Tetrahedron 65 (2009) 2711-2715

Contents lists available at ScienceDirect

Tetrahedron

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

Thermodynamic aspects of the host-guest chemistry of pyrogallol[4]arenes and peralkylated ammonium cations

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ARTICLE INFO

Article history: Received 19 September 2008 Received in revised form 6 January 2009 Accepted 7 January 2009 Available online 20 January 2009

ABSTRACT

The stability constants (K), standard free energy (ΔG°), enthalpy (ΔH°), and entropy changes (ΔS°) for the complexation of pyrogallol[4]arenes with ammonium cations of different size and shape have been determined in ethanol at 298 K by isothermal titration calorimetry. The trends observed in the thermodynamic parameters for 1:1 and/or 1:2 host-guest complexation correspond to the systematic structural changes of the guest molecules. On the basis of the results obtained we compare the complexation properties with two other resorcin[4]arenes and discuss the thermodynamic aspects of this supramolecular host-guest interactions.

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1. Introduction

The design of selectively and effectively binding host-guest systems is an important challenge in modern supramolecular chemistry. Calix[4]arenes are potent size-selective receptors for a variety of substrates, in particular, for inorganic and organic cations.¹ During the last two decades, pyrogallol[4]arenes—members of the resorcin[4]arene family-have attracted broad interest in supramolecular chemistry and molecular recognition chemistry. The first successful synthesis of this type of macrocycles according to the procedure of Högberg² was carried out by Tite et al., who reported in 1989 a new type of the lipophilic macrocyclic host molecules containing multiple ferrocenyl centers.³ In the early 90s Dalcanale et al. studied not only the conformation and configuration of these macrocycles by NMR techniques in great detail but also the preparation, physico-chemical characterization, and mesomorphic properties of a new class of pyrogallol[4]arene-based columnar liquid crystals.⁴ In their pioneering studies, Cram et al. used pyrogallol[4]arenes as building blocks in the synthesis and investigation of hemicarcerands.⁵ Those covalently bonded dimeric capsules provided the basis for intensive studies of the host-guest complexation. Reinhoudt et al. introduced the term 'carceplexes'

for rigid container molecules of nanometer-size cavity obtained by combining calix[4]arenes and pyrogallol[4]arene subunits.⁶ Sherman et al. combined the topic of self-assembly with the formation of carceplex and elucidated the template formation and encapsulation processes in pyrogallol[4]arene-based carceplex by using highly stable, guest-selective self-assembling structures,⁷ Reinhoudt et al. investigated the immobilization of pyrogallol[4]arenebased carceplexes on a gold surface and the complexation of neutral and cationic compounds with such a synthetic receptor for the first time.⁸ The supramolecular association is driven predominantly by electrostatic interactions between the guest molecule and the electron-rich cavity of the macrocyclic host. In the following years several reports were published on different self-assembled dimeric pyrogallol[4]arene-based hosts that can encapsulate a wide variety of inorganic and organic guest compounds in solution and in gas phase.⁹ In 1999, Mattay et al. reported that pyrogallol[4]arenes exist as unique hexameric self-assembled capsules in the solid state.¹⁰ Later, works of the groups of Atwood et al.,¹¹ Rebek and Shivanyuk,¹² and Cohen and Avram¹³ showed that those hexamers are stable also in solution. Especially the introduction of diffusion NMR techniques to this research field by Cohen had a great impact on the analysis and characterization of the aggregation properties of resorcin[4]arene and its derivatives. Studies of these aggregates in the solid state were mainly done by the group of Atwood et al.¹⁴ Later Rissanen et al. contributed greatly to the supramolecular study of these pyrogallol-based macrocycles. For example, they reported the original method for the synthesis of pyrogallol[6]arenes¹⁵ and the complete derivatization of pyrogallol[4]arenes.¹⁶ Rissanen et al. further investigated the inclusion phenomena of





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^{0040-4020/\$ -} see front matter © 2009 Elsevier Ltd. All rights reserved. doi:10.1016/j.tet.2009.01.066

alkylammonium cations with resorcin[4]arenes and pyrogallol analogues.¹⁷ The complexation of quaternary ammonium ions as cationic guests resembles to some bioorganic processes based on cation $-\pi$ interactions, such as the recognition of the acetylcholine by acetylcholine-esterase.^{18,19} The first experimental study in this context was reported by Schneider et al. in 1988 for the systems composed of tetraphenolate of resorcin[4]arenes and a series of quaternary ammonium cations.²⁰ In 2000, Lemaire et al. revealed that resorcin[4]arenes have a significant affinity to cesium ion (165 pm in radius) as a guest in solution.^{9d} Two years later Mattay et al. came to the same conclusion on the basis of the results from the gas-phase experiments.^{9f} Bearing those results in mind, it is reasonable to elucidate the influence of larger cations on the complexation behavior of resorcin[4]arene and its derivatives in the gas phase. The limited access to inorganic cations larger than >180 pm and the high toxicity of francium cation were also the reason why peralkylated ammonium cations were chosen as potential guests for the resorcin[4]arene-based host systems in addition to their paramount importance in biological processes. Therefore, Nissinen et al. published the first study on the synthesis of C-methylated pyrogallol[4]arene and its affinity toward small quaternary tri- and tetraalkylammonium cations in solid state, in solution and in gas phase.^{17c} Supplementary to this very detailed study on the complexation of pyrogallo[4]arenes with ammonium cations, we now report the results of our thermodynamic study on the complexation of resorcin[4]arenes 1 and 2 and pyrogallol-[4] arene **3** (Fig. 1) with a series of tetraalkylammonium cations 4-12 (Fig. 2).

2. Results and discussion

2.1. Determination of thermodynamic quantities

A wide variety of experimental methods have been employed for determining the thermodynamic parameters for the complexation reactions of calix[4]arenes and resorcin[4]arenes.²¹ These include calorimetry,²² electronic absorption,^{20,23} steady-state fluores-cence,^{20,24} nuclear magnetic resonance,^{20,25} vapor pressure osmosis,²⁶ atomic force microscopy,²⁷ and mass spectrometry.²⁸ These techniques are frequently employed to determine the equilibrium constants for resorcin[4]arene complexation. The choice of the spectrometric method and the experimental procedure depends on the spectral properties of the used guest and host molecules. However, calorimetry is the only direct method for determining the reaction enthalpy. In view of the long history of calorimetry as an established methodology, it is somewhat surprising that this is not so widely used in the study of the complexation thermodynamics of resorcin[4]arene and its derivatives. This is apparently due to a combination of the need for a relatively large amount of the sample, sophisticated and delicate equipment, and some expertise



Figure 1. Resorcin[4]arenes 1 and 2, pyrogallol[4]arene 3 as host systems for the complexation of quaternary ammonium cations.



Figure 2. Quaternary ammonium cations 4-12 used in this study.

required to obtain reliable results. To perform test reactions it is strongly recommended to ensure the correct and precise microcalorimetric determinations. Nevertheless, the titration microcalorimetry is the most reliable method for determining the thermodynamic parameters at present time.

2.2. Complexation and aggregation properties of pyrogallol[4]arenes

As the method of choice for elucidating the thermodynamic properties of these systems, we chose the isothermal titration calorimetry (ITC), which enables the direct determination of thermodynamic parameters (i.e., complex stability constant (*K*), standard free energy (ΔG^{0}), enthalpy (ΔH^{0}), and entropy changes (ΔS^{0})) in solution. Further, we can determine the composition of formed aggregates from the analysis of the binding isotherm.

In the ITC experiment, we observed essentially the same complexation behavior as Nissinen et al. described in their paper.^{17c} They reported that pyrogallol[4]arenes and the ammonium cations 4 and 7 form dimeric capsules in the crystals formed upon cocrystallization from methanol. Regarding the complexation properties of pyrogallol[4]arenes in the gas phase, they observed that the formation of both monomeric 1:1 and dimeric complexes of the pyrogallol[4]arene species with 4 and 7 is possible. Furthermore, it was concluded that in the case of tetramethylammonium cation, the dimeric aggregate is more abundant than the monomeric 1:1 complex, which is in agreement with our results.^{9f} A similar trend was observed in the NMR experiments, which revealed that the formation of dimeric complex is favored for **4**, rather than **7**. In this relation, it is to note that pyrogallol[4]arene 3 exclusively forms dimeric species in ethanol solution because of their ability to form an unique hydrogen bonding network in the dimer, whilst resorcin[4]arenes 1 and 2 do not show such a phenomenon.

2.3. Complex stability and size complementary

In order to elucidate the relationship between the complex stability constant and the guest size, we first examined the complexation behavior of resorcin[4]arene **1** with the smallest tetraalkylated ammonium cation **4** in ethanol to obtain a small *K* of 350 M^{-1} , suggesting inherently low affinities of resorcin[4]arenes to ammonium ions. We suspected that the origin of the low affinity is the shallow cavity of the resorcin[4]arene and hence introduced a methyl group on each aromatic ring of the upper rim of **1** to give resorcin[4]arene **2**. Indeed, this host gave a larger *K* of 1100 M⁻¹, most probably due to the expanded hydrophobic cavity. To further

increase the complex stability, we employed pyrogallol[4]arene **3** as a better host for **4** in the next experiment with an expectation that the extra hydroxyl group at the upper rim enhances the electrostatic interactions in comparison to the less polarized scaffolds **1** and **2**. For the stoichiometric 1:1 complex formation, we obtained the *K* of 1900 M^{-1} , which is appreciably larger than that for the complex **4**@**2**.

Interestingly, a second molecule of pyrogallol[4]arene 3 is bound to **4@3** to form a 1:2 dimeric complex **4@3**₂ with a much higher *K* of 14,000 M^{-1} . The slightly larger guest **5** also forms both 1:1 and 1:2 guest-host complexes. The K_1 value for the formation of **5@3** is larger by a factor of 3 than that for **4@3**, while the *K*₂ value for the formation of 5@3₂ is sixfold smaller than that for 4@3₂. Upon further enlargement of the guest size by introducing two ethyl groups, only the formation of monomeric 1:1 complexes was observed in ethanol solution with the K of 6900 M^{-1} for **6@3** and 7500 M^{-1} for **7@3**. This result is not consistent with those obtained in gas phase or solid state, but would be reasonable, since in solution the solvation shell of bound ethanol molecules around the guest molecule hinders the formation of a dimeric species. By further expanding the guest size, the *K* value starts to decrease to give 2400 M^{-1} for 8@3, 1500 M^{-1} for 9@3, 850 M^{-1} for 10@3, ca. 50 M^{-1} for 11@3, and eventually extremely weak interactions with 12, which is compatible with that observed in gas phase. To support our conclusions drawn from the thermochemical data and to relate our conclusions to structural features of the host-guest complexes. we examined in the framework of Kohn-Sham DFT model compound with R=Me (instead of R=n-Bu) for the three chosen host-guest complexes 4@3, 7@3, and 12@3. For each of these, we optimized the structure of one preselected conformer equilibrium structures and counterpoise corrected (see Details of calculations) formation energies in the gas phase at T=0 K were calculated. Spacefilling representations of the optimized structure are presented in Figure 3. The counterpoise corrected formation energies in kJ/mol (the zero point energy-corrected values in the parentheses) are -56.4 (-48.4), -40.6 (-33.0), and -3.9 for 4@3, 7@3, and **12@3**, respectively. The gradual decrease in the complex formation energy with increasing steric demand of the ammonium cation is clearly demonstrated. We believe that this trend is caused by the increasing distance between the pyrogallo[4]arene's dipole and the barycentre of the overall positively charged ammonium cation's charge cloud, because the ion-dipole interaction should be the dominating part of the electrostatic interaction between the guest and the host. Dispersive interactions could be disregarded, since RIMP2 and BP86 optimized structures are in close agreement (see Details of calculations). From Figure 3 one can easily deduce that the chosen conformation of 4@3 should also be important in solution at room temperature, i.e., when both molecules are rovibrating because 4 fits nicely into 3. The shown conformation of 7@3 should be less stable in solution at room temperature compared to the situation in vacuum at 0 K, because of the increased steric demands of the rovibrating ethyl groups. The same, with an even



Figure 3. BP86/TZVP optimized structures of the complexes of pyrogallo[4]arene 3 with the ammonium cations 4 (left), 7 (middle), and 12 (right).

decreased population probability compared to **7@3**, should hold true for the shown conformation of **12@3**.

2.4. Complexation thermodynamics

As can be seen from the data in Table 1, the complexation of tetraalkylammonium cations (**4**–**10**) with resorcin[4]arenes (**1**, **2**) and pyrogallol[4]arene (**3**) is driven primarily by the enthalpic gains. However, the enthalpy change (ΔH^0) and the entropy change (ΔS^0) obtained are significantly different between these two types of hosts. Upon complexation with tetramethylammonium ion (**4**), resorcinarenes **1** and **2** give moderate enthalpic gains ($-\Delta H^0$) of 14–16 kJ mol⁻¹ with slightly positive entropic gain ($T\Delta S^0$) of 1–2 kJ mol⁻¹, while pyrogallol[4]arene **3** affords a much larger enthalpic gain of 47 kJ mol⁻¹ and an entropic loss of 28 kJ mol⁻¹. The critical difference in the enthalpic gain may be attributed to the stronger cation– π interactions in pyrogallol[4]arene than in resorcin[4]arene. On the other hand, this enthalpic gain is canceled to some extent by the entropic penalty arising from the more severe structural freezing in the pyrogallol[4]arene complex.

It is to note that the enthalpic gain upon 1:1 complexation with pyrogallol[4]arene **3** is comparable for tetramethylethylammonium (**4**) and trimethylethylammonium (**5**) (45–47 kJ mol⁻¹), but suddenly decreases by introducing another ethyl group to the ammonium ion and reaches a plateau of 31–37 kJ mol⁻¹ for bulkier ammonium ions **6–10**, indicating that the introduction of two ethyl (or bulkier) groups to the guest ammonium critically damages the cation– π interactions. This observation may be taken as a guideline for designing best fitting ammonium guests that only one alkyl group in quaternary ammonium cation can be modified without damaging the strong cation– π interactions.

3. Experimental

3.1. General

The host molecules **1–3** are synthesized according to our recently published procedure.²⁹ The one-pot synthesis yields the most thermodynamically stable C_{4v} -symmetrical bowl-shaped product, which is stabilized by an intramolecular hydrogen bonding network between the aromatic subunits.

The synthesis of the guest molecules **4–12** was carried out by the base assisted exhaustive alkylation. All commercially available starting materials of the best available quality were purchased from Wako Chemicals and used without further purification.

3.2. Microcalorimetric measurements

An isothermal calorimetry instrument, purchased from Microcal Inc., Northampton, MA, was used for all microcalorimetric experiments. The ITC instrument was periodically calibrated electrically using an internal electric heater. The instrument was also calibrated chemically by measuring the enthalpy of neutralization of HCl with NaOH and the ionization enthalpy of TRIS buffer. These standard reactions gave excellent agreement ($\pm 1-2\%$) with the literature data.³⁰

Titration microcalorimetry allowed us to determine simultaneously the enthalpy value and equilibrium constant from a single titration curve. Each microcalorimetric titration experiment consisted of 20–40 successive injections: 20 successive injections were performed when 1:1 complexation (ΔH_1 and K_1) was expected, with 40 successive injections performed when a stepwise 2:1 complexation was expected (ΔH_1 , K_1 , ΔH_2 , and K_2).³⁰ In both cases, a constant volume (5 µL/injection) of pyrogallol[4]arene solution was injected into the reaction cell (1.36 mL) charged with a guest solution in the same organic solvent; initial concentrations of guest

Table 1

Complex stability constant (K), standard free energy (ΔG°), enthalpy (ΔH°), and entropy changes ($T\Delta S^{\circ}$) for the complexation of selected quaternary ammonium cations^a with resorcin[4]arenes and pyrogallol[4]arenes in ethanolic solution at 298.15 K

Complexation reaction	$K^{\rm b}/{\rm M}^{-1}$	$\Delta G^{ m o}/{ m kJ}{ m mol}^{-1}$	$\Delta H^{\rm o}/{ m kJ}{ m mol}^{-1}$	$T\Delta S^{\rm o}/{\rm kJ}~{ m mol}^{-1}$
$1+(CH_3)_4N^+Cl^-(4)=[1\cdot(CH_3)_4N^+]Cl^-](4@1)$	350±70	$-14.5{\pm}0.6$	$-14{\pm}1$	0.5±1
$2 + (CH_3)_4 N^+ Cl^- (4) = [2 \cdot (CH_3)_4 N^+] Cl^- (4@2)$	$1100 {\pm} 100$	$-17.4{\pm}0.2$	$-15.5{\pm}0.3$	1.9±0.4
$3 + (CH_3)_4 N^+ Cl^- (4) = [3 \cdot (CH_3)_4 N^+] Cl^- (4@3)$	1900±400	$-18.7{\pm}0.6$	$-47{\pm}4$	-28 ± 4
$[3 \cdot (CH_3)_4 N^+]Cl^- + 3 = [3_2 \cdot (CH_3)_4 N^+]Cl^- (4@3_2)$	14,000±1000 (K ₂)	$-23.7{\pm}0.3$	$-29{\pm}4$	$-5{\pm}4$
$3+(CH_3)_3(C_2H_5)N^+Cl^-(5)=[3\cdot(CH_3)_3(C_2H_5)N^+]Cl^-(5@3)$	5300±1000	-21.3 ± 0.6	-45 ± 4	-24 ± 4
$[3 \cdot (CH_3)_3(C_2H_5)N^+]Cl^- + 3 = [3_2 \cdot (CH_3)_3(C_2H_5)N^+]Cl^- (5@3_2)$	2100±500 (K ₂)	$-19.0{\pm}0.7$	$-48{\pm}4$	$-29{\pm}4$
$3 + (CH_3)_2(C_2H_5)_2N^+Br^-$ (6)=[$3 \cdot (CH_3)_2(C_2H_5)_2N^+$]Br ⁻ (6@3)	$6900 {\pm} 400$	$-21.9{\pm}0.2$	$-35.3{\pm}0.5$	$-13.4{\pm}0.5$
$3+(CH_3)(C_2H_5)_3N^+Cl^-(7)=[3\cdot(CH_3)(C_2H_5)_3N^+]Cl^-(7@3)$	7500±300	-22.1 ± 0.1	$-35.3{\pm}0.4$	$-13.2{\pm}0.4$
$3 + (C_2H_5)_4N^+Cl^- (8) = [3 \cdot (C_2H_5)_4N^+]Cl^- (8@3)$	2400±100	$-19.3{\pm}0.1$	-37.3 ± 0.4	$-18.0{\pm}0.4$
$3 + (C_2H_5)_2(C_3H_7)_2N^+Br^-$ ($9 = [3 \cdot (C_2H_5)_2(C_3H_7)_2N^+]Br^-$ ($9@3$)	1500±100	$-18.1{\pm}0.2$	$-30.7{\pm}0.4$	$-12.6{\pm}0.5$
$3 + (C_2H_5)(C_3H_7)_3N^+Br^-$ (10)= $[3 \cdot (C_2H_5)(C_3H_7)_3N^+]Br$ (10@3)	850±100	$-16.7{\pm}0.3$	$-34.6{\pm}0.6$	$-17.9{\pm}0.7$
$3 + (C_3H_7)_4N^+Cl^-(11) = [3 \cdot (C_3H_7)_4N^+]Cl^-(11@3)$	≈50 (±150)		≈-30 (±50)	
$3 + (C, H_{0}) \cdot N^{+} C^{-} (12) - [3 \cdot (C, H_{0}) \cdot N^{+}] C^{-} (12)$	c			

^a In ITC experiments a solution of the quaternary ammonium salt in ethanol (0.2 mM), placed in the reaction cell of the microcalorimeter, was titrated with a solution of pyrogallo[4]arene (4 mM) in ethanol. Typical ITC experiment consists of 25–50 injections (10 μL each) of the pyrogallo[4]arene solution into the cell.

^b Stability constant for 1:1 complex, unless noted otherwise; K_2 for 1:2 guest-host complexation.

^c Very low affinity; it cannot be determined under the experimental conditions employed.

and pyrogallol[4]arenes in each run are indicated in Table 1. The heat of dilution when the pyrogallol[4]arene solution was added to the blank solution without a guest was determined in each run using the same number of injections and concentration of pyrogallol[4]arene as used in the titration experiments. The dilution enthalpies determined in these control experiments were subtracted from the enthalpies measured in the titration experiments. It should be emphasized that the enthalpies of dilution obtained in all runs were of the same order of magnitude as the enthalpies of dilution of simple electrolytes such as NaCl at the same concentration.

The ORIGIN software (Microcal Inc.), which was used to calculate the equilibrium constant and standard molar enthalpy of reaction from the titration curve in the cases of simple 1:1 and stepwise 2:1 complexations, gave a standard deviation based on the scatter of the data points in a single titration curve. The accuracy of the calculated thermodynamic quantities for 1:1 complexations was checked by performing several independent titration runs. The uncertainties in the observed thermodynamic quantities for 1:1 complexation (Table 1) are two standard deviations of the mean value unless otherwise stated. Detailed descriptions of each step of 1:1 and 2:1 complexation processes are given in Table 1.

3.3. Details of calculations

The Kohn–Sham DFT calculations reported herein were performed with the Gaussian 03^{31} programme, using the BP86 density functional (containing the B88³² gradient correction for exchange, the VWN-(III)³³ correlation functional and the P86³⁴ gradient correction for correlation), combined with the TZVP³⁵ basis set (triple zeta quality, polarization functions on all centers). No significant differences between the optimized structures of **3** (with R=H) on the BP86/SVP and RIMP2/SVP hypersurfaces were found, indicating an acceptable accuracy of the chosen density functional.

In the structure optimization (normal mode analyses) a pruned integration grid of 99 (75) radial shells with 590 (302) angular points per shell for all atoms was used. The threshold for maximum force (maximum displacement in internal coordinates) was 4.5×10^{-4} a.u. $(1.8 \times 10^{-3}$ a.u.), resulting in equilibrium structures with energies consistent to 10^{-7} a.u., the same accuracy as for the electronic energy. In the structure optimization and in the normal mode analyses the charge density fitting approximation for Coulomb integrals³⁶ with automatically generated auxiliary basis sets was used.

For **3**, **4**, **7**, and **12** the normal mode analysis was performed on the BP86/TZVP hypersurfaces, but those for **4@3** and **7@3** were performed

on the BP86/SVP hypersurfaces (at the stationary points on these hypersurfaces), because of the huge number of basis functions. For **12@3** even on the BP86/SVP hypersurface no normal mode analysis could be achieved due to unsolvable technical problems. All other structures reported herein (and in the ESI) were confirmed to be true minima by the normal mode analyses.

Because the calculation of electronic energies for weakly interacting complexes (such as those examined here) within the supramolecular approach (as in this work) is affected by the basis set superposition error (BSSE)³⁷ we performed counterpoise corrections³⁸ to get BSSE-free formation energies. In the needed single point calculations we did not use the charge density fitting and took care of the integration grid points on the ghost atoms. The reaction energies given in the text are the counterpoise corrected formation energies (the zero point energy-corrected values are given in the parentheses).

Cartesian coordinates and electronic energies are available in Supplementary data.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (SFB 613) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.066.

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