Calorimetric Investigation of Nano-Basket's Binding

BAHRAM MOKHTARI and KOBRA POURABDOLLAH*

Razi Chemistry Research Center, Shahreza Branch, Islamic Azad University, Shahreza, Iran

*Corresponding author: Fax: +98 321 3213103; Tel: +98 912 5143351; E-mail: pourabdollah@iaush.ac.ir

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Eleven scaffolds of di-ionizable calix[4]arene conformers bearing two pendant groups of N-phenyl-sulfonyl carboxamides were synthesized and examined using isothermal titration calorimetry. The binding mechanisms of those conformers towards alkali metal cations were evaluated and two main interactions were assessed including cation- π interaction between alkali metal cation and the aromatic unit of conformer as well as the strong binding ion-dipole interaction between nitrogen atoms in the pendant groups and alkali cation. The isothermal titration calorimetry data revealed that the bindings of cone and partial-cone conformers towards alkali metal cations exhibited one-step mechanism, while both 1,2-alternate and 1,3-alternate conformers bound the alkali metal cations in a two-steps mechanism.

Key Words: Nano-basket, Calixarene, Calorimetry, Binding.

INTRODUCTION

Isothermal titration calorimetry (ITC) as an analytical tool directly determines the binding heat of two species¹ and are used to characterize the binding thermodynamics in the chemical and the biological systems such as complexation of isoleucine by phosphorylated calix[4]arene², solvation changes in cyclodextrin complexes³, complexation of glyco- and tauro-conjugated bile salts with modified β -cyclodextrins⁴, association of surfactants with β -cyclodextrin⁵ and proteins⁶. The other hosts:guests interactions of cations and anions⁷ using isothermal titration calorimetry has been reported in the literatures. Not only isothermal titration calorimetry determines the binding stoichiometry and affinity as well as the binding entropy and enthalpy, but also it used to characterize the self-association of some polymers⁸ and the binding constant of water-soluble calix[4,6]arene sulfonates towards acetylcholine⁹. Mun *et al.*¹⁰ used isothermal titration calorimetry to investigate interactions between cycloamylose and three surfactants with C₁₂ non-polar tail groups and charged or non-charged head-groups.

Nano-baskets of calixarenes have been subjected to extensive researches in development of transporters, extractants, stationary phases, electrode ionophores and optical sensors over the past decades¹¹⁻²⁸. Therefore, the aim of this study is to highlight the role of isothermal titration calorimetry in calixarene-base researches, in which the interactions of calixarenic hosts and cationic guests are assessed. Moreover, the binding constants of di-ionizable *p*-tert-butylcalix[4]arene conformers towards dissolved alkali metal cations were

determined. Fig. 1 shows the hierarchical structures of complexes were studied. As depicted in Fig. 1, eleven scaffolds were used to assess the binding constants of isoconformations using isothermal titration calorimetry experiments.

EXPERIMENTAL

Synthesis procedure: Methylation of *p*-tert-butylcalix[4]arenes (**1**) with 1 equivalent of K₂CO₃ in MeCN and methyl tosylate at reflux for 40 h yielded 88 % dimethoxycalix[4]arene (**2**). Initially, more than 2 equivalents of BrCH₂CO₂Et was added to the reaction mixture, then another one equivalent was added after 4 h. The reaction was terminated after another 3 h. Owing to the low electrophilic reactivities of BrCH₂CO₂Et and ICH₂CO₂Et, highly polar DMF was used as the solvent, which greatly facilitate the nucleophilic reaction comparing to MeCN. Diester **3** was obtained in 80 % yield. To avoid trapping of metal cations, diester **3** was hydrolyzed with tetramethylammonium hydroxide in aqueous THF at reflux to provide 95 % yields of calix[4]arene dicarboxylic acid (**4**). This derivative was refluxed with oxalyl chloride in benzene to give the corresponding di(acid chloride), which were used without further purification for reactions with the sodium salt form of appropriate sulfonamide to give **6** in 80 % yield. Other isoconformers were synthesized using the first scaffold of 1,2-alternate and partial-cone. Fig. 2 illustrated the synthesis procedure of calix[4]arenes bearing two N-(X) sulfonyl carboxamides pendant groups.

All of the experiments carried out using nine conformations of di-ionizable *p*-tert-calix[4]arene di-[N-(phenyl)-

sulfonyl carboxamide]. According to the synthesis procedure that is shown in Fig. 2, two cone conformers (**7** and **8**), two 1,3-alternate conformers (**9** and **10**), three 1,2-alternate conformers (**11-13**) and four partial-cone conformers (**14-17**) were synthesized to extract alkali metals. The *cis/trans* symbols refer to the direction of two di-ionizable moieties and the *ortho/para*

para depict the relative situation of two di-ionizable moieties. Fig. 3 shows the chemical structure of those nine conformations **7-17** (R group is defined as: $-\text{OCH}_2\text{CONHSO}_2\text{Ph}$). Fig. 3 shows the chemical structure of selected di-ionizable calix[4]arene conformers.

Fig. 1. Hierarchical structure of complexes were investigated using isothermal titration calorimetry experiments

Fig. 2. Synthesis procedure of calix[4]arenes with elongated N-(X)sulfonyl carboxamides

Fig. 3. Structures of di-ionizable *p*-*tert*-butylcalix[4]arene conformers 7-17

Calorimetric setup and procedure: The micro-calorimetry system (MCS) was manufactured by MicroCal Inc. (Northampton, MA) including an isothermal titration calorimetry unit. The isothermal titration calorimetry unit was combined with an external water bath (Isothemp Model 3016 D) and the hosts: guests interactions were recorded using the MCS Observer software. Using a basic solvent, the proton-ionizable calix[4]-arene conformers were de-protonated in methanol. 5 mM tetrabutylammonium hydroxide in dried methanol was used as the solvent for both the alkali metal chloride solutions and the di-ionized calix[4]arene conformers. Solutions of calix[4]arene conformers and alkali metal chloride were prepared in a concentration range of 1 mM and 8-20 mM, respectively. A 2.5 mL glass syringe with a long needle was

used to inject the sample and the reference solutions into the isothermal titration calorimetry cells. The reference cell was filled with *ca.* 1.7 mL of methanol and the calixarenic solution was injected into the sample cell after rinsing it. The solution of alkali metals was loaded into a 250 μ L injection syringe through a holder assembly.

RESULTS AND DISCUSSION

Thermodynamics of conformer's binding: Solvent extraction results showed that sodium, potassium and rubidium cations were selectively extracted by the cone di-ionizable *p*-*tert*-butylcalix[4]arene derivatives (7, 8), conformers (9-11) and 1,2-alternate conformers (12, 13), respectively. The extractions using partial-cone conformers (14, 15) were un-

selective, while derivatives (**16**, **17**) showed a high selectivity towards potassium. For conformers (**16**, **17**) no extraction tendency was found for cesium and rubidium cations. However, for all conformers one or two-step bindings for sodium cations were obtained as shown in Table-1. For ligands with two-step bindings at the same binding site or two binding sites, the first binding is often stronger than the second by at least two orders of magnitude in the K values. The exceptions are symmetric conformers (**10**, **12**, **13**), in which the K values are same. The comparison of $\log K$ for the first binding is more significant.

TABLE-1
STOICHIOMETRIES AND BINDING CONSTANTS FOR
INTERACTION OF SODIUM WITH CONFORMERS 7-17

Conformers	Binding stages	n_1	$\log K_1$	n_2	$\log K_2$
7	1	0.58	6.36 ± 0.08	-	-
8	1	0.62	6.54 ± 0.06	-	-
9	2	0.92	7.87 ± 0.08	0.72	4.64 ± 0.02
10	2	0.80	7.70 ± 0.10	0.80	7.68 ± 0.08
11	2	0.42	4.31 ± 0.02	0.53	3.48 ± 0.05
12	2	0.50	3.12 ± 0.04	0.50	3.13 ± 0.04
13	2	0.50	3.11 ± 0.03	0.50	3.13 ± 0.03
14	1	0.26	1.11 ± 0.02	-	-
15	1	0.24	1.00 ± 0.01	-	-
16	1	0.12	0.64 ± 0.01	-	-
17	1	0.18	0.68 ± 0.01	-	-

Calix[4]arene derivatives (**7**, **8**) in cone conformation showed clear one-step binding. Derivatives (**9**-**13**) depicted two-step binding towards with $\log K$ differences of **1** to **3** between the first and second binding constants. Conformers (**14**-**17**) in partial-cone conformer showed one-site binding. The raw data from isothermal titration calorimetry experiments using conformers (**8**-**11**) is showed in Fig. 4, respectively.

Influence of the conformation variation: Conformational variation had an important influence on cation binding affinity for conformers (**7**-**17**). As shown in Table-1, the $\log K$ values for sodium binding decreased from the 1,2-alternate conformation to the partial-cone conformers. In this case, the isothermal titration calorimetry results were consistent with the solvent extraction results, which are illustrated in Fig. 5. In the solvent extraction results, the 2-alternate conformers (**14**, **15**) did not show outstanding extraction selectivity.

Sodium cations could have an ion-dipole interaction with the nitrogen atoms on the lower rim of cone conformers **7**, **8**. However, the binding is not contributed to the π interaction between alkali metal cation and the aromatic units in conformers due to opposite situation of them. The bindings of **7**, **8** with alkali metal cations both exhibited one-step mechanism.

The interaction of alkali metal cations with two nitrogen donors of the N-phenyl-sulfonyl carboxamides substituents is not favourable due to the steric repulsion. The proposed binding sites may be contributed by ion-dipole interaction of one alkali metal cation with one nitrogen donor of the N-phenyl-sulfonyl carboxamides substituent. According to Table-1, the conformers **7**, **8** exhibited one-step binding and slightly weaker binding affinity towards sodium cations than **9**, **10**. Fig. 6 (C1) depicted a proposed model for binding of cone calix[4]arene conformer **7** towards sodium cations. In similar way, the conformer **8** binds to the sodium cations.

The bindings of **9**-**13** with alkali metal cations exhibited two-steps mechanisms. In the first step, one metal cation is bonded with one or two nitrogen atoms at the lower rim. The second step is proposed when another metal cation is bonded to the other side of calixarene scaffold. As show in Table-1, in conformer **9** the first step of binding is stronger than the second with 3.2 orders of magnitude difference in K values towards sodium cations. On the other hand, owing to the steric symmetry of conformers **10**, **12**, **13** there were not any significant differences in the K values towards sodium cations. Fig. 6 (C2 and C3) illustrated the schematic of the first step as well as the second step for 1,3 alternate conformer **10** (also **9**).

According to Table-1, in conformers **11**-**13** there are two steps for binding to sodium cations, in which both of them are presented schematically in Fig. 6 (C4 and C5). Among three conformers in form of 1,2 alternate, derivatives **12**, **13** are symmetric and there are not any difference in K values towards sodium cations, as presented in Table-1. While in conformer **11**, the first step binding is stronger than the second step because of a two-way interaction between cation and the calixarene scaffold including the cation- π interaction between alkali metal cation and the inverted aromatic units in conformers as well as the ion-dipole interaction with the nitrogen atoms on the lower rim. Fig. 6 (C4 and C5) shows the schematic of the first and the second steps for 1,2 alternate conformer **11** (also conformers **12**, **13**).

Base upon the data in Table-1, in conformers **14**-**17** an one-step binding to sodium cations was distinguished. An ion-dipole interaction between sodium and nitrogen atom(s) as well as a weak π interaction between cation and the inverted aromatic unit in conformers is responsible for complex formation. A second stage binding towards sodium cations was not distinguished and it shows that the steric affect in the upper rim of partial-cone conformers **14**-**17** constraints the binding mechanism to one-step. Such steric affect was related to three *t*-butyl moieties on the upper rim. Fig. 6 (C6) depicted the binding schematic for conformer **16** as well as **14**, **15**, **17**.

Fig. 4. Raw data from isothermal titration calorimetry titrations present one-step binding for **8**-**11** scaffolds towards Rb^+

Fig. 5. Solvent extraction results using conformers 7-17

Conclusion

The isothermal titration calorimetry characterized the binding thermodynamics of di-ionizable calix[4]arene conformers bearing two pendant groups of N-phenyl-sulfonyl carboxamides towards alkali metal cations. Base upon the

isothermal titration calorimetry data, the binding mechanisms in di-ionizable calix[4]arene conformers were evaluated, in which they were contributed by the cation- π interaction between alkali metal cation and the aromatic unit in the conformer scaffolds as well as the strong binding ion-dipole

Fig. 6. Proposed binding mechanism of cone **7** (and **8**), 1,3-alternate **10** (and **9**), 1,2-alternate **11** (and **12,13**) and partial-cone **16** (and **14, 15, 17**) conformers towards Na^+

interactions between nitrogen atoms in the pendant groups of N-phenyl-sulfonyl carboxamides and alkali metal cation. The bindings of cone and partial-cone conformers towards alkali metal cations exhibited one-step mechanism, while it was two-step mechanism when 1,2 alternate and 1,3-alternate conformers were used.

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