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Synthesis of a Water-Soluble Carboxylatobiphen[4]arene and Its Selective Complexation toward Acetylcholine

Junwei Ma,[†] Qingbin Meng,[*,‡] Xiaoshi Hu,[§] Bin Li,[†,‡] Suxiang Ma,[†] Bingwen Hu,[§] Jian Li,[†] Xueshun Jia,[*,†,∥] and Chunju Li[*,†]

[†]Department of Chemistry, Center for Supramolecular and Catalytic Chemistry, Shanghai University, Shanghai 200444, P. R. China

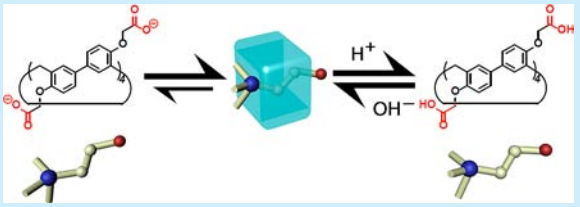
[‡]State Key Laboratory of Toxicology and Medical Countermeasures, Beijing Institute of Pharmacology and Toxicology, Beijing 100850, P. R. China

[§]School of Physics and Materials Science, Shanghai Key Laboratory of Magnetic Resonance, East China Normal University, Shanghai 200062, P. R. China

[∥]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

Supporting Information

ABSTRACT: The first water-soluble biphen[4]arene containing eight carboxylato moieties (carboxylatobiphen[4]arene, CBP4) has been synthesized. Selective molecular recognition of acetylcholine (**ACh**) against choline (**Ch**) and betaine (**Bt**) and pH-responsive host–guest complexation in aqueous media are described.



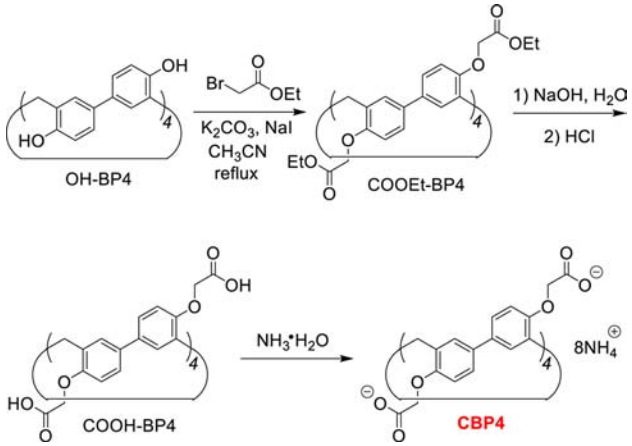
Macrocyclic receptors are important toolboxes in supramolecular chemistry. The introduction of new-generation macrocycles with novel topological structures and interesting complexation properties could bring new vitality into this field. The popular and classic hosts include crown ethers, cryptands, cyclodextrins, calixarenes, calixpyrroles, cucurbiturils, and pillararenes; they have totally different geometries and cavity properties.[1−4] These macrocycles have attracted considerable interest because of their wide applications in porous materials, sensors, drug/gene delivery systems, responsive supramolecular polymers, etc.[5,6]

Recently, our group brought a new class of macrocycles, biphen[*n*]arenes (*n* = 3, 4), to the supramolecular world.[7,8] The geometries of biphenarenes, a distorted triangular-prism structure for biphen[3]arene and a cuboid-like structure for biphen[4]arene,[7] are absolutely different from those of other macrocyclic arenes such as calixarenes, resorcinarenes, and pillararenes. Especially, biphen[4]arene can be viewed as a π-electron-rich molecular box and exhibits efficient binding toward a series of cationic and neutral guests.

In this work, we report the synthesis of a negatively charged biphen[4]arene bearing multiple carboxylato moieties (CBP4, Scheme 1) and its host–guest properties in water. Molecular recognition of synthetic receptors in aqueous media is a topic of great interest from not only a supramolecular chemistry but also biological/environmental/analytical application points of view.[9−11] The guests used here include the biological molecules choline (**Ch**), acetylcholine (**ACh**), and betaine (**Bt**), the medicinal molecule 1-adamantanamine hydrochloride (**AdA**), and the herbicides paraquat (**PQ**) and diquat (**DQ**). The water-soluble CBP4 is demonstrated to sequentially selectively complex **ACh** → **Ch** → **Bt**. The pH-controllable assembly/disassembly behavior was also studied.

Scheme 1 shows the synthetic route to water-soluble CBP4. Perhydroxylated biphen[4]arene (OH-BP4) was conveniently prepared from EtBP4. Ethoxycarbonylmethoxy-substituted biphen[4]arene (COOEt-BP4) was first obtained from OH-BP4 and excess ethyl bromoacetate under basic conditions (K_2CO_3) in a yield of 82%. Carboxylic acid-substituted biphen[4]arene (COOH-BP4) was synthesized by hydrolysis

Scheme 1. Synthesis of the CBP4 Host



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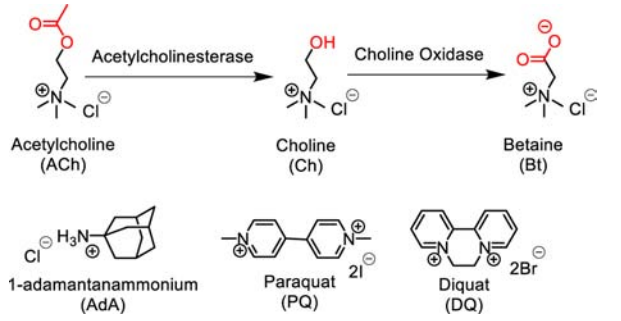
of COOEt-BP4 in NaOH solution followed by acidification with aqueous HCl (92%). COOH-BP4 was insoluble in water. Treatment of COOH-BP4 with aqueous ammonia solution afforded water-soluble biphen[4]arene (CBP4) quantitatively.

The binding between CBP4 and the cationic guests shown in Scheme 2 was then tested. From Figure 1B, in the presence of

Scheme 2. Structures of Cationic Guests



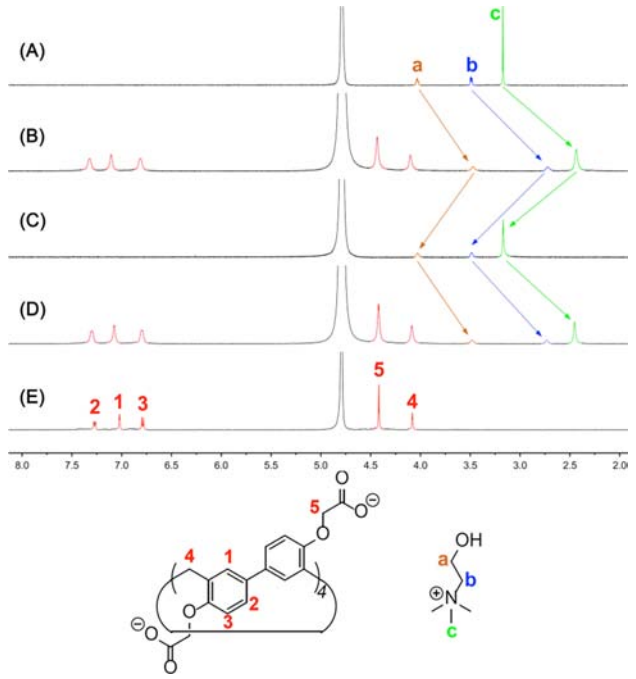


Figure 1. ^{1}H NMR spectra (500 MHz, 296 K) of (A) **Ch** (1.1 mM), (B) CBP4 (1.0 mM) + **Ch** (1.1 mM), (C) after addition of 2.0 μL of aqueous DCl solution (35 wt %) to (B), (D) after addition of 2.2 μL of aqueous NaOD solution (30 wt %) to (C), and (E) CBP4 (1.1 mM) in D_2O.

CBP4, all of the protons of guest **Ch** exhibited remarkable upfield shifts ($\Delta\delta$ = −0.56, − 0.77, and −0.73 ppm for a, b, and c). These results suggest that the guest is bound inside CBP4's cavity and experiences inclusion-induced shielding effects. In addition, the host shows similar binding behaviors toward the cationic guests **ACh**, **AdA**, **PQ**, and **DQ**; the peaks of the guests appear significantly shifted upfield (Figures S7 and S9). For **Bt**, no obvious NMR changes were observed (Figure S8), suggesting that **Bt** containing both positive ammonium and negative carboxylate groups cannot interact with the host or at least has very weak affinity. The electrostatic interactions[12] between CBP4's negative carboxylate groups and cationic guests play a dominant role in the present host−guest system.

The complexation of two reference hosts, CBP monomer and smaller biphen[3]arene CBP3 (Scheme S1) were then examined. The proton signals of **Ch** and **ACh** do not shift in the presence of 4 equiv of CBP and show very small changes ($\Delta\delta$ < 0.1 ppm) in the presence of CBP3 (Figures S10−S13).[13] This is reasonable since CBP is not cyclic and biphen[3]arene (having a distorted triangular-prism structure) does not have an effective cavity.[7] From the ^{1}H NMR results, the resonance signals of **Ch** and **Ach** show much more remarkable changes upon addition of CBP4 (Figures 1, S7, and S10−S13) than those upon addition of CBP or CBP3, suggesting that CBP4 and the guests do not form simple ion pairs but indeed form inclusion complexes.

2D NOESY results further confirmed the formation of an inclusion complex (Figure S15). The spectrum of a mixture of **ACh** and CBP4 exhibited unequivocal correlation peaks between the guest's protons $H_{a,c,d}$ and the host's aromatic protons H_1, which are denoted as A, B, and C. In addition, there were correlations between $H_{a,d}$ and the host's H_2 protons (NOE cross-peaks C and D). However, no appreciable cross-peaks between H_{a-d} and CBP4's methylene protons $H_{4,5}$ were found; this is reasonable since H_4 and H_5 are toward the outside of the biphen[4]arene cavity.[7] These observations indicate that **ACh** is engulfed by CBP4 to form a host−guest complex.

In order to investigate quantitatively the binding thermodynamics of the host−guest complexation of CBP4 with these guests, isothermal titration microcalorimetry (ITC) experiments were performed (Figure 2) to yield both the association constants (K_a) and the thermodynamic parameters (enthalpy and entropy changes, $\Delta H°$ and $\Delta S°$). These cationic guests, except for **Bt**, form stable complexes with CBP4 in water (Table 1). In particular, CBP4 exhibited sequential binding selectivity for **ACh** → **Ch** → **Bt**, with the same sequence as the

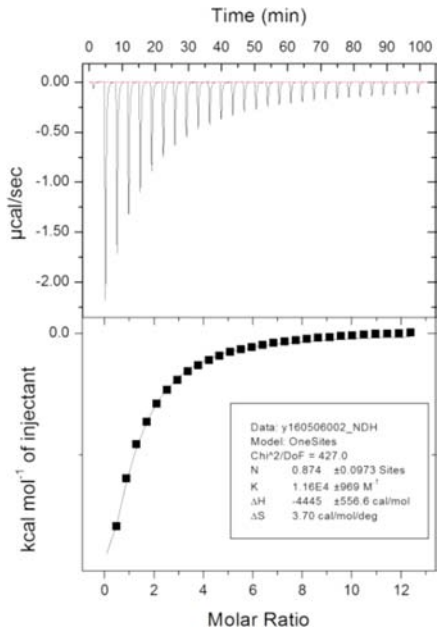


Figure 2. ITC experiment for CBP4 with **ACh**. Top: Raw ITC data for 29 sequential injections of the guest solution into a CBP4 solution. Bottom: Net reaction heat obtained from the integration of the calorimetric traces. For experimental details, see the Supporting Information.

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Table 1. Association Constants (K_a) and Thermodynamic Parameters (in kJ mol^{-1}) for the Guests with CBP4 in H_2O at 25 °C

guest[a]	n[b]	K_a (M^{-1})	$\Delta G°$	$\Delta H°$	$T\Delta S°$
Ch	1.14	(3.51 ± 0.42) × 10^3	−20.2 ± 0.3	−3.69	16.6
ACh	0.87	(1.16 ± 0.10) × 10^4	−23.2 ± 0.2	−18.6	4.61
Bt	–[c]				
AdA	1.02	(2.46 ± 0.21) × 10^4	−25.1 ± 0.2	−6.26	18.8
PQ	0.94	(2.52 ± 0.23) × 10^4	−25.1 ± 0.2	−52.3	−26.9
DQ	1.23	(2.60 ± 0.16) × 10^4	−25.2 ± 0.2	−31.6	−6.37

[a][guest] = 1.91−11.0 mM, [host] = 0.10 mM. [b]The value of n is the binding stoichiometry. The values were between 0.87 and 1.23, indicating 1:1 complexation. [c]ITC titrations showed no detectable heat effect; no obvious binding was found in the ^{1}H NMR experiments (Figure S8).

enzymatic reaction (Scheme 2). The K_a value for **ACh** is 3.3 times larger than that for **Ch**, while no obvious complexation was found for **Bt** (Figure S8). It should be pointed out that a widely used water-soluble calixarene, *p*-sulfonatocalix[4]arene, does not exhibit guest selectivity for **ACh** versus **Ch**; the association constants for these guests are almost the same.[14] The selective binding of the neuromodulator **ACh** is interesting since it plays important roles in cognitive and cerebral functions. Furthermore, the sequential selectivity for **ACh** → **Ch** → **Bt** by CBP4 could find potential applications in monitoring sequential enzymatic reactions using Nau's supramolecular tandem assay principle.[14a,15]

For the herbicides **PQ** and **DQ** as well as the medicinal molecule **AdA**, the binding affinities are as high, on the order of 10^4 M^{-1}, further indicating the excellent host−guest properties of this anionic box-type receptor. Thermodynamically, the interaction of the ammonium guests **Ch**, **ACh**, and **AdA** is synergistically enabled by both the enthalpy and entropy changes, while those for pyridinium-based **PQ** and **DQ** are entirely enthalpy-driven with unfavorable entropy changes.

As mentioned above, although the anionic CBP4 has good water solubility, protonated COOH-BP4 is neutral and not soluble in water. These features led us to consider that the resulting complexes between CBP4 and the cationic guests could be reversibly switched off (and back on) by protonation (and deprotonation) of the carboxylato groups on the host's cavity portals (Figure S14).

^{1}H NMR experiments were examined to study the pH-controllable disassembly/reassembly process. As mentioned above, **Ch** and CBP4 form an inclusion complex according to the NMR results (Figure 1B). Upon addition of aqueous DCl solution to the mixture of CBP4 and **Ch**, a white precipitate appeared and no biphen[4]arene NMR signals were observed (Figure 1C). Apparently, the precipitate represents the carboxylic acid-substituted biphen[4]arene, COOH-BP4 (Scheme 1). Meanwhile, the resonances of the guest **Ch** moved back to the original positions as for the isolated guest (Figure 1A,C). These observations indicated the disassembly process unambiguously.

When NaOD was added, the precipitate dissolved, and the host and guest signals (Figure 1D) were similar to those for the original host−guest mixture (Figure 1B). It is reasonable that the base leads to the recovery of water-soluble CBP4 from the insoluble COOH-BP4. Therefore, the ^{1}H NMR results definitely confirmed the ability to perform disassembly/reassembly of the **Ch**⊂CBP4 complex by pH control.

In conclusion, a water-soluble biphen[4]arene has been synthesized for the first time. This negatively charged macrocycle displays strong binding affinities toward selected cationic guests to form inclusion complexes. In particular, the CBP4 host exhibits sequential selectivity for **ACh** → **Ch** → **Bt**. Furthermore, the host−guest complexation can be reversibly controlled by adjusting the pH. Considering its facile preparation, moderate cavity size, and excellent host−guest properties, this water-soluble biphen[4]arene could find broad applications in, for example, chemosensors, drug delivery, supramolecular amphiphiles, etc.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03005.

Synthesis, characterizations, ^{1}H and ^{13}C NMR spectra, and UV−vis and ITC experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nankaimqb@sina.com.
*E-mail: xsjia@mail.shu.edu.cn.
*E-mail: cjli@shu.edu.cn.

Notes

The authors declare no competing financial interest.

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(13) We performed ITC experiments to determine the thermodynamic parameters for CBP3 and **Ch**/**ACh**. However, the reaction heat changes were so small that the association constants could not be accurately determined. In accordance with the NMR results, ITC also indicates weak interactions between the smaller CBP3 and **Ch**/**ACh**.

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