 153.2, 139.1, 132.7, 122.6, 122.2, 119.3, 99.6, 60.9, 31.3, 16.1; FAB$^-$-MS (NBA) m/z 1367 $(M-H)^-$. Selected spectral data for **4**: ^{1}H NMR (300 MHz, D_2O) δ 7.83 (s, 4H, Ar*H*), 7.65 (s, 8H, Ar*H*), 7.48 (s, 4H, Ar*H*), 5.92 (d, J=7.27 Hz, 4H, ArOCH_{out}H$_{in}$OAr), 4.96 (s, 8H, ArCH_2O), 4.94 (q, J=7.40 Hz, 4H, C*H*CH$_3$), 4.35 (d, J=7.30 Hz, 4H, ArOCH$_{out}$$H_{in}$OAr), 1.79 (d, J=7.39 Hz, 12H, CHCH_3); ^{13}C NMR (75 MHz, D_2O) δ 175.0, 158.1, 153.6, 139.9, 138.4, 122.8, 122.2, 118.5, 100.6, 61.6, 31.8, 15.7.
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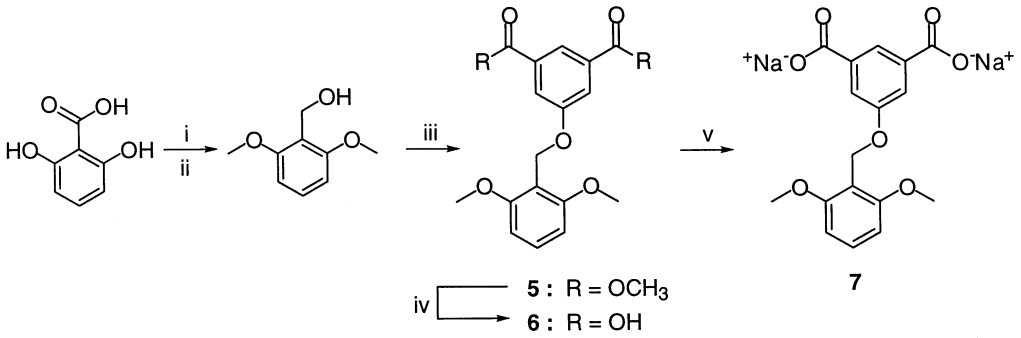
8. We checked the concentration-dependent ^{1}H NMR chemical shifts from 0.2 to 10 mM.
9. A reference host molecule (**7**) was prepared using Mitsunobu coupling as a key step.



Reagents and conditions. (i) MeI, K_2CO_3; (ii) $LiAlH_4$, reflux; (iii) 5-hydroxy-dimethylisophthalate, PPh_3, DEAD; (iv) NaOH, THF/MeOH/H_2O, rt, HCl (1N); (v) NaOH.

Selected spectral data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H, Ar*H*), 7.93 (s, 2H, Ar*H*), 7.31 (t, J=8.40 Hz, 1H, Ar*H*), 6.60 (d, J=8.38 Hz, 2H, Ar*H*), 5.25 (s, 2H, ArCH_2OAr), 3.94 (s, 6H, ArCO$_2$CH_3), 3.85 (s, 6H, ArOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 159.4, 159.3, 131.4, 130.5, 122.6, 120.5, 112.0, 103.7, 59.9, 55.8, 52.3; EI-MS m/z 360 (M^+). Selected spectral data for **6**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.27 (s, 2H, ArCO$_2$*H*), 8.05 (s, 1H, Ar*H*), 7.71 (s, 2H, Ar*H*), 7.35 (t, J=8.38 Hz, 1H, Ar*H*), 6.71 (d, J=8.40 Hz, 2H, Ar*H*), 5.12 (s, 2H, ArCH_2OAr), 3.80 (s, 6H, ArOCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 159.0, 158.9, 132.6, 130.9, 122.1, 119.3, 111.3, 104.0, 59.4, 55.9; EI-MS m/z 332.0904 (M^+). Selected spectral data for **7**: ^{1}H NMR (300 MHz, D_2O) δ 7.78 (s, 1H, Ar*H*), 7.49 (s, 2H, Ar*H*), 7.26 (t, J=8.43 Hz, 1H, ArH), 6.61 (d, J=8.46 Hz, 2H, ArH), 5.11 (s, 2H, ArCH$_2$OAr), 3.70 (s, 6H, ArOCH$_3$); ^{13}C NMR (75 MHz, D_2O) δ 175.0, 159.2, 158.1, 138.3, 131.7, 122.5, 118.5, 112.0, 105.0, 60.5, 56.3.

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