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Remote control of anion binding by CH-based receptors†

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We show that the substitution of tetra(benzimidazole)resorcin-[4]arenes with electron withdrawing groups on the upper rim enhances anion binding at the opposite edge by more than three orders of magnitude. Moreover, selective anion binding at either the OH/NH or CH binding sites is demonstrated.

Organic and inorganic anions of various shapes and properties are inherently present in biotic and abiotic environments. Their selective detection and capture by anion receptors constitute an important subfield of supramolecular chemistry[1] and find applications in extraction,[2] sensing,[3] catalysis,[4] materials science,[5] and drug discovery.[6] Classical hydrogen-bond-forming anion receptors are based on NH or OH groups.[7] Recently, there has been a burgeoning interest in CH-based anion receptors due to their resistance to deprotonation.[8,9] Although the CH···anion hydrogen bond is weaker than the classical hydrogen bond,[10] high-density multipoint interactions and polarisation effects significantly amplify the binding affinity of CH-based receptors for anions. Polarisation effects induced by electron withdrawing groups (EWGs) are typically observed for CH donors that constitute a part of the aromatic rings (*e.g.* 1,2,3-trifluorobenzenes or 1,2,3-triazoles)[11] or acyclic systems (*e.g.* cyanostilbenes[12] or nitrones[13]). In this paper, we demonstrate that (1) a CH donor can also be located at an π-electron-rich aromatic ring, and (2) its polarisation can originate from remote unconjugated positions.[14] These discoveries significantly expand the design principles for constructing and modulating the properties of CH-based anion receptors.

Resorcin[4]arenes are π-electron-rich macrocycles known to interact with cationic guests.[15] However, recently, we[16,17] and others[18] demonstrated that resorcin[4]arenes can also interact with anions in numerous different ways. Those possessing OH groups, *e.g.* **1**, bind anions *via* classical OH···anion hydrogen bonds (Fig. 1a).[16] Those with OAlk groups, *e.g.* **2** and **3**, interact with anions at the lower rim *via* CH···anion hydrogen bonds (Fig. 1b and c).[17] The interactions of **2** with anions are weak ($K_a(Cl^-)$ = 144 M^{-1} in THF), but, after substitution with EWG groups (–NO_2), as for **3**, the interactions with anions become remarkably efficient ($K_a(Cl^-) > 10^5$ M^{-1} in THF). Both observations were non-trivial because **2** and **3** belong to π-electron-rich rings, which have not been considered before as capable of CH···anion interactions.

In this work we evaluate the possibility of remote modulation of anion binding properties using a series of resorcin[4]arenes **4–9** (Fig. 1d). Their cores are substituted with linkers (benzimidazoles) and their properties are modulated by increasing the

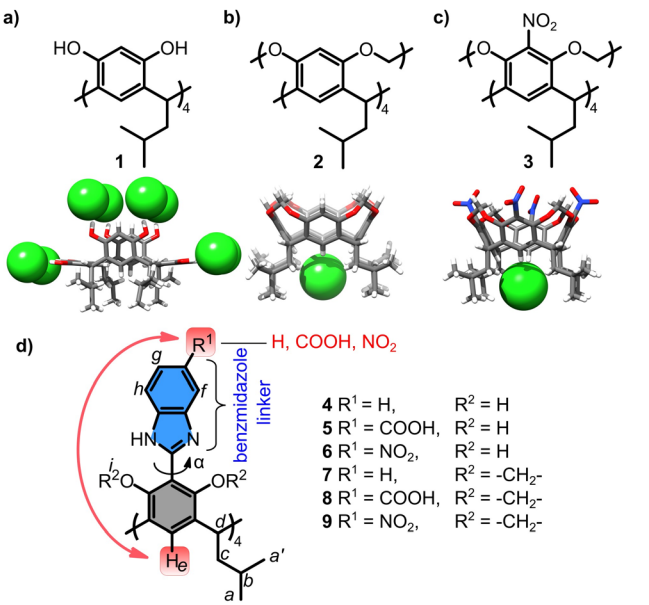

Fig. 1 Anion binding by resorcin[4]arenes based on: (a) OH···anion interactions [ref. 16]; (b) and (c) CH···anion interactions [ref. 17]; (d) receptors studied in this work along with the notation of signals for NMR and definition of torsion α angle.

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EWG character of the substituent at the linker (R^1 = –H, –COOH, $–NO_2$). It should be noted that the linker is attached to resorcinol rings *via* a single aryl–aryl bond; therefore, it is not conjugated and can adopt various dihedral angles between the aromatic units (α = 0–90°). Additional modulation comes from modifications of hydroxyl groups (R^2 = H or $–CH_2–$) that alter the electronic properties of the basic core, modulate the α angle, and can also form a competitive OH/NH-type binding site. Compounds **4**, **5**, **7**, and **8** were synthesized previously for a different purpose.[19] The synthesis of **6** and **9** is reported in the ESI.†

For the initial assessment of the properties, DFT calculations[20] were performed for **3a–9a** (analogues of **3–9** devoid of lower rim alkyl substituents, which have a negligible influence on the relevant parameters, Fig. S36, ESI†), **10** (monomer) and **11** (a derivative with nitrophenylene substituent). The results show a surprisingly large variation of the electrostatic surface potentials (ESPs, Fig. 2) at the lower rim depending on (a) remote substitution at the upper rim, and (b) substitution of OH groups. Derivatives **4a–6a**, which contain free OH groups, form 12 intramolecular hydrogen bonds, which stabilize conformations with coplanar phenolic and benzimidazole rings ($\alpha = 1° \pm 1°$). The ESP potential at the lower rim becomes more positive with the increase of the electron-withdrawing character of the substituent at the upper rim (–H < –COOH < $–NO_2$) and reaches 200 kJ mol^{-1} for **6a**. For *O*-bridged derivatives **7a–9a**, due to a lack of intramolecular hydrogen bonds, the benzimidazole and resorcinol rings are twisted ($\alpha = 35° \pm 1°$). Despite this twist, which reduces the resonance effects, the ESPs at the lower rim are also largely affected by the upper rim EWG substituents and reach even 221 kJ mol^{-1} for **9a**. It should be noted that the ESPs reach higher values for *O*-bridged derivatives than for their analogues with free OH groups (*e.g.*, compare **6a** and **9a**). Furthermore, the crucial role of the concentration of ESP in the apex area is clearly seen by the comparison of **9a** with monomer **10** (87 kJ mol^{-1}, $\alpha = 26°$). In summary, theoretical calculations suggest that substituent effects transfer over large distances and even through a system of twisted biaryl connections. These remote modulations result in ESP values for **9a** (221 kJ mol^{-1}) that are only slightly lower than for resorcinarene **3a** (247 kJ mol^{-1}),[17] in which the EWG substituent is directly attached to the core.

To experimentally support the above hypotheses, anion binding properties were evaluated by ^{1}H NMR titration of **4–6** with But_4NBr in THF-d_8 and **6**, **8**, and **9** in mixtures of THF-d_8:DMSO-d_6 (for solubility reasons). We were unable to obtain **7** of purity suitable for titrations (due to co-eluting partially substituted derivatives); therefore, **7** was excluded from the quantitative determination of K_a, but qualitative experiments show that it follows the trends observed for other derivatives.

During the ^{1}H NMR titrations of **4–9** with But_4NBr, the most pronounced changes were observed for the H_e signals (+0.8 ppm), and H_c (+0.5 ppm) indicating that anion binding occurs in the apex area of the lower rim (Fig. 3). The $K_a(Br^-)$ values increase in the order **4** < **5** < **6** < **8** < **9** (Table 1). The results show that the Br^- binding affinity increases by two orders of magnitude (68 M^{-1} for **4** and 6000 M^{-1} for **6**). A further increase in Br^-

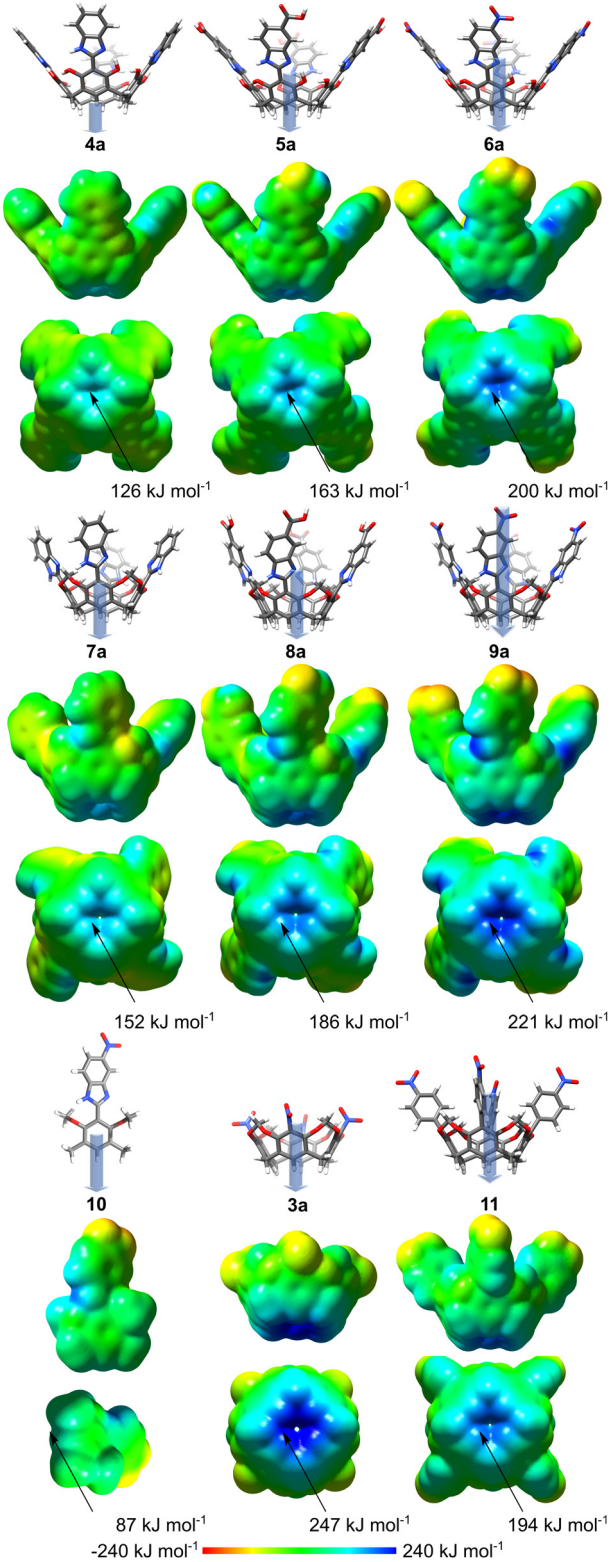

Fig. 2 Theoretical calculations of molecular properties by DFT B3LYP 6-31+G(D,P) using the SMD solvent model (THF). ESPs are mapped on electron density isosurfaces (0.0004 e au^{-3}), and relative dipole moment values (μ, D) are depicted as blue-grey arrows.

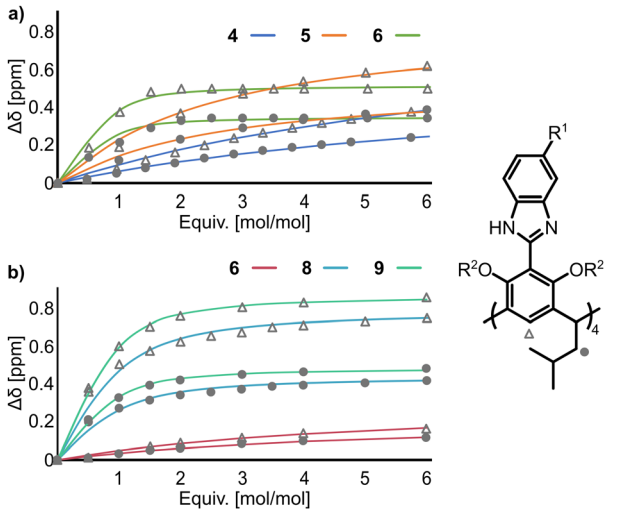

Fig. 3 ^{1}H NMR titrations of receptors **4–9** (2 mM) with But$_4$NBr (a) in THF-d$_8$ and (b) in THF-d$_8$:DMSO-d$_6$ (9 : 1, v : v).

binding affinity by more than an order of magnitude was observed upon *O*-bridging – K_a(**9**, Br$^-$) in THF-d$_8$:DMSO-d$_6$, 90 : 10, v : v, is almost 30 times higher than K_a(**6**, Br$^-$) in the same solvent. This trend agrees with the calculated ESPs and proves experimentally that the effect of remote EWG substitution on anion binding at the binding site is remarkable (reaching more than three orders of magnitude).

The mechanism by which the effect of the EWG group is transferred over such a large distance and through twisted aryl–aryl bonds is not fully clear to us, and, most likely, many factors are correlated. Apparently, the resonance effect is not determining, because of the insensitivity of the effects to the aryl–aryl dihedral angle (compare **6a** and **9a**). Inductive effects and the polarisability seem to play a crucial role. This is illustrated by the comparison of the ESP values for **9a**, which possesses long polarisable benzimidazole linkers (H$_e$···NO$_2$ 11.1 Å), with **11**, which possesses a shorter but less polarisable phenylene linker (H$_e$···NO$_2$ = 9.2 Å). As a result of these two factors, large dipole moments of the receptors are induced, which seem to be correlated with anion binding affinity.

Table 1 Apparent association constants K_a (M^{-1}) for anion binding in various solvents (1 : 1 model, determined by ^{1}H NMR titrations with But$_4$NX)

Receptor	Anion	THF	THF : DMSO 98 : 2, v : v	THF : DMSO 90 : 10, v : v
4	Br$^-$	68 (±1%)	34 (±1%)	<10
5	Br$^-$	270 (±4%)	<10	<10
6	Br$^-$	6000 (±25%)	800 (±24%)	124 (±3%)
8	Br$^-$	—[a]	—[a]	1800 (±6%)
9	Br$^-$	—[a]	7000 (±14%)	3400 (±6%)
9	Cl$^-$	—[a]	1900 (±11%)	760 (±6%)
9	I$^-$	—[a]	2900 (±23%)	—[b]
9	ClO$_4^-$	—[a]	450 (±2%)	—[b]

[a] Determination not possible due to low solubility. [b] Titrations were not performed.

The selectivity of the receptors is determined by several factors, including spatial fit and the strength of the interactions. Receptor **9** favours Br$^-$ over Cl$^-$ by a factor of 3.7 (Table 1), despite Cl$^-$ forming stronger hydrogen bonds, indicating that the binding site may have geometric preference for Br$^-$. Unprecedented site-selective binding is demonstrated for receptor **6**, which possesses free OH groups. The comparison of the titrations of **6** with But$_4$NCl and But$_4$NBr in THF-d$_8$ (Fig. 4) suggests that receptor **6** binds to Br$^-$ on the lower rim while Cl$^-$ on the upper rim. Thus, during Br$^-$ binding, the H$_e$ signal is downfield shifted, indicating binding in the lower rim (Fig. 4b and d). On the contrary, during Cl$^-$ binding all signals of **6** substantially broaden and, after lowering of the temperature, substantial downfield shifts of its OH/NH signals are observed (Fig. 4c and Fig. S34, ESI†). The H$_d$ signal splits into two, of which only one shifts substantially downfield and the changes saturate after 2 equiv. of Cl$^-$ are added (Fig. S33, ESI†). This is in agreement with the binding of two Cl$^-$ in the upper rim, between the arms in the opposite corners of the macrocycle, using OH/NH···Cl$^-$ hydrogen bonds (Fig. 4e). The geometry-optimized structure of **6a**·(Cl$^-$)$_2$ has C_{2v} symmetry, which is in agreement with the observed doubling of the signals, downfield shift of eight out of 12 NH/OH signals and two of the four H$_d$ signals. The hypothetical geometry-optimized structure **6a**·(Br$^-$)$_2$ has less favourable geometry (*e.g.* less hydrogen bonds, ESI†). This site-selective Cl$^-$/Br$^-$ binding can result from geometrical reasons. It can also originate from the fact that Cl$^-$ is a 'hard' anion and therefore prefers a 'hard' binding site, whereas Br$^-$ has a more diffuse charge and therefore a higher affinity toward a more surface-diffused CH-based binding site.

In summary, we have introduced novel macrocyclic anion receptors derived from benzimidazole functionalized resorcin[4]-arenes. Our findings demonstrate that substituting an electron-withdrawing group at the upper rim can remarkably enhance anion

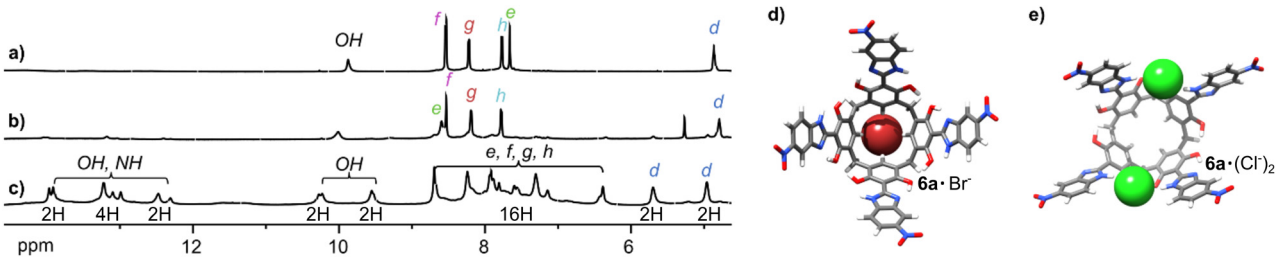

Fig. 4 Anion binding modes for receptor **6**. ^{1}H NMR spectra of: (a) **6**; (b) **6** + But$_4$NBr; (c) **6** + But$_4$NCl (2 mM each, THF-d$_8$ at 233 K). Suggested structures of: (d) **6a**·Br$^-$; (e) **6a**·(Cl$^-$)$_2$.

binding at remote lower rim positions by more than three orders of magnitude. Specifically, Br^- is bound at the lower rim apex of the cone through CH···anion hydrogen bonds. The cone geometry plays a pivotal role in generating a positive electrostatic potential and a large vertical dipole moment for the receptor. Additionally, we have unveiled an unexpected site-selective differentiation in the binding of Cl^- and Br^-. The Cl^- anions exhibit a preference for OH/NH-based binding sites, whereas the Br^- anions favour the CH-based binding site within the same receptor.

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Conflicts of interest

There are no conflicts to declare.

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