

Binding affinities of cucurbit[*n*]urils with cations†Shuai Zhang,^{‡,a} Laura Grimm,^{‡,b} Zsombor Miskolczy,^{‡,c} László Biczók,^{‡,c} Frank Biedermann^{‡,*b} and Werner M. Nau^{‡,*a}Cite this: *Chem. Commun.*, 2019, 55, 14131Received 30th September 2019,
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High binding constants of 19 inorganic cations with the cucurbit[*n*]uril homologues (CB*n*, *n* = 5, 6, 7, 8) in water were determined and the far-reaching consequences and interferences of the high affinities (millimolar to micromolar) are discussed.

The design of artificial receptors for inorganic cations has underpinned the development of supramolecular chemistry.^{1,2} Through advances in the understanding of non-covalent interactions,³ carefully designed supramolecular receptors for (earth) alkaline cations emerged in the 1980's such as Cram's spherands^{4,5} displaying high selectivity for Li⁺. Conversely, Lehn's cryptands^{6,7} and the more recently introduced orthoester cryptands by von Delius^{8,9} can strongly and selectively bind (earth) alkali cations. In contrast to these designer hosts, other classes of macrocyclic receptors were originally tailored for organic guests but later also found to be interesting metal ion binders, for example, *p*-sulfonatocalix[4]arene (CX4). For supramolecular applications, this behavior is often undesirable because alkali ion binding competes for the binding of the target guests (e.g., choline) in biologically relevant, aqueous saline media.^{10,11} Likewise, cucurbit[*n*]uril (CB*n*, Fig. 1) macrocycles were long known to interact with (earth) alkaline cations, leading to an increase in their aqueous solubility but a decrease in their organic-guest binding affinities.^{12–17} CB*n* have found widespread use as solubility enhancers,¹⁸ for materials applications,^{19,20} and for assay development,^{17,21} which often take place in buffered aqueous media.^{12,16,22,23} The influence of metal cation binding to CB*n* macrocycles is therefore a critical factor. However, while the interaction of CB6 with Ca²⁺ was inferred already a century ago,²⁴ and

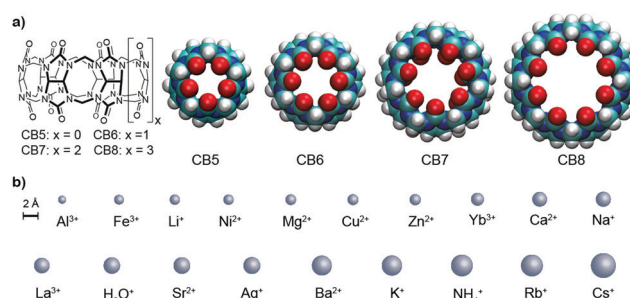


Fig. 1 (a) Chemical structures and their 3D representation (space filling model) of CB*n* and (b) of the metal cations investigated in this study, with sizes drawn to scale with respect to CB*n*; the portal diameters are 2.4 Å for CB5, 3.9 Å for CB6, 5.4 Å for CB7, and 6.9 Å for CB8.

while absolute affinity values for some ions such as Na⁺ have been reported,^{23,25–29} (see also Table S1 in the ESI†) binding affinities for metal cations to CB*n* in water have not been systematically studied across the homologous series and associated structure-affinity relationships are unknown.

We now provide a comprehensive data set for the complexation of 19 inorganic cations with CB5, CB6, CB7, and CB8 in water. The determination of cation–CB*n* binding is challenging because their interaction does not provide a diagnostic signal change in conventional NMR or UV-vis absorption spectra and phase-extraction protocols³⁰ are inapplicable for water-soluble hosts such as CX4 or CB*n*. As alternatives, fluorescence displacement titrations and isothermal titration calorimetry (ITC) experiments came to mind for the determination of macrocycle-cation binding constants (K_a).^{10,31,32} The experimental details are shown in the ESI† and the aggregated log K_a values are shown in Table 1, along with the ionic radii and their hydration free energies in order to correlate with size fitting and desolvation effects. Additional reference data for classical cation-receptor macrocycles such as 18-crown-6,^{2,33,34} *p*-sulfonatocalix[4]arene (CX4),^{10,32,35,36} and Cryptand [2.2.2]^{6,31,37,38} are also shown. Monovalent alkali metal ions, Ag⁺, NH₄⁺, and H₃O⁺, divalent earth alkaline ions, transition metal ions, and trivalent cations were investigated. It transpires from Table 1 and from the

^a Department of Life Sciences and Chemistry, Jacobs University, Campus Ring 1, 28759, Bremen, Germany. E-mail: w.nau@jacobs-university.de

^b Institute of Nanotechnology, Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz Platz 1, 76344 Eggenstein-Leopoldshafen, Germany. E-mail: frank.biedermann@kit.edu

^c Institute of Materials and Environmental Chemistry, Research Centre for Natural Sciences, P. O. Box 286, 1519 Budapest, Hungary

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‡ These authors contributed equally.



Table 1 Binding constants ($\log K_a$ values) of cations with CBn ($n = 5-8$) and reported values with 18-crown-6, CX4, and Cryptand [2.2.2] in water

Cations	r^a (Å)	$-\Delta G_{\text{hyd}}^b$ (kJ mol $^{-1}$)	CB5 ^c	CB6 ^d	CB7 ^e	CB8 ^f	18-Crown-6 ^g	CX4 ^h	Cryptand [2.2.2] ⁱ
H ₃ O ⁺	1.12	—	≤0.5	1.06 ^k	2.22	—	1.46	1.6	(9.66) ^l
NH ₄ ⁺	1.48	285	2.59	3.79	2.82	—	1.23	2.22	—
Li ⁺	0.69	475	2.02	2.41	2.34	1.69	~0	2.14	1.3
Na ⁺	1.02	365	3.94	3.89	3.41	2.49	0.8	2.26	3.9
K ⁺	1.38	295	4.73	3.81	3.46 (3.29)	2.66	2.03	2.33	5.3
Rb ⁺	1.49	275	3.22	4.30	3.43 (3.42)	2.64	1.56	2.40	4.2
Cs ⁺	1.70	250	2.61	5.31	3.50 (3.51)	2.55	0.99	2.88	1.4
Ag ⁺	1.15	430	— ^j	3.87	3.54	2.32	1.50	2.43	9.6
Mg ²⁺	0.72	1830	2.50	2.57	3.24	2.72	~0	3.58	<0
Ca ²⁺	1.00	1505	2.64	4.22	4.25 (4.01)	3.31	1.26	3.89	4.4
Sr ²⁺	1.13	1380	5.16	4.91	4.79 (4.31)	3.63	2.72	3.66	8.0
Ba ²⁺	1.36	1250	6.44	5.29	5.28 (4.78)	3.95	3.87	3.83	9.5
Ni ²⁺	0.69	1980	2.73	2.59	3.50	2.73	—	3.75	<2.0
Cu ²⁺	0.73	2010	—	2.88	3.75	2.86	—	3.75	6.8
Zn ²⁺	0.75	1955	—	2.45	3.40	2.67	—	3.75	<2.5
Al ³⁺	0.53	4525	— ^j	3.81	2.90	2.90	—	—	—
Fe ³⁺	0.65	4265	3.66	5.17	4.18	3.0 ^m	—	—	—
Yb ³⁺	0.87	3570	3.71	3.50	4.42	3.44	—	3.81	—
La ³⁺	1.05	3145	4.17	4.16	5.28	3.76	—	4.23	6.45
Mean $\log K_a$ value ⁿ			3.42 (3.74)	3.68 (4.03)	3.66 (3.93)	2.90 (2.85)	1.58 (1.65)	3.09 (3.18)	4.67 (4.22)
StDev of $\log K_a$ value ⁿ			1.42 (1.27)	1.10 (0.92)	0.82 (0.87)	0.55 (0.64)	0.97 (1.13)	0.80 (0.75)	2.97 (2.94)

^a Ionic radius, from ref. 39. ^b Hydration free energy, from ref. 39. ^c By ITC experiments with desalinated CB5 and the respective nitrate salts at 283 K; error \pm 0.10. ^d By fluorescence displacement titrations with the reporter pair CB6-DSMI at 298 K; error \pm 0.10. ^e By fluorescence displacement titrations with the reporter pair CB7-BE at 298 K; error \pm 0.10; values in parentheses determined by ITC experiments with CB7 at 298 K; error \pm 0.10. ^f By UV-vis displacement titrations with CB8-PDI at 298 K; error \pm 0.10. ^g From ref. 10, 34 and 40. ^h From ref. 10, 32, 35 and 36. ⁱ From ref. 6, 31, 37 and 38. ^j Large heats of dilution compared to binding heats prevented determination of $\log K_a$ by ITC. ^k Derived from ref. 41 by using the affinity for cyclohexylmethylamine from ref. 42 extrapolated for neat water. ^l Cryptand [2.2.2] is being protonated. ^m From fluorescence displacement titrations, error \pm 0.3. ⁿ Mean $\log K_a$ values and standard deviations for each host type; values in parentheses are for subset of alkali and earth alkaline metal ions.

comparison to the data for the established hosts that CBn are highly competitive inorganic cation receptors, although they are much better known for their tight binding of organic guests. Correlations of the $\log K_a$ values with ionic cation radius are shown in Fig. 2; the interconnected lines for the alkali and alkaline earth ions reveal a general trend in favour of a stronger binding for the larger and less strongly hydrated metal ions; only for the smallest CB5 a bell-shaped curve for the alkaline metal ions is obtained, which points to an ideal size matching as an additional determinant (see Fig. 1 for size comparison). Within a homologous series, the most rigid macrocycle, CB5 in our series, is in general known to display a pronounced peak selectivity.^{6,31} Rb⁺ and Cs⁺ appear to be too large to penetrate into the carbonyl portal region of CB5, where the dipolar interaction with the oxygen lone pairs is most effective. Ag⁺ follows the trend for the alkaline metal ions, but NH₄⁺ and H₃O⁺ fall binding-wise below the correlation for (similarly sized) monovalent ions (Fig. 2), presumably because they engage as

potent hydrogen bond donors in bulk water. This demonstrates that the formation of hydrogen bonds to the cucurbituril portals presents no significant driving force for organic guest complexation. Instead, the enhanced binding of organic guests upon introduction of cationic groups can be satisfactorily explained by ion-dipole interactions with the portals. Cationic centers that do not act as hydrogen-bond donors and that are less strongly hydrated, such as quaternary ammonium groups, present accordingly the better choice if optimized binding to CBn is desired.⁴³ Hydrogen-bond proximity patterns, that are frequently observed in crystal structures of CBn,^{14,44,45} do not reflect on the driving force of host-guest binding in aqueous solution.

Ion-dipole interactions are supported by the dependence on metal ion valency, with the general trend trivalent > divalent > monovalent at comparable ionic radius, see colour coding in Fig. 2. The three divalent transition metal ions Ni²⁺, Zn²⁺, and Cu²⁺ bind with similar affinity, as expected from their similar

**Fig. 2** Plots of $\log K_a$ vs. cation radius for different CBn.

Consequently, thermochemical parameters measured for CB n in the presence of buffer cations, including our own measurements, contain a systematic error and are incorrect in absolute terms. Strictly speaking, they do not only report on the host-guest binding event, but on the differences in complexation enthalpies between guest and cation binding.

Another sequential but severe shortcoming is that the apparent binding constants in the presence of buffers have already been used in the literature as benchmark values not only to evaluate the performance of computational methods in so-called challenges,^{52–54} but in some cases also for the parameterization and calibration of computational methods.⁵⁵ Assuming that the experimental values underestimate the binding by up to three orders of magnitude (Table 2), corresponding to 17 kJ mol⁻¹ at 298 K, an incorrect calibration of computational methods, which aim in part for an accuracy better than 8 kJ mol⁻¹, may have resulted. It appears essential that computational challenges that aim at host-guest binding of CB n or other ion receptors either explicitly consider the presence of buffer ions or address the true guest affinities, namely those in neat water.

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Conflicts of interest

There are no conflicts of interest to declare.

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