How to cite: Angew. Chem. Int. Ed. 2023, e202318261
doi.org/10.1002/anie.202318261

Supramolecular Chemistry

Tuning CH Hydrogen Bond-Based Receptors toward Picomolar Anion Affinity via the Inductive Effect of Distant Substituents

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Abstract: Inspired by nature, artificial hydrogen bond-based anion receptors have been developed to achieve high anion selectivity; however, their binding affinity is usually low. The potency of these receptors is usually increased by the introduction of aryl substituents, which withdraw electrons from their binding site through the resonance effect. Here, we show that the polarization of the C(sp^3)-H binding site of bambusuril receptors, and thus their potency to bind anions, can be modulated by the inductive effect. The presence of electron-withdrawing groups on benzyl substituents of bambusurils significantly increases their binding affinities to halides, resulting in the strongest iodide receptor reported to date with an association constant greater than 10^{13} M^{-1} in acetonitrile. A Hammett plot showed that while the bambusuril affinity toward halides linearly increases with the electron-withdrawing power of their substituents, their binding selectivity remains essentially unchanged.

Anion receptors with a high affinity and selectivity are needed in many areas, including ion-selective electrodes,[1–3] gold mining,[4–6] or nuclear waste remediation.[7–9] Therefore, there is a general need to design highly potent receptors to improve or expand their applications. Increasing the anion binding affinity of acyclic neutral receptors, including ureas, thioureas, and squaramides, is usually achieved by connecting their binding sites directly with aromatic systems bearing electron-withdrawing groups. Therefore, the enhanced binding potency is the result of π-conjugation between the binding site and aromatic systems.[10–17] The most potent hydrogen bond-based anion receptors are highly preorganized structures capable of multiple binding interactions, which goes hand in hand with macrocyclic structures,[18–23] cages,[24–26] and foldamers.[27,28] Whereas the modification of acyclic receptors by a variety of substituents can be done relatively easily, this presents a significant challenge in the case of macrocyclic structures.

Compared to macrocycles utilizing N–H and C(sp^2)-H binding motives, bambus[6]urils[29] (bambusurils in short, Figure 1) are a rare example of receptors which bind anions using C(sp^3)-H hydrogen bonding interactions.[26,30] Bambusurils feature a deep cavity defined by six alternating glycoluril units. The anion is usually bound in the center of the electropositive cavity stabilized by 12 weak C–H···anion interactions. The macrocycle portals are decorated by 12 substituents, which can be varied on demand.[31] Recent studies showed that the binding affinity of bambusurils to anions in water[32] and acetonitrile[33] can be influenced by the attachment of different substituents to the macrocycle

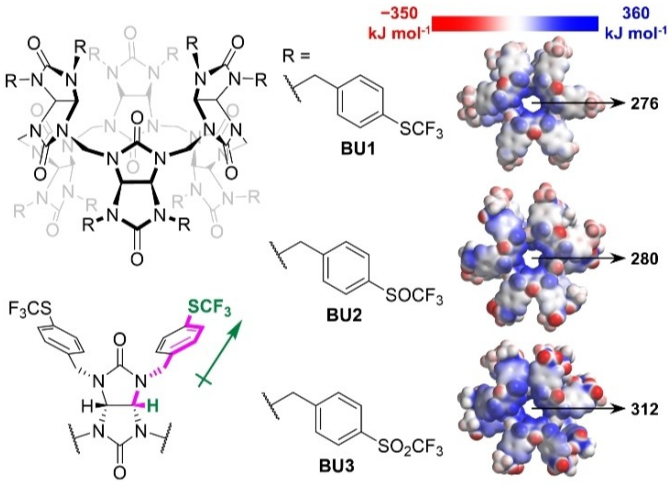

Figure 1. Structures of the bambusurils **BU1**-**BU3** used in this work. The bonds through which the C–H bond is polarized by the electron-withdrawing groups are visualized on a single glycoluril unit in magenta colour. The calculated electrostatic potential maps show the electron deficient cavities (blue color) inside the macrocycles and the potential values inside the BU cavities are indicated. These calculations were performed in Spartan'18 1.4.4 after the structures were optimized with the semi-empirical PM6 method in vacuum.

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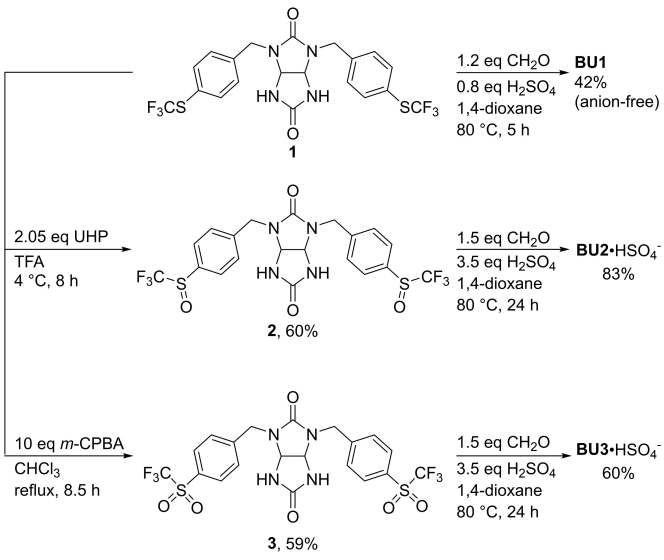
portals. In this work, we demonstrate that the binding potency of bambusurils can be controlled purely by changing the electron-withdrawing groups 8 bonds away from the binding pocket of bambusurils, while the selectivity of the macrocycle is maintained. The revealed structure–activity relationship resulted in a bambusuril with subpicomolar affinity towards iodide.

We have devised a series of structurally similar bambusurils, which differ in the group attached to their benzyl substituents (Figure 1). While **BU1** bears -SCF_3 moieties, **BU2** and **BU3** are decorated with the more potent electron-withdrawing groups –$SOCF_3$ and –SO_2CF_3, respectively. To the best of our knowledge, these oxidized forms of the –SCF_3 group have not been used to increase the binding efficiency of anion receptors. This is in contrast to the less potent but more common –SCF_3 group. Calculated electrostatic potential maps of the macrocycles (Figure 1) revealed that going from **BU1** to **BU3**, less electron-density is present inside the cavity of the bambusurils. Thus, the models showed that a higher attraction of anionic species by bambusurils can be expected by installing the increasingly oxidized electron-withdrawing groups on the benzyl substituents of the macrocycles. We decided to experimentally test these computational results and report the results of these experiments here.

The synthesis of bambusuril **BU1** was already published.[33] Bambusurils **BU2** and **BU3** were prepared by oxidation of glycoluril building block 1, followed by the macrocyclization reaction (Scheme 1). The oxidation of the –SCF_3 groups of **1** to sulphoxides was achieved in trifluoroacetic acid (TFA) using urea hydrogen peroxide adduct (UHP) as an oxidizing agent with a better defined hydrogen peroxide content than aqueous H_2O_2 solutions.[34] Careful control of the amount of oxidizing agent and conducting the reaction at low temperature were necessary to avoid over-oxidation to sulphone. The sulphone glycoluril derivative **3** was prepared by reacting **1** with an excess of *m*-CPBA at elevated temperature. The macrocyclization reactions of **2** and **3** with paraformaldehyde in 1,4-dioxane in the presence of sulphuric acid, acting simultaneously as an acid catalyst and template, yielded **BU2** and **BU3** as their complexes with hydrogen sulphate.



Scheme 1. Synthesis of **BU1**, **BU2**, and **BU3**.

To compare the binding affinities of the prepared bambusuril derivatives, we decided to measure their association constants (K_a) with halides in CD_3CN by ^1H and ^{19}F NMR spectroscopy, using tetrabutylammonium salts. Halide complexes of **BU1** were expected to be too stable for their determination by a direct NMR titration. Therefore, we first studied the much weaker complex of **BU1** and $CF_3SO_3^-$. The addition of $CF_3SO_3^-$ aliquots into a solution of **BU1** resulted in continuous shifts of the bambusuril signals (Figure S29). The experimental data were fitted using a 1:1 binding isotherm to obtain a K_a value of $1.0\times10^5\ M^{-1}$ (Table 1).

Originally, we aimed to determine the K_a of **BU1** for halides using competition experiments with $CF_3SO_3^-$. However, $CF_3SO_3^-$ proofed to be a too weak competitor in this regard. Thus, a sequence of anions for which **BU1** had an increasing anion affinity was used to achieve our goal. We started with the titration of ReO_4^- into the solution containing **BU1** with an excess of $CF_3SO_3^-$, which resulted in changes in chemical shifts of the bambusuril proton signals *a-f* (Figure 2b). Moreover, the titration was also monitored by ^{19}F NMR spectroscopy revealing a gradual shift of the fluorine signal of **BU1** (Figure 2a). Global analysis of all these binding isotherms was employed (Figure 2c and SI) to reveal a selectivity of 149 for ReO_4^- over $CF_3SO_3^-$, corresponding to a K_a value of $1.5\times10^7\ M^{-1}$ for the 1:1 complex between **BU1** and ReO_4^-.

Similarly, we continued with the competitions of ReO_4^- *vs.* ClO_4^-, then ClO_4^- *vs.* Cl^-, Cl^- vs. Br^- and finally Cl^- vs. I^- and obtained K_a values for the corresponding complexes (Tables 1 and S3). Most of the investigated anion⊂**BU1** complexes corresponded to a 1:1 stoichiometry of host–guest binding. However, in the case of Cl^-, the applied global analysis was able to reveal the existence of weak complexes of 1:2 stoichiometry (Tables 1 and S1). Surprisingly, this was possible despite 9 orders of magnitude

Table 1: Apparent association constants (K_a) of **BU1** complexes with various anions in CD_3CN determined by global fitting of the changes in chemical shifts of ^1H and ^{19}F nuclei to a 1:1 or 1:2 binding model.[a]

Anion	K_a (1:1) (M^{-1})	K_a (1:2) (M^{-1})	Competitor anion
$CF_3SO_3^-$	$(1.0\pm0.2)\times10^5$	–[c]	-[b]
ReO_4^-	$(1.5\pm0.6)\times10^7$	–[d]	$CF_3SO_3^-$
ClO_4^-	$(3.8\pm1.9)\times10^9$	–[d]	ReO_4^-
Cl^-	$(4.2\pm2.1)\times10^{10}$	$(2.7\pm1.3)\times10^1$	ClO_4^-
Br^-	$(6.0\pm3.1)\times10^{11}$	–[d]	Cl^-
I^-	$(1.6\pm0.7)\times10^{12}$	–[d]	Cl^-

[a] All anions were used as their tetrabutylammonium salts. The ion pairing of the salts in acetonitrile was not considered for K_a determination. The uncertainties are represented as confidence intervals at 95% probability. For detailed uncertainty analysis, see the SI. All titrations have been performed 3–4 times. [b] Direct titration. [c] See Section 4.5 in the SI. [d] 1:2 binding mode was not observed.

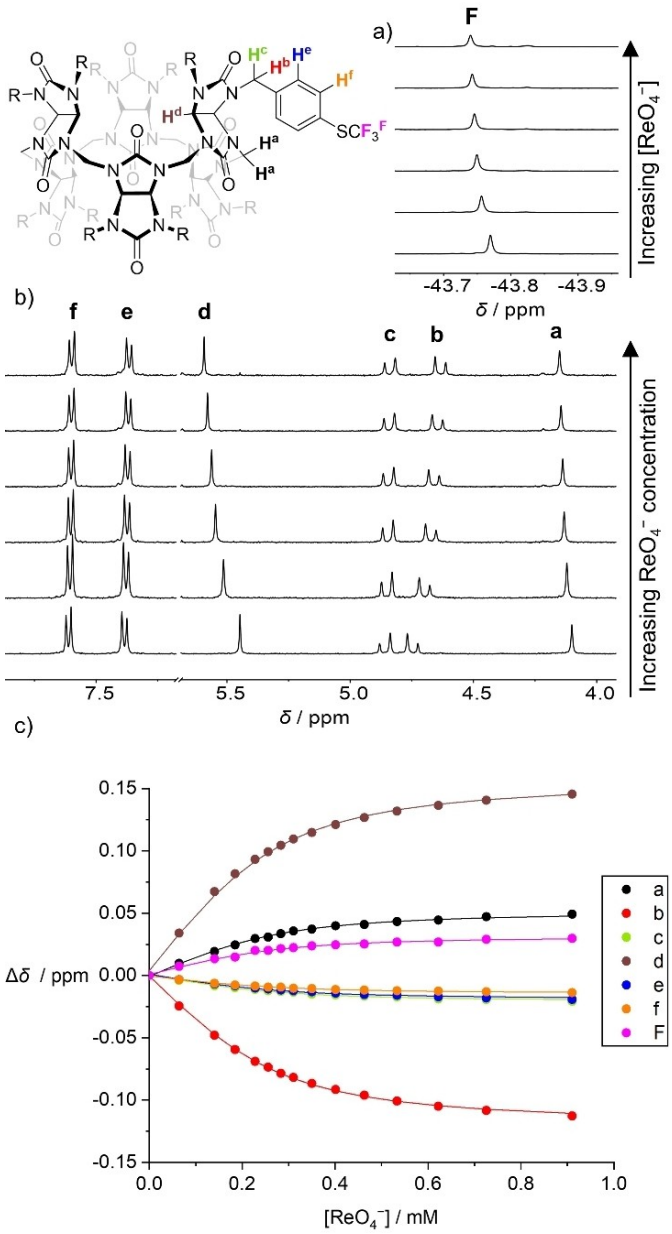


Figure 2. Titration of **BU1** (0.24 mM) in the presence of the tetrabutylammonium (TBA) salt of $CF_3SO_3^-$ (11 mM) with a $TBAReO_4$ solution in CD_3CN. a) Changes in the chemical shift of fluorine nuclei observed by ^{19}F NMR spectroscopy; b) changes in the chemical shifts of protons *a-f* observed by ^1H NMR spectroscopy; c) global fitting of the obtained data to a 1:1 model (Equation S7).

difference between the binding affinity of the first and second anion.

The determined binding affinities for the 1:1 complexes spanned more than 7 orders of magnitude when going from $CF_3SO_3^-$ to I^- (Table 1). The order of anion binding affinities for **BU1** is in agreement with the one previously determined for bambusurils in chloroform[35] and water[36,37] and correlates with the energy of solvation and the charge density of the anions. The only exception is ClO_4^-, which was bound weaker to **BU1** than Cl^-, Br^-, and I^-. In contrast, previous studies in water and chloroform showed that bambusurils bind ClO_4^- stronger than all halides. This shows that the polarity of solvents has profound effects on the selectivity of anion binding by bambusurils, as predicted in a recent study.[38]

In contrast to the case of **BU1**, we were not able to completely remove the HSO_4^- templating anion from the macrocycles **BU2** and **BU3**. Therefore, we converted **BU2** and **BU3** to pure complexes of the macrocycles with Cl^-, Br^-, and I^- by treating them with tetrabutylammonium (TBA) salts of the corresponding halide. The complexes were subjected to a competition with **BU1** to determine the association constants of the corresponding complexes. We took advantage of the high resolution of ^{19}F NMR spectroscopy and the slow exchange rate between all investigated bambusurils and halides on the ^{19}F NMR chemical shift time scale. For example, upon mixing of anion-free **BU1** with the TBACl complex of **BU3** in CD_3CN, anion-free **BU1** scavenged a part of the chloride from the $Cl^-\subset$**BU3** complex. As a result, the formation of 2 new signals corresponding to the TBACl complex of **BU1** and anion-free **BU3** was observed in the ^{19}F NMR spectra (Figure S45). Simple integration of the corresponding signals together with the already determined K_a values of the $Cl^-\subset$**BU1** complex allowed calculating log K_a of 11.5 (average value from several experiments) for the $Cl^-\subset$**BU3** complex (see Section 5 in the Supporting Information for details about the calculation). The same approach was adapted to determine log K_a values of the remaining complexes of **BU2** and **BU3** and halides (Figure 3 and **Table S5**), revealing ultrahigh binding of **BU3** to iodide, characterized by log $K_a = 13.1$.

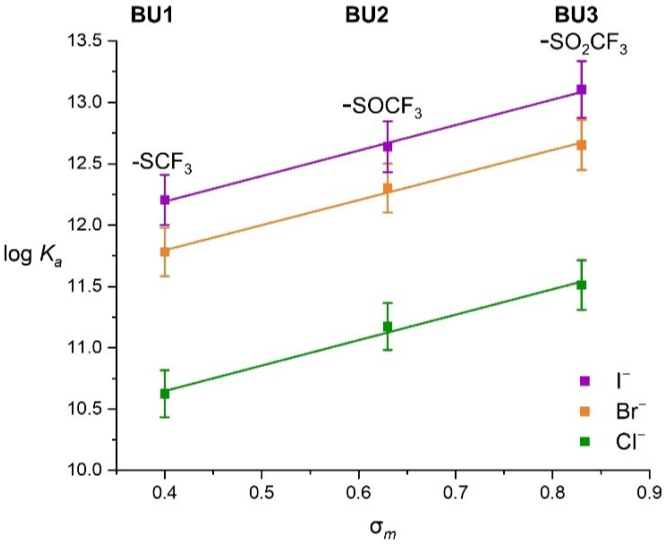


Figure 3. Hammett plot between the **BU1**-**BU3** bambusurils and halides in CD_3CN. The slopes of the fitted lines are 2.04 (Cl^-), 2.07 (Br^-) and 2.08 (I^-).

In agreement with the theoretical models, we observed that the anion binding strength increases with the increasingly potent electron-withdrawing substituents from **BU1** to **BU3** (Figure 3). Surprisingly, the substituents modulate the binding ability of the C(sp^3)-H hydrogen bonds of the macrocycles despite their large distance from the binding site and the absence of full conjugation (Figure 1). The polarization of the bambusuril cavity, the binding site of these receptors, is obtained by transfer of electron density from the glycoluril framework to the aromatic rings of the benzyl substituents. As the aromatic part of the benzyl substituent is directly affected by the potency of the electron-withdrawing groups, this effect is translated through the C–C and C–N sigma bonds to the polarization of the cavity. This is in big contrast to anion receptors published until now, in which the polarization of the binding site, usually based on N–H and C(sp^2)-X (where X is a hydrogen, halogen, or chalcogen atom), has been achieved through the delocalization of π electrons into directly attached aromatic systems.[11,15–17,39] Moreover, the modulation is possible despite the ultrahigh binding affinities of bambusurils, resulting in the I^-⊂**BU3** complex (log K_a = 13.1) being the most stable 1:1 supramolecular complex for iodide ever reported.

The anion affinities of all investigated bambusurils increase in the order Cl^-, Br^-, I^-, which correlates well with the decrease of the charge density of the anions. We also constructed a linear free energy relationship using Hammett substituent constants (σ_m)[40] as a measure of the electron-withdrawing ability of the substituent attached to the benzyl groups of the bambusurils (Figure 3). The plot revealed that going from the -SCF_3 group with the lowest σ_m value to -$SOCF_3$ and -SO_2CF_3 groups, the binding affinity of the corresponding bambusurils increases by about one order of magnitude. The increase is identical for Cl^-, Br^-, and I^-. The results show that the electron-withdrawing power of the group is translated into the decrease of electron density inside the macrocycle cavity, which is reflected by the increase in anion binding in the row **BU1** < **BU2** < **BU3**. Equal increases of association constants of **BU1**, **BU2**, and **BU3** complexes with all three halides are due to the well-defined cavity, which maintains its size and shape and thus its selectivity.

Inspired by reviewers' comments, we synthesized additional bambusuril **BU4**, in which the –SCF_3 groups were replaced by less electron-withdrawing –OSO_2CH_3 groups. In agreement with our findings, the binding affinity of this bambusuril for all halides significantly decreased compared to **BU1**—**BU3** (see Supporting Information for affinities and linear free-energy relationship plots).

The ability of the prepared fluorinated bambusurils to respond to the presence of halide anions by changes of their ^{19}F NMR spectra is highly appealing for sensing of anions, particularly in biofluids.[41–44] ^1H and ^{13}C NMR spectroscopy cannot be used in this respect due to undesired background signals. In contract, endogenous fluorine is generally absent in biological samples and therefore it does not interfere with the measurements. Moreover, the prepared bambusurils contain 36 equivalent fluorine atoms, which highly enhances the macrocycle sensitivity for anions by using ^{19}F NMR spectroscopy. Thus, the anion concentration can be directly determined by the integration of the signal corresponding to the anion-bambusuril complex. Taking together, the high sensitivity coupled with the high binding affinity for inorganic anions makes bambusurils outstanding chemosensors with the ability to detect up to subpicomolar concentrations of halides.

In conclusion, we report a series of three structurally similar bambusurils **BU1**, **BU2**, and **BU3**, which differ by –SCF_3, –$SOCF_3$, and –SO_2CF_3 groups attached to their benzyl substituents. Up to subpicomolar affinities for the bambusuril complexes of Cl^-, Br^-, and I^- in CD_3CN were determined using competitive ^1H and ^{19}F NMR titrations. We observed that the affinity of bambusurils to all halides gradually increases in the series **BU1** < **BU2** < **BU3**, which corresponds well with the increasing electron-withdrawing ability of the substituent of the macrocycles. The modulation of receptor structures resulted in outstanding binding affinities of **BU3** with Cl^- (log K_a = 11.5), Br^- (log K_a = 12.7), and I^- (log K_a = 13.1) in acetonitrile. The similar slopes of the Hammett plots for all three halides showed that the binding selectivity of the macrocycles is maintained, while their binding potency is improved. These exceptional properties are due to the bambusuril structure, which is unique among anion receptors. Especially, its well-defined deep cavity preserves its selectivity despite modifications on its portals. Moreover, even the distant electron-withdrawing groups on benzyl substituents of bambusurils are able to lower the electron density in the macrocycle cavity through the inductive effect and significantly influence the binding potency of the macrocycle toward anion binding. This is in contrast to most currently used receptors, in which the binding site is polarized through the delocalization of π-orbital electrons. Our finding highlights that bambusurils represent an unique family of anion receptors, which ultrahigh affinity can be further modulated by the attached substituents. More importantly, it justifies the need to develop new well-defined cavitands, which are still extremely under-investigated in the field of anion receptors.

Supporting Information

Experimental procedures, compound characterization and data analysis. The authors have cited additional references within the Supporting Information.[45–53,40,54]

Acknowledgements

This work was supported by the Czech Science Foundation (No. 23-05271S). Authors thank the RECETOX Research Infrastructure (No. LM2018121) financed by the Ministry of Education, Youth and Sports, and the Operational Programme Research, Development and Education (the CETOCOEN EXCELLENCE project No. CZ.02.1.01/0.0/0.0/17_043/0009632) for supportive background. This project was supported by the European Union's Horizon 2020

Research and Innovation Programme under grant agreement No. 857560. MC is a Research Fellow and HV is a Research Associate of the Fonds de la Recherche Scientifique—FNRS. This publication reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains. We acknowledge Proteomic Core Facility of CIISB, Instruct-CZ Centre, supported by MEYS CR (LM2018127) and and the National Infrastructure for Chemical Biology (CZ-OPEN-SCREEN, LM2023052).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Anion Binding · Bambusurils · Host–Guest Chemistry · Macrocycles · NMR Spectroscopy

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Manuscript received: November 29, 2023
Accepted manuscript online: December 8, 2023
Version of record online: ■■, ■■

Communications

Supramolecular Chemistry

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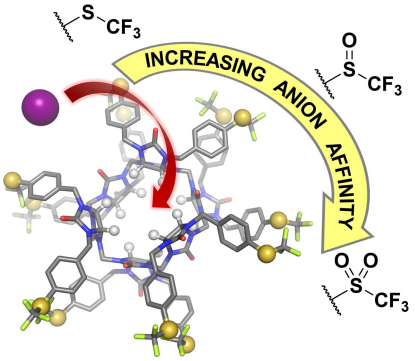
Tuning CH Hydrogen Bond-Based Receptors toward Picomolar Anion Affinity via the Inductive Effect of Distant Substituents



Ultrahigh binding affinity of bambusuril receptors toward halides is achieved and continuously increases with increasing electron-withdrawing power of groups installed on its benzyl substituents, as measured by ^{1}H and ^{19}F NMR spectroscopy.