Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *Org. Biomol. Chem.*, 2023, **21**, 6636

Received 20th June 2023,
Accepted 28th July 2023

DOI: 10.1039/d3ob00975k

rsc.li/obc

Large anion binding in water

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Large water-soluble anions with chaotropic character display surprisingly strong supramolecular interactions in water, for example, with macrocyclic receptors, polymers, biomembranes, and other hydrophobic cavities and interfaces. The high affinity is traced back to a hitherto underestimated driving force, the *chaotropic effect*, which is orthogonal to the common hydrophobic effect. This review focuses on the binding of large anions with water-soluble macrocyclic hosts, including cyclodextrins, cucurbiturils, bambusurils, biotinurils, and other organic receptors. The high affinity of large anions to molecular receptors has been implemented in several lines of new applications, which are highlighted herein.

Introduction

The binding of "mineral water" anions such as F^-, Cl^-, CO_3^{2-}, SO_4^{2-}, PO_4^{3-}, and NO_3^- in water has been in the focus of anion binding by supramolecular receptors, among others, due to their biological and environmental importance. These common anions are strongly solvated in aqueous solution, which presents a challenge for the supramolecular design of the associated receptors.[1–4] In contrast, the binding of large anions such as I^-, SCN^-, ClO_4^-, and PF_6^-, which have a lower charge density and are weakly hydrated, has received comparably less attention, among others, due to the fact that they play, with the notable exception of I^-, less critical natural roles.[5–9] On the other hand, the diametrically opposed effects that the two groups of anions can exert on biological systems have been recognized since long by the Hofmeister series, which conventionally classifies the character of ions as being salting-out (kosmotropic) or salting-in (chaotropic) in nature.[10] Recently, the supramolecular chemistry of long-known synthetic cluster anions of the borate-[11,12] and polyoxometalate-type[13] has moved into the focus, driven by the observation that

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Werner M. Nau was born in Fulda, Germany, in 1968. Following his Bachelor's and Master's studies in chemistry in Germany and Canada, he obtained his PhD from the University of Würzburg in 1994 in spectroscopy and organic chemistry. Following his postdoc at the University of Ottawa, Canada, with J.C. Scaiano in photochemistry, he completed his habilitation in physical chemistry with J. Wirz at the University of Basel, Switzerland, where he became Assistant Professor in 2000. Since 2002, he has been Professor of Chemistry at Constructor University, Germany, and since 2012 he has been Dean of Science. His research combines supramolecular chemistry with organic photochemistry and focuses on applications in enzyme and membrane transport assays.

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their affinity with hydrophobic binding sites does exceed,[14] against expectation, those of hydrophobic guest molecules.[15–17] These large anions were recognized to expand the traditional Hofmeister series as so-called superchaotropic anions,[14,18–34] and their peculiar supramolecular chemistry has revived the interest in large anion binding in water.[14,25,26,35–49] The present review provides a short historical background and a summary of the most recent developments in this emerging field. Amphiphilic anions, which are composed of long hydrophobic chains and kosmotropic head groups, such as sodium dodecyl sulphate, are also large anions in the metric sense, but display entirely different properties and are not the subject of this review. Also excluded from further discussion are hydrophobic anions, such as Ph_4B^-, which in contrast to superchaotropic anions display positive hydration free energies.[18]

Historical developments in large anion binding and initial empirical observations (up to 2015)

Cyclodextrins[17,50,51] (CDs, Fig. 1) are the oldest and most intensively studied class of macrocyclic hosts, and they are also the first ones that were found to display sizable affinity towards large anions, despite their known propensity to preferentially complex hydrophobic guests inside their cavity.[5–8,52–54]

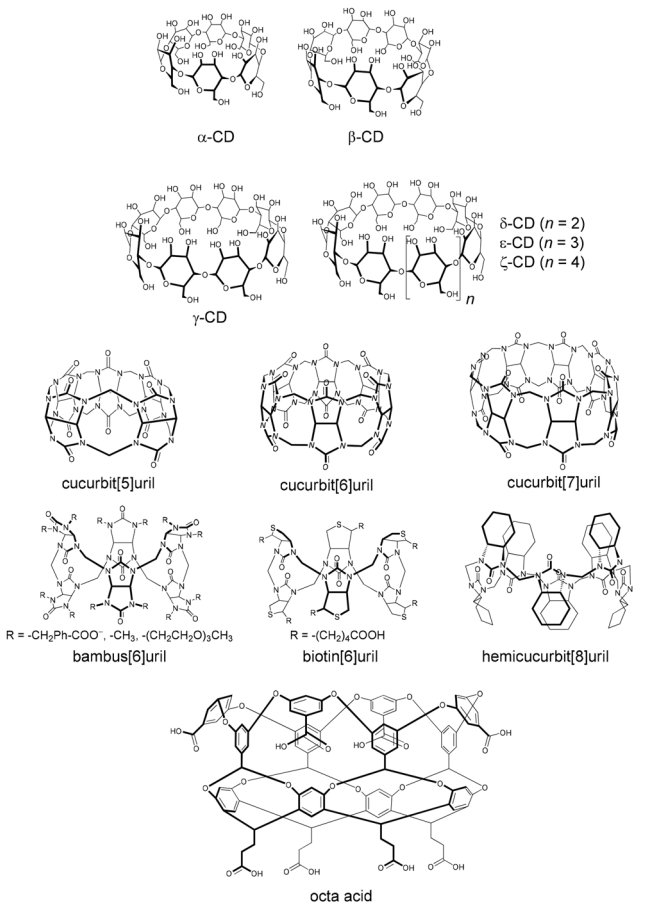

Fig. 1 Chemical structures of macrocyclic receptors with sizable affinity to large anions in aqueous solution.

The first qualitative observation for the binding of a large anion, namely I^-, by α-CD was made by Schlenk and Sand 60 years back.[5] Soon after that, the first binding constant (K_a) between ClO_4^- and α-CD was determined by Cramer *et al.*, who found that this large anion competed with the binding of 4-nitrophenolate.[55] This binding could be readily followed by optical titration through the color change of the organic guest, incidentally also setting up the putative first example for an indicator displacement assay in host–guest chemistry. The binding was sizable for an inorganic anion (K_a = 29 M^{-1}), but insufficiently high to draw attention at that time. Cramer also established the binding of NO_3^- with α-CD, while no binding was observed for SO_4^{2-} and PO_4^{3-}.[55] Several subsequent studies showed that α-CD also binds many other anions, such as PF_6^-, I_3^-, and SCN^-, with a sizable binding affinity,[56–59] while for anions such as F^-, Cl^-, and Br^-, the affinity was very low, if at all detectable.[60,61] In addition, the next larger homologous host, β-CD, also displayed a sizable but lower affinity to large anions.[6,8] The study by Wojcik and Rohrbach from 1975 reported a range of 10–29 M^{-1} for the binding of SCN^-, I^-, and ClO_4^- to α-CD. Matsui *et al.* used NMR spectroscopy to study the complexation-induced chemical shifts of the CD protons (including α-, β-, and γ-CD) for different anions,[52] which again revealed a preferential binding of certain anions (N_3^-, I^-, SCN^-, and ClO_4^-), with the most stable inclusion complexes being observed with α-CD. In contrast, anions such as F^-, HCO_3^-, $H_2PO_4^-$, HPO_4^{2-}, and SO_4^{2-} showed no or negligible changes in the chemical shifts. Similarly, Taraszewska and Wójcik studied systematically the complexation of inorganic anions with β-CD.[8] Although the reported association constants of the anions were lower (<9 M^{-1}) than for α-CD (up to 29 M^{-1}), the weakly hydrated anions showed stronger binding than strongly hydrated ones (such as PO_4^{3-}), Table 1.

The original study by Cramer *et al.* did not allude to the factors responsible for the large anion binding by CDs. Subsequently, through the investigation of a series of different anions, an empirical relationship between their binding affinities and their chaotropic (water-structure breaking) character emerged.[8,52,58] Wojcik and Rohrbach related the trend in binding constants of anions to their B^- viscosity coefficient,[58] a coefficient of the linear term of the concentration-dependence of proton relaxation rates, which has later become an accepted parameter for the water-structural entropic properties (chaotropicity) of ions.[62,63] A linear correlation between the binding constants[58] of the anions and their B^- coefficient was established. Matsui *et al.* explicitly interpreted the differential binding of anions to CDs in terms of their chaotropic or "anti-chaotropic" character,[52] a qualification which has later been replaced by the term "kosmotropic", but a detailed interpretation in terms of the underlying intermolecular interactions remained elusive. Similarly, Taraszewska and Wójcik studied systematically the complexation of inorganic anions with β-CD[8] and related the magnitude of their affinities to their position in the Hofmeister series as well.

The higher binding affinity of the anions to CDs is also related to the size/shape complementarity, which is reflected

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Table 1 Association constants (K_a) of selected large anions to water-soluble macrocycles in aqueous solution, sorted according to the anion size and grouped according to the type of macrocycle; see Fig. 1

Host	Anion	Radius[a]/pm	$K_a \times 10^3/M^{-1}$	Technique[b]	Year[c]	Ref.
α-CD[j]	Br^-	196	0.01	NMR	1993	98
α-CD[j]	NO_3^-	200	0.02	NMR	1993	98
α-CD	SCN^-	213	0.03[d]	NMR, cond., calor.	1975	7, 52, 53, 56 and 58
α-CD[j]	SCN^-	213	0.36	NMR	1993	98
α-CD	I^-	220	0.02[d]	NMR, cond., calor.	1967	7, 52, 53, 55, 56, 58 and 60
α-CD[j]	I^-	220	0.20	NMR	1993	98
α-CD	ClO_4^-	240	0.04[d]	NMR, cond., calor.	1967	7, 52, 53, 55–58, 61 and 82
α-CD[j]	ClO_4^-	240	0.33	NMR	1993	98
α-CD	$CF_3SO_3^-$	255[e]	0.04	Calor. and optical	1996	57
α-CD	I_3^-	285	270[d]	Electr.	1947	64 and 99–101
α-CD	PF_6^-	295	0.04	Calor. and optical	1996	57
α-CD[i]	$Fe(CN)_6^{4-}$	343	300	Electr.	1996	102
α-CD[i]	$Fe(CN)_6^{3-}$	380	2	Electr.	1996	102
α-CD	$B_{10}H_{10}^{2-}$	393[f]	0.04	NMR	2019	37
α-CD	$B_{12}H_{12}^{2-}$	400[f]	0.1	NMR	2015	14
α-CD	$Re_6S_8(CN)_6^{4-}$	580[g]	0.73	ITC	2019	81
α-CD	$Re_6Se_8(CN)_6^{4-}$	590[g]	0.03	ITC	2019	81
α-CD	$Re_6Te_8(CN)_6^{4-}$	600[g]	—[h]	ITC	2019	81
β-CD	SCN^-	213	0.01[d]	Cond., NMR, calor.,	1975	6–8, 52, 56 and 58
β-CD	I^-	220	0.01[d]	Cond., NMR, optical	1977	7, 52, 56 and 103
β-CD[l]	I^-	220	0.04	NMR	1993	98
β-CD	ClO_4^-	240	0.01[d]	NMR, calor., optical	1977	6–8, 52, 56, 57 and 103
β-CD	$CF_3SO_3^-$	255	0.06	Calor.	1996	57
β-CD	I_3^-	285	3.03	Electr.	1947	99, 100 and 64
β-CD	PF_6^-	295	0.09	Calor.	1996	57
β-CD[m]	$Fe(CN)_6^{4-}$	343	800	Electr.	1996	102
β-CD[m]	$Fe(CN)_6^{3-}$	380	4	Electr.	1996	102
β-CD	$B_{10}H_{10}^{2-}$	393[f]	0.11	NMR	2019	37
β-CD	$B_{12}H_{12}^{2-}$	400[f]	0.2	NMR	2015	14
β-CD	Ph_4B^-	425[e]	0.01	Electrophoresis	2001	104
β-CD	$B_{21}H_{18}^-$	425[k]	130	ITC	2020	85
β-CD	$Re_6S_8(CN)_6^{4-}$	580[g]	0.88	ITC	2019	81
β-CD	COSAN-1	583[k]	26	ITC	2019	35
β-CD	COSAN-2	583[k]	710	ITC	2019	35
β-CD	COSAN-3	583[k]	21	ITC	2019	35
β-CD	COSAN-4	583[k]	19	ITC	2019	35
β-CD	COSAN-5	583[k]	24	ITC	2019	35
β-CD	COSAN-6	583[k]	38	ITC	2019	35
β-CD	COSAN-7	583[k]	180	ITC	2019	35
β-CD	COSAN-8	583[k]	55	ITC	2019	35
β-CD	COSAN-9	583[k]	59	ITC	2019	35
β-CD	$Re_6Se_8(CN)_6^{4-}$	590[g]	0.75	ITC	2019	81
β-CD	$Re_6Te_8(CN)_6^{4-}$	600[g]	0.08	ITC	2019	81
β-CD	$PMO_{12}O_{40}^{3-}$	692[f]	2	ITC	2015	46
γ-CD	SCN^-	213	4.1	NMR	1997	52
γ-CD	I^-	220	4.9	NMR	1997	52
γ-CD[o]	I^-	220	0.02	NMR	1993	98
γ-CD	I_3^-	285	0.5	Electr.	1985	64
γ-CD[p]	$Fe(CN)_6^{4-}$	343	1000	Electr.	1996	102
γ-CD[p]	$Fe(CN)_6^{3-}$	380	5	Electr.	1996	102
γ-CD	$B_{10}H_{10}^{2-}$	393[f]	0.06	NMR	2019	37
γ-CD	$B_{12}H_{12}S^{2-}$	400[f]	9.2	ITC	2015	14
γ-CD	Ph_4B^-	425[e]	108	Electrophoresis	2001	104
γ-CD	$B_{21}H_{18}^-$	425[k]	1800	ITC	2020	85
γ-CD	$H_3NB_{10}Cl_9^-$	500[k]	5.9	ITC	2019	36
γ-CD	$Me_3NB_{10}Cl_9^-$	500[k]	77	ITC	2019	36
γ-CD	$B_{12}Cl_{12}^{2-}$	525	17	ITC	2015	14
γ-CD	$H_3NB_{10}Br_9^-$	530[k]	2.4	ITC	2019	36
γ-CD	$Mr_3NB_{10}Br_9^-$	530[k]	430	ITC	2019	36
γ-CD	$Me_3NB_{10}I_9^-$	558[k]	78	ITC	2019	36
γ-CD	$H_3NB_{10}I_9^-$	558[k]	3.8	ITC	2019	36
γ-CD	$B_{12}Br_{12}^{2-}$	560[f]	960	ITC	2015	14
γ-CD	$Re_6S_8(CN)_6^{4-}$	580[g]	0.9	ITC	2018	83
γ-CD	COSAN-1	583[k]	191	ITC	2019	35
γ-CD	COSAN-2	583[k]	3000	ITC	2019	35
γ-CD	COSAN-3	583[k]	300	ITC	2019	35
γ-CD	COSAN-4	583[k]	3600, 90[n]	ITC	2019	35

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Table 1 *(Contd.)*

Host	Anion	Radius[a]/pm	$K_a \times 10^3/M^{-1}$	Technique[b]	Year[c]	Ref.
γ-CD	COSAN-5	583[k]	1300	ITC	2019	35
γ-CD	COSAN-6	583[k]	6, 8000[n]	ITC	2019	35
γ-CD	COSAN-7	583[k]	72	ITC	2019	35
γ-CD	COSAN-8	583[k]	12	ITC	2019	35
γ-CD	COSAN-9	583[k]	720	ITC	2019	35
γ-CD	$H_2W_{12}O_{40}^{6-}$	590[g]	0.02	NMR	2021	93
γ-CD	$BW_{12}O_{40}^{5-}$	590[g]	1.03	ITC	2021	93
γ-CD	$SiW_{12}O_{40}^{4-}$	590[g]	17.2, 0.56[n]	ITC	2021	93
γ-CD	$PW_{12}O_{40}^{3-}$	590[g]	2.92	ITC	2021	93
γ-CD	$SiW_{11}MoO_{40}^{4-}$	590[g]	17.7, 0.371[n]	ITC	2021	94
γ-CD	$PW_{11}VO_{40}^{4-}$	590[g]	8.5, 0.22[n]	ITC	2021	94
γ-CD	$PW_{11}VO_{40}^{5-}$	590[g]	0.164	ITC	2021	94
γ-CD	$SiW_{11}MoO_{40}^{5-}$	590[g]	0.478	ITC	2021	94
γ-CD	$SiW_{11}VO_{40}^{5-}$	590[g]	0.618	ITC	2021	94
γ-CD	$SiW_{11}VO_{40}^{6-}$	590[g]	—[h]	ITC	2021	94
γ-CD	$SiW_{11}MoO_{40}^{6-}$	590[g]	—[h]	ITC	2021	94
γ-CD	$Re_6Se_8(CN)_6^{4-}$	590[g]	1.5, 13[n]	ITC	2018	83
γ-CD	$B_{12}I_{12}^{2-}$	590[f]	67	ITC	2015	14
γ-CD	$Re_6Te_8(CN)_6^{4-}$	600[g]	38, 13[n]	ITC	2018	83
γ-CD	$PMO_{12}O_{40}^{3-}$	692[f]	40, 1[n]	ITC	2015	46
γ-CD	$P_2W_{18}O_{62}^{6-}$	701[f]	3.2, 0.37[n]	ITC	2017	25
δ-CD	$B_{12}Cl_{12}^{2-}$	525[f]	2500	ITC	2016	44
δ-CD	$B_{12}Br_{12}^{2-}$	560[f]	2600	ITC	2016	44
δ-CD	$B_{12}I_{12}^{2-}$	590[f]	67	ITC	2016	44
ε-CD	$B_{12}Cl_{12}^{2-}$	525[f]	29	ITC	2016	44
ε-CD	$B_{12}Br_{12}^{2-}$	560[f]	140	ITC	2016	44
ε-CD	$B_{12}I_{12}^{2-}$	590[f]	2100	ITC	2016	44
ζ-CD	$B_{12}Cl_{12}^{2-}$	525[f]	2	ITC	2016	44
ζ-CD	$B_{12}Br_{12}^{2-}$	560[f]	6	ITC	2016	44
ζ-CD	$B_{12}I_{12}^{2-}$	590[f]	8	ITC	2016	44
Bambusuril[q]	F^-	133	0.1	NMR	2015	45
Bambusuril[q]	F^-	133	0.01	ITC	2015	45
Bambusuril[q]	Cl^-	181	0.91	NMR	2015	45
Bambusuril[q]	Cl^-	181	0.4	ITC	2015	45
Bambusuril[q]	CN^-	191	1.1	NMR	2015	45
Bambusuril[q]	Br^-	196	140	NMR	2015	45
Bambusuril[q]	Br^-	196	33	ITC	2015	45
Bambusuril[q]	NO_3^-	200	480	NMR	2015	45
Bambusuril[q]	I^-	220	10 000	NMR	2015	45
Bambusuril[q]	I^-	220	2000	ITC	2015	45
Bambusuril[q]	BF_4^-	230	4300	NMR	2015	45
Bambusuril[q]	ClO_4^-	240	55 000	NMR	2015	45
Bambusuril[q]	IO_4^-	250	6.5	NMR	2015	45
Bambusuril[q]	ReO_4^-	260	30	NMR	2015	45
Bambusuril[q]	PF_6^-	295	2200	NMR	2015	45
Bambusuril[r]	Cl^-	181	1.2	ITC	2022	77
Bambusuril[r]	CN^-	191	21	NMR	2022	77
Bambusuril[r]	N_3^-	195	21	ITC	2022	77
Bambusuril[r]	Br^-	196	120	ITC	2022	77
Bambusuril[r]	NO_3^-	200	330	ITC	2022	77
Bambusuril[r]	SCN^-	213	1200	ITC	2022	77
Bambusuril[r]	I^-	220	32 000	ITC	2022	77
Bambusuril[r]	$SeCN^-$	229[e]	2800	ITC	2022	77
Bambusuril[r]	BF_4^-	230	1300	ITC	2022	77
Bambusuril[r]	ClO_4^-	240	47 000	ITC	2022	77
Bambusuril[r]	IO_4^-	250	56	ITC	2022	77
Bambusuril[r]	ReO_4^-	260	470	ITC	2022	77
Bambusuril[r]	PF_6^-	295	1600	ITC	2022	77
Bambusuril[r]	$[Au(CN)_2]^-$	320	1300	ITC	2022	77
Bambusuril[r]	$[Ag(CN)_2]^-$	330	13	ITC	2022	77
Biotin[6]uril	Cl^-	181	0.06	NMR	2015	47
Biotin[6]uril	Cl^-	181	0.03	ITC	2015	47
Biotin[6]uril	N_3^-	195	0.79	NMR	2015	47
Biotin[6]uril	N_3^-	195	0.4	ITC	2015	47

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Table 1 *(Contd.)*

Host	Anion	Radius[a]/pm	$K_a \times 10^3/M^{-1}$	Technique[b]	Year[c]	Ref.
Biotin[6]uril	Br^-	196	1	NMR	2015	47
Biotin[6]uril	Br^-	196	0.5	ITC	2015	47
Biotin[6]uril	NO_3^-	200	0.08	NMR	2015	47
Biotin[6]uril	NO_3^-	200	0.05	ITC	2015	47
Biotin[6]uril	CNO^-	203	0.01	NMR	2015	47
Biotin[6]uril	CNO^-	203	0.06	ITC	2015	47
Biotin[6]uril	SCN^-	213	32	NMR	2015	47
Biotin[6]uril	SCN^-	213	13	ITC	2015	47
Biotin[6]uril	I^-	220	4[d]	NMR	2015	47
Biotin[6]uril	I^-	220	2.5	ITC	2015	47
Biotin[6]uril	$SeCN^-$	229[e]	20	NMR	2015	47
Biotin[6]uril	$SeCN^-$	229[e]	10	ITC	2015	47
Biotin[6]uril	ClO_4^-	240	0.5	NMR	2015	47
Biotin[6]uril	ClO_4^-	240	0.25	ITC	2015	47
Octa acid	NO_3^-	200	<0.01	NMR	2011	66
Octa acid	SCN^-	213	0.03	NMR	2011	66
Octa acid	SCN^-	213	0.04	ITC	2016	105
Octa acid	ClO_3^-	220[e]	<0.01	NMR	2011	66
Octa acid	I^-	220	0.01	NMR	2011	66
Octa acid	I^-	220	0.02	ITC	2016	105
Octa acid	BH_3CN^-	225[e]	0.15	ITC	2016	105
Octa acid	ClO_4^-	240	0.10	NMR	2011	66
Octa acid	ClO_4^-	240	0.1	ITC	2016	105
Octa acid	$N(CN)_2^-$	240[e]	0.04	ITC	2016	105
Octa acid	IO_4^-	250	0.24	ITC	2016	105
Octa acid	$CF_3SO_3^-$	255[e]	0.31	ITC	2016	105
Octa acid	$CH_3SO_2S^-$	260[e]	0.66	ITC	2016	105
Octa acid	ReO_4^-	260	0.37	ITC	2016	105
Octa acid	$Cl_2CHCO_2^-$	270[e]	0.05	ITC	2016	105
Octa acid	$Cl_3CCO_2^-$	283[e]	6.34	ITC	2016	105
Octa acid	PF_6^-	295	0.79	ITC	2016	105

[a] Taken from ref. 106 and 107. [b] The applied techniques for the determination of association constants are abbreviated as follows: cond. stands for conductometric titration; NMR stands for ^{1}H NMR titration; calor. stands for calorimetry titration; optical stands for competitive optical titration (UV-Vis or fluorescence spectroscopy); electr. stands for electrochemical (potentiometric) titration; and ITC stands for isothermal titration calorimetry. [c] Year refers to the first report. [d] Given as an averaged value from different reports. [e] Approximate values based on the calculated molecular volume using HyperChem(TM) Professional 8.0 software,[108] with the assumption of a spherical shape from which the radius was obtained. [f] From ref. 18. [g] Calculated from the diameters obtained from XRD structures. [h] Very weak binding; K_a was not determined. [i] Hexakis(6-deoxy-6-amino-)-α-CD. [j] Mono[6-(1-pyridinio)-6-deoxy]-α-CD. [k] Values correspond to the cluster core; calculated from the diameters obtained from the geometry-optimized structures. [l] Mono[6-(1-pyridinio)-6-deoxy]-β-CD. [m] Heptakis(6-deoxy-6-amino-)-β-CD. [n] 1 : 2 host–guest complexation was reported. [o] Mono[6-(1-pyridinio)-6-deoxy]-γ-CD. [p] Octakis(6-deoxy-6-amino)-γ-CD. [q] Functionalized bambusuril with R = $-CH_2Ph-COO^-$, see Fig. 1. [r] Functionalized bambusuril with R = $-(CH_2CH_2O)_3CH_3$, see Fig. 1.

in the higher affinity of the large anions (I^-, SCN^-, and ClO_4^-),[52] because only those are able to fill the hydrophobic cavity to a significant extent. The binding constant of I_3^- decreased from α- to β- to γ-CD.[64] Due to the large cavity size of γ-CD, only few examples of the binding of classical anions by this host have been reported.[52,64] A summary of anion binding to CDs is shown in Table 1, which clearly indicates that the binding affinity of anions to CDs increases with the chaotropicity/size of the anions. However, even though independent correlations between the binding affinities of inorganic anions with CDs and their chaotropicity became apparent, the unusual affinity pattern received little attention, presumably because the absolute binding affinities were too small to have major practical implications.

While studying Hofmeister effects on the binding of an organic guest (adamantanecarboxylate) with an aromatic host (octa acid, Fig. 1),[65,66] it eventually emerged that large anions, *e.g.* ClO_4^-, showed also sizable binding to this macrocycle (95 M^{-1}).[66,67] The chaotropic anion competed with the binding of adamantanecarboxylate in the same manner as Cramer had previously observed for the 4-nitrophenolate-α-CD couple.[55] The binding affinity of adamantane carboxylic acid to octa acid was found to slightly increase in the presence of kosmotropic anions such as F^-, an observation which was linked to the enhanced hydrophobic effect caused by the presence of such anions. In contrast, chaotropic anions such as SCN^- and ClO_4^- lowered the binding affinity of adamantane carboxylic acid, which was attributed to the ability of chaotropic anions to weaken the hydrophobic effect and, thereby, the competition with the hydrophobic guest for the hydrophobic cavity of octa acid.[66] Although the driving force for ClO_4^- binding was not discussed, it transpired that the phenomenon of large anion binding to hydrophobic pockets was more general and not limited to CDs.[68] One tentative explanation involved the presence of high-energy water inside these hosts, which could account for an "intrinsic" driving force that would drive the encapsulation process regardless of the precise chemical nature or the charge status of a suitably sized spheri-

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cal guest.[69,70] In 2010, upon successful synthesis of a new macrocyclic host derived from a glycoluril derivative through an acid condensation reaction with formaldehyde, Sindelar and co-workers noticed by X-ray diffraction of the obtained hexamer receptor (bambusuril, Fig. 1) that the cavity of this molecular container accommodated a Cl^- ion.[71] The macrocycle was later intensively investigated for its binding to halides with high affinity and selectivity (see below).[38,39,72–77]

Recent developments in large anion binding and mechanistic interpretations (after 2015)

The tentative idea that the release of high-energy water from the macrocycles presents the major driving force for the complexation of large anions needed to be abandoned in 2015 when an exceptionally strong binding of several large anions to different macrocycles (Fig. 1) was established by several research groups.[14,45–47] The affinities reached micromolar values and rivaled, *e.g.* for CDs,[14] the affinities of hydrophobic guests, which until then had been considered as the tightest binding motifs.[15,78,79]

Besides classical large anions with chaotropic character such as I^-, PF_6^-, and ClO_4^-, which showed much stronger binding to bambusuril and biotinuril than to CDs,[45,47] two classes of very large, highly charged, synthetic anions, namely boron clusters and polyoxometalates (Fig. 2), were found to complex very strongly to γ-CD[14,25,26,35–37,40,46,80] as well as to the larger homologues (ε-CD, δ-CD, and ζ-CD,[44] see Fig. 1). In the course of two independent investigations, it turned out, by employing classical Hofmeister salting-in[14] and cloud point measurements,[21,23] that the large cluster anions behave as superchaotropic anions which expand the Hofmeister series to the chaotropic side and which outperform classical chaotropic anions such as ClO_4^- in regard to their salting-in properties.[21]

While it became apparent that the binding strength to the hydrophobic cavity increased with the chaotropicity of the anion (up to the turning point where the anion size largely exceeded the cavity size),[14,44,81] the underlying driving forces remained more difficult to pinpoint. A first hint came from the thermochemical signature of the binding process, which showed that the binding of the superchaotropic anions is enthalpically driven.[14] In retrospect, one of the first studies that pointed to an enthalpic driving force for the complexation of large inorganic anions by macrocycles was published in 1973, in which the binding of ClO_4^- to α-CD had shown a favorable enthalpic contribution of −9.7 kcal mol^{-1} and an unfavorable entropy.[82] Similar signatures were reported on several occasions.[52,56,57]

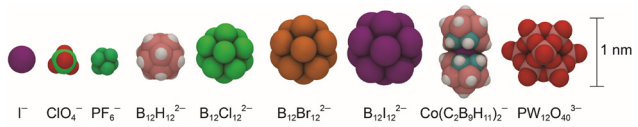

Fig. 2 Molecular structures and size comparison of large (chaotropic) anions with sizable binding affinity to macrocyclic receptors in water.

The effect became very pronounced when large anions were investigated.[14,25,44,83] For example, the thermochemical trend was also observed for the complexation of dodecaborate anions with CDs, and it was for the first time linked to their chaotropic character; the generic driving force was accordingly referred to as the chaotropic effect, to differentiate from the entropically driven (classical) hydrophobic effect.[14,44] Following the theory of Marcus for the aqueous solvation of ions, the large favorable enthalpy and unfavorable entropy were related to water structure recovery upon the relocation of the anion into the cavity as well as to the dispersion interaction between the highly polarizable guests and the cavity walls. Roughly speaking, the larger and more polarizable an anion, the lower its charge density, and the better delocalized its charge, the higher its chaotropicity (Fig. 2), until a turning point, when an ion adopts more hydrophobic ionic character (such as BPh_4^-) on a continuous scale of aqueous solvation.[18]

Cyclodextrins as receptors for boron cluster anions

Dodecaborate anions of the type $B_{12}X_{12}^{2-}$ (X: H, Cl, Br, and I, Fig. 2) form stable complexes with CDs, in particular with γ-CD, in aqueous solution,[14] as reflected in their high binding affinities (*e.g.*, *ca.* 10^6 M^{-1} for $B_{12}Br_{12}^{2-}$ with γ-CD, see Table 1 for the binding affinity of other clusters).[14] The single-crystal X-ray structure of the $B_{12}Br_{12}^{2-}$/γ-CD complex is shown in Fig. 3a. Although the chaotropic effect has in common with the hydrophobic effect that the involved guests are weakly hydrated, they are conceptually distinct in that chaotropic anions interfere differently with the solvation-shell water structure than the hydrophobic species do. The contrasting solvation behavior is borne out by the diametrically opposed thermodynamic fingerprints of boron cluster anions *versus* hydrophobic residues.[18] Since chaotropic agents are thought to "break" the water structure in the solvation shell (as assessed through large positive water-structural contributions to the hydration entropy), one may argue that their relocation into the hydrophobic cavity is not characterized by the positive entropic dehydration component characteristic of the hydro-

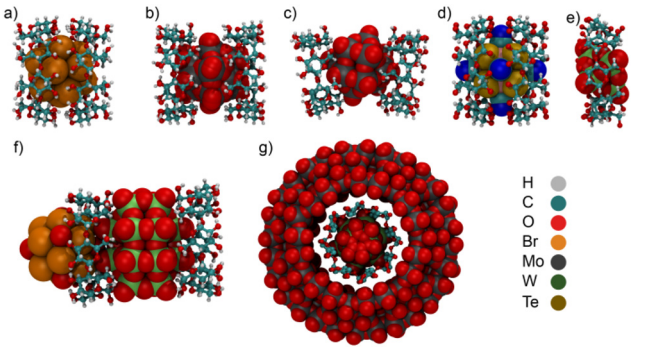

Fig. 3 Single-crystal X-ray structures of different superchaotropic anion complexes with CDs. (a) γ-CD/$B_{12}Br_{12}^{2-}$, (b) γ-CD/$PMO_{12}O_{40}^{3-}$, (c) β-CD/$PMO_{12}O_{40}^{3-}$, (d) γ-CD/$Re_6Te_8(CN)_6^{4-}$, (e) γ-CD/$M_6O_{19}^{2-}$, (f) γ-CD/$P_2W_{18}O_{62}^{6-}$/$[Ta_6Br_{12}(H_2O)_6]^{2+}$, and (g) γ-CD/$[Mo_{154}O_{462}H_{14}(H_2O)_{70}]^{14-}$/$P_2W_{18}O_{62}^{6-}$.

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phobic effect, but rather by a strongly negative enthalpic one. High binding affinities of boron cluster anions have also been obtained for large-ring CDs (δ-, ε-, and ζ-CD).[84] For example, the binding affinity of $B_{12}Br_{12}^{2-}$ with δ-CD (2.60×10^6 *versus* 0.96×10^6 M^{-1}) even exceeded that with γ-CD, while $B_{12}I_{12}^{2-}$ was found to strongly associate with the large ζ-CD cavity, with $K_a = 2.1 \times 10^6$ M^{-1}, Table 1.[44] A weaker binding affinity was obtained for the smaller $B_{10}H_{10}^{2-}$ cluster with CDs,[37] while the binding affinity of the larger $B_{21}H_{18}^{-}$ cluster to CDs exceeded that of $B_{12}Br_{12}^{2-}$.[85] Other boron cluster anions of the type $[H_3NB_{10}X_9]^-$ and $[Me_3NB_{10}X_9]^-$ also showed sizable binding affinity to γ-CD. The complexation of the mono-anionic ammonium-substituted decaborate derivatives with γ-CD was, however, in general weaker than that of the di-anionic dodecaborate clusters (Table 1).[36] The variation of binding constants pointed to an interesting structure–activity relationship.

Very recently, metallacarboranes, another class of sandwich inorganic boron clusters, have been found to form stable complexes with CDs in aqueous solution.[35] Cobalt bis(1,2-dicarbollide) and its derivatives (COSANs, Fig. 4), as mono-anionic clusters, associate strongly with the cavity of β- and γ-CD, Table 1.[35] The complexation of COSANs with CDs was investigated by NMR and UV–visible spectroscopy, as well as mass spectrometry, all of which confirmed the strong binding. Isothermal titration calorimetry (ITC) revealed high association constants up to 10^6 M^{-1}.[35] The interaction between COSAN and the glucose moiety has also been studied in the context of biopolymeric interactions,[86] and they were found to bind to cationic peptides, which enables their use as membrane carriers.[87] Recently, the ability of COSANs to solubilize hydrophobic substances in water has been reported.[88] At first sight, this mimics the "salting-in" feature known for chaotropic and superchaotropic ions,[14] but the mechanism turned out to be more involved in this case.

Cyclodextrins as receptors for polyoxometalates and related inorganic cluster anions

In 2015, Stoddart and co-workers investigated the complexation of polyoxometalates with CDs.[46] The binding of

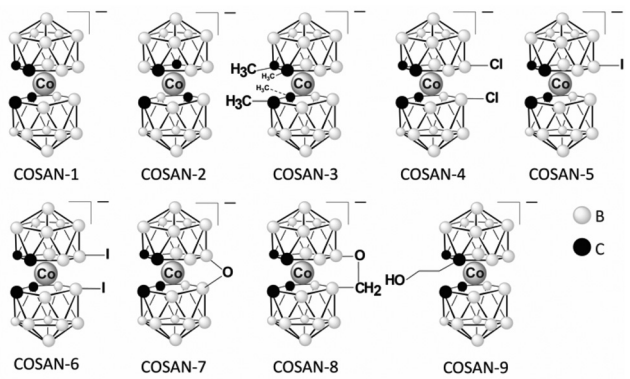

Fig. 4 Chemical structures of cobalt bis(1,2-dicarbollide) anions, which form stable complexes with β- and γ-CD in aqueous solution; valencies are saturated with hydrogens (B–H or C–H) unless substituents are shown explicitly.

$PMO_{12}O_{40}^{3-}$ with β- and γ-CD was established in solution and in the solid state. ^{1}H NMR experiments confirmed the formation of inclusion complexes, in 1 : 1 and 2 : 1 host–guest stoichiometry with β- and γ-CD, respectively. The association constants were measured by ITC. The obtained binding affinity with β-CD was found to be 2×10^3 M^{-1}, while the two-step sequential binding fitting for the complexation with γ-CD resulted in $K_{a1} = 4 \times 10^4$ and $K_{a2} = 1 \times 10^3$ M^{-1}.[46] The crystal structures of the $PMO_{12}O_{40}^{3-}$ complexes with γ-CD and β-CD are shown in Fig. 3b and 3c. The complexation of $PMO_{12}O_{40}^{3-}$ with (chiral) CDs was recognized to induce chirality of the encapsulated cluster in aqueous solution.[89]

Three-component organic–inorganic systems were constructed based on the supramolecular interaction between γ-CD and the Dawson-type polyoxometalate, $P_2W_{18}O_{62}^{6-}$, and a cationic cluster $[Ta_6Br_{12}(H_2O)_6]^{2+}$.[25] X-ray analysis (Fig. 3f) revealed that the cationic cluster is trapped between two CD units, while the anionic cluster facilitates the assembly by linking the CD units from the narrow rim.[25] A two-site binding model was used to analyse the ITC data, Table 1. The $P_2W_{18}O_{62}^{6-}$ anion afforded association constants of 3.2×10^3 and 3.7×10^2 M^{-1} for the 1 : 1 and 2 : 1 host–guest stoichiometries, respectively. Higher affinity values were obtained for the inclusion complexes of the cationic cluster, 1.5×10^5 M^{-1} for the 1 : 1 and 1.3×10^5 M^{-1} for the 2 : 1 host–guest stoichiometry. In a similar manner, hierarchical architectures were prepared by using γ-CD as a host in combination with the metallic cationic cluster $[\{Re_6Se_8\}(H_2O)_6]^{2+}$ as well as the anionic ones $[\{Re_6Se_8\}(CN)_6]^{4-}$ and $P_2W_{18}O_{62}^{6-}$.[90] The solid-state structures of the ternary assemblies indicated that two γ-CD units interact with $P_2W_{18}O_{62}^{6-}$ through the primary rim (partial inclusion), while the $[\{Re_6Se_8\}(H_2O)_6]^{2+}$ cluster is positioned at the secondary rim. For the anionic $[\{Re_6Se_8\}(CN)_6]^{4-}$ cluster, a 2 : 1 host–guest inclusion complex is formed, in which the cluster remains entrapped within two γ-CD units facing each other from the wider rims, while the polyoxometalate acts as a linker that connects the CD units through the association with the outer surface.[90] Another three-component hybrid assembly of the $[Mo_{154}O_{462}H_{14}(H_2O)_{70}]^{14-}$ molecular wheel (Mo_{154}) encapsulating a sandwich-type complex between $P_2W_{18}O_{62}^{6-}$ and two γ-CDs was reported (Fig. 3g), which revealed the association of these large anions with CDs in aqueous solution by NMR and solid-state structural analysis.[26]

Water-soluble salts of anionic chalcogenide octahedral rhenium clusters ($Re_6X_8(CN)_6^{4-}$, X = S, Se, Te) form stable inclusion complexes with CDs in aqueous solution.[81,83,91] A partial inclusion of the large anions was obtained for $Re_6X_8(CN)_6^{4-}$ with α- and β-CD, while deeper inclusion complexes were observed with γ-CD.[81,83] In the case of α-CD, only the $Re_6S_8(CN)_6^{4-}$ anion was found to be complexed between two CD units near the secondary rim. The $Re_6X_8(CN)_6^{4-}$ anions are partially embedded between the β-CD rings through their primary rims. Similar to the single-crystal structure of $B_{12}Br_{12}^{2-}$/γ-CD, the $Re_6Se_8(CN)_6^{4-}$ and $Re_6Te_8(CN)_6^{4-}$ clusters were entrapped between two γ-CD rings (Fig. 3d), while the smallest anion, $Re_6S_8(CN)_6^{4-}$, formed a partial inclusion

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complex with γ-CD, in which the anion interacts with the secondary rims of γ-CD. In ^{1}H NMR aqueous-solution spectra, the complexation-induced chemical shifts confirmed the formation of inclusion complexes, as indicated by the large downfield shifts of the inner protons of γ-CD. In addition, ^{77}Se and ^{125}Te NMR experiments supported the complexation pattern in solution. The binding affinities of the anions to γ-CD were determined using ITC experiments, which showed that the complexation is enthalpically driven, in agreement with the chaotropic effect.[83] With the smallest CD homologue, α-CD, only the smallest cluster, $Re_6S_8(CN)_6^{4-}$, showed a sizable 1 : 1 binding affinity of 730 M^{-1}. The larger clusters showed much weaker binding affinity to α-CD. The complexation of the three clusters to β-CD showed size complementarity, that is, the binding constants decreased with increasing size of the cluster, Table 1.[81] The affinity of $Re_6S_8(CN)_6^{4-}$ to β-CD (K_a = 900 M^{-1}) was slightly higher than that to α-CD. Interestingly, the oxidized form of the rhenium cluster showed higher affinity to β-CD ($K_{a1:1}$ = 2.3 × 10^5 M^{-1}) compared to the parent one.[91] This difference in binding affinity can be attributed to the higher chaotropicity of the oxidized form ($Re_6S_8(CN)_6^{3-}$), induced by its lower charge density.[91] Most recently, Leclerc *et al.* reported the formation of a 1 : 1 exclusion complex between γ-CD and a Preyssler-type anion, $[NaP_5W_{30}O_{110}]^{14-}$.[92] The large and highly charged anion interacts with the primary face of the γ-CD as revealed by single-crystal X-ray diffraction and ^{1}H NMR experiments.

Structural analysis in the solid-state indicated the formation of 1 : 1 inclusion complexes between Lindqvist $M_6O_{19}^{2-}$ ions and γ-CD (Fig. 3f), in which the anion is encapsulated inside the cavity. ^{1}H NMR analysis also confirmed the complexation.[80] Very recently, Yao *et al.* studied the complexation of Keggin-type polyoxotungstate anions with γ-CD in aqueous solution.[93] Despite the fact that the investigated anions have similar structure and size, their binding affinity to γ-CD was found to decrease with increasing charge density on the anions, following the order $H_2W_{12}O_{40}^{6-}$ < $BW_{12}O_{40}^{5-}$ < $SiW_{12}O_{40}^{4-}$ < $PW_{12}O_{40}^{3-}$.[93] Similarly, the host–guest complexation of $[XW_{11}MO_{40}]^{n-}$ Keggin-type anions (X = P or Si and M = $Mo^{V/VI}$ or $V^{IV/V}$) by γ-CD, in which the anionic net charge can vary from 3− to 6−, indicated that the binding affinity is highest for the anion with lower charge density.[94] Such trends can be directly related to the variation of their chaotropicity, which decreases with increasing charge.[18] γ-CD was also found to form host–guest complexes with metal chloride clusters ($[M_6Cl_{14}]^{2-}$, M = Mo and W).[95]

The cationic cluster, $[Nb_6Cl_{12}(H_2O)_6]^{2+}$, binds to γ-CD with an association constant of 2.2 × 10^3 M^{-1} in water.[96] Despite its cationic nature, the complexation thermodynamics showed a large favorable enthalpic energy gain counterbalanced by a strong entropic penalty, a trend that is similar to the binding of superchaotropic anions, and which is consistent with the chaotropic effect. Cationic palladium(II)-oxo clusters, $[Pd_6^{II}O_{12}M_8\{(CH_3)_2AsO_2\}_{16}(H_2O)_8]^{4+}$ (M = Ce^{IV} and Th^{IV}), have been recently synthesized and showed strong binding affinity (K_a > 10^5 M^{-1}) to negatively charged macrocyclic hosts, namely 4-sulfonatocalix[*n*]arenes (*n* = 4, 6, and 8).[97] The binding events were again enthalpically driven. This observation may allow the classification of such large cations (*e.g.* $[\{Re_6Se_8\}(H_2O)_6]^{2+}$, $[Nb_6Cl_{12}(H_2O)_6]^{2+}$, and $[Ta_6Br_{12}(H_2O)_6]^{2+}$) as being superchaotropic in nature, thereby constituting the first examples of the area of "large cation binding in water" that is not further scrutinized here.

Cucurbiturils, bambusurils, and biotinurils

Cucurbit[*n*]urils, Fig. 1, are water-soluble macrocyclic host molecules that are known for their high binding affinity towards cationic and neutral guest molecules, Fig. 1.[109–111] Their cavity is classified as hydrophobic and it is accessible through two identical carbonyl rims. Examples of the encapsulation of anions inside CBs are rare,[112–119] which can be attributed to the high barrier required to cross the negatively charged openings. Although there is no evidence for the inclusion of anions inside CBs in solution, single-crystal X-ray structures revealed several cases.[118] For example, chloride and nitrate ions were found inside the cavity of CB5 and its permethylated derivatives, in which the complexation is assisted by the docking of the counter cations at the rims.[113–115]

In contrast to CB*n*, bambusurils (Fig. 1) have been recognized as anion receptors in both organic and aqueous solutions.[38,45,71–73,120] The X-ray structure of bambus[6]uril revealed anions inside its cavity, such as Cl^-, which indeed acts as a template in the synthesis of bambusurils.[72] Cl^- can be displaced by other halides, such as I^-, in a mixture of methanol and chloroform, as confirmed by ^{1}H NMR experiments.[71] The recognition propensity of a water-soluble bambusuril was tested with various anions (F^-, Cl^-, Br^-, I^-, CN^-, IO_4^-, ReO_4^-, NO_3^-, PF_6^-, BF_4^-, and ClO_4^-) in water, see Table 1. The measured association constants were surprisingly high (K_a > 10^2 M^{-1}) even for highly solvated ions, such as F^-, and reached values of 10^7 M^{-1} for I^- and ClO_4^-.[45] ITC data in water verified a 1 : 1 binding mode in solution and showed that the complexation was associated with large favourable enthalpy values compensated by entropic penalties.[45] Systematic analysis of the binding of halides to a bambusuril derivative, soluble in various solvents, was also performed.[120] The obtained results indicated that halide binding in water and chloroform is invariably driven by favorable enthalpic effects, modulated by an entropic penalty, while in alcohols and nonpolar solvents both a favorable enthalpy and entropy contribute to anion binding, most pronounced for large anions.[120]

The acid-mediated reaction between biotin and formaldehyde in hydrochloric acid led to the selective formation of a 6 + 6 macrocycle (biotin[6]uril, Fig. 1).[121] A templating effect of the halide anions was assigned as the driving force for hexamer formation in H_2SO_4. In analogy to bambusuril, biotin[6]uril binds a variety of inorganic anions in water.[47,121] The affinity followed the order Cl^- < NO_3^- < ClO_4^- < N_3^- < Br^- < I^- < $SeCN^-$ < SCN^-, Table 1. With the exception of ClO_4^-, which may be too large, this ordering follows again the chaotropicity of the anions. The thermodynamics of complexation was

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found to be enthalpically favorable and entropically unfavourable.[47] The single-crystal X-ray structure of I^- entrapped inside the cavity of biotin[6]uril is shown in Fig. 5.

Hemicucurbit[*n*]urils are another congener of the cucurbituril family.[122–124] Their formation (n = 6 and 8) during the synthesis was found to be controlled by the presence of anions (templating effect), such that the formation of cyclohexanohemicucurbit[6]uril (cycHC[6]) is predominant with halides, while carboxylates and PF_6^- selectively facilitate the formation of cycHC[8].[125] The chiral (all-*R*)-cyclohexanohemicucurbit[8]uril was found to selectively bind large anions in methanol.[123] The highest association constant was measured for SbF_6^- (K_a = 2.5 × 10^5 M^{-1}). In the gas phase, the order $SbF_6^- \approx PF_6^- > ReO_4^- > ClO_4^- > SCN^- > BF_4^- > HSO_4^- > CF_3SO_3^-$ for anion complexation was obtained, Fig. 6.

It is worth mentioning that the association of chaotropic anions with macrocyclic hosts is not limited to the interaction with macrocyclic cavities and the formation of inclusion-type complexes, but it applies similarly to the interaction with the outer walls, to form exclusion-type of complexes.[118,126–140] For example, superchaotropic anions, such as polyoxometalates and dodecaborate clusters, associate with the hydrophobic exterior of CB*n* macrocycles (Fig. 7), which results in the formation of hybrid aggregates.[134–136]

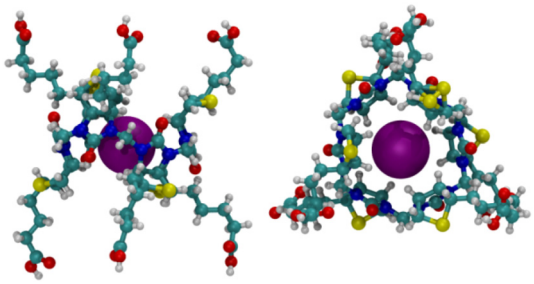

Fig. 5 Single-crystal X-ray structure of biotin[6]uril encapsulating an iodide ion.[121]

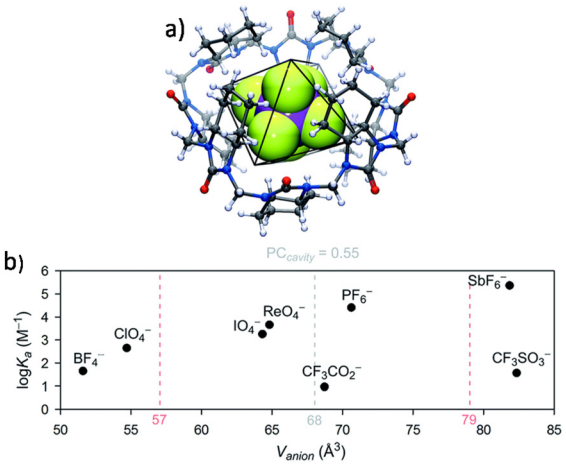

Fig. 6 (a) Crystal structure of the cyclohexanohemicucurbit[8]uril·SbF_6^- complex. (b) Binding affinities (log K_a) of large anions to cyclohexanohemicucurbit[8]uril as a function of the anion volume (V_{anion}). Note the clear trend of increasing affinity with the anion size when the two perfluorinated organic ions at the bottom are excluded. Reproduced from ref. 123 with permission from the Royal Society of Chemistry.

Octa acid and other macrocyclic hosts

Gibb and co-workers found that chaotropic anions have sizable affinity to the hydrophobic concavity of the octa acid host (Fig. 1).[65–67,105] An extended series of anions (as sodium salts) was studied (F^-, SO_4^{2-}, AcO^-, Cl^-, Br^-, NO_3^-, ClO_3^-, I^-, SCN^-, and ClO_4^-).[67,68,105,141] ^{1}H NMR displacement experiments provided evidence for the actual inclusion of large anions into octa acid, while ITC experiments revealed association constants (1–100 M^{-1}, Table 1) in the order $NO_3^- < ClO_3^- < I^- < SCN^- \ll ClO_4^-$. The binding of other anions to octa acid was further investigated by ^{1}H NMR and ITC.[105] The largest affinities were measured for $Cl_3CCO_2^-$ (K_a = 6340 M^{-1}) and PF_6^- (K_a = 790 M^{-1}). The thermodynamic signature of the binding of these anions is in line with the chaotropic effect established for CDs.

Examples of the binding of large anions to other molecular receptors and cages have also been documented.[142–148] The stability of dodecaborate anions with CDs and tetrathiafulvalene (Fig. 8) was established in the gas phase.[149] Nitschke and co-workers reported on the encapsulation of dianionic clusters, $Mo_6O_{19}^{2-}$ and $B_{12}F_{12}^{2-}$, inside a metal–organic cage in acetonitrile with relatively high binding constants of 2.9 × 10^3 and 2.2 × 10^3 M^{-1}, respectively, which were one order of magnitude higher than those measured for monoanionic guests, such as BPh_4^-, $CB_{11}H_{12}^-$, and $B(C_6F_5)_4^-$, which pointed to a dominant electrostatic effect.[150] The $Mo_6O_{19}^{2-}$ cluster was found to form an inclusion complex with a coordination cage

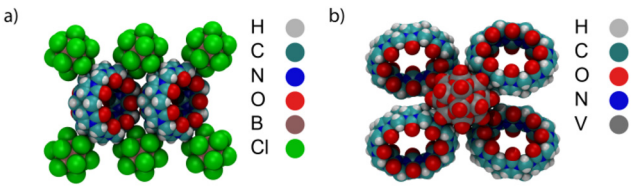

Fig. 7 Single-crystal X-ray structure of the exclusion complexes of superchaotropic anions with CB7. (a) CB7-$B_{12}Cl_{12}^{2-}$ and (b) CB8-$V_{18}O_{42}^{12-}$.

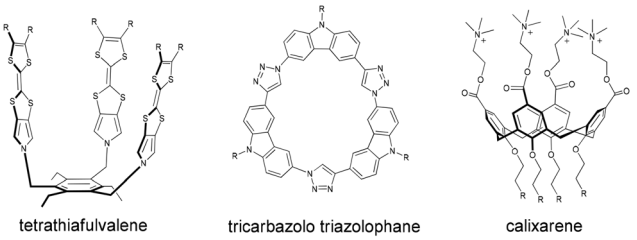

Fig. 8 Example of other molecular receptors with established affinity to large anions.

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in organic solvents as supported by NMR and ESI-MS results.[151] The association of conventional chaotropic anions with other molecular receptors was also observed, in non-aqueous solution. The weakly coordinating anion PF_6^- showed very high affinity to the tricarbazolo triazolophane macrocycle (Fig. 8) in organic solvents.[152] The C5-symmetric penta-*t*-butylpentacyanopentabenzo[25]annulene macrocycle, known as cyanostar, showed also high association constants for large anions (*e.g.*, PF_6^- and ClO_4^-).[153] Evidently, since the aqueous desolvation effect does not play a role here, dispersion interactions of the large anions must also be important.

Potential applications of large anion binding

The earliest application of a supramolecular host–guest complex of a large anion is the famous color reaction of I^- (I_3^-) with starch that has been discovered more than 200 years ago.[154] Although not macrocyclic but helical in structure, starch is the polymeric equivalent of the oligomeric CDs, such that the driving force for large anion binding is the same: the chaotropic effect.

With large superchaotropic anions a new high-affinity binding motif or anchoring unit for CDs has been identified, which opens several lines of applications.[41,43,49,96,155,156] For example, the dodecaborate anion $B_{12}H_{11}SH^{2-}$, as an auxiliary anchor residue, has been tethered to an organic moiety to synthesize water-soluble anchor dyes with high affinity to CDs.[43] Upon complexation with CDs, dodecaborate-substituted dyes showed marked changes in their UV-visible and fluorescence properties, which enabled their application for indicator displacement assays.[43] Another carboxyfluorescein dye of this type, with $B_{12}Br_{11}OR^{2-}$ as the anchoring unit, has also been reported.[157] Other hybrid organic–inorganic derivatives of dodecaborate clusters were synthesized by tethering nitroanilines to the $B_{12}H_{12}^{2-}$ anion.[158] These new aniline-substituted dodecaborates showed higher basicity than the parent nitroanilines and were able to form stable inclusion complexes with β- and γ-CD.[158]

Larsen and Beeren have recently exploited this affinity in biotechnology, namely, in a templated directed synthesis of CDs (Fig. 9).[49,159] For example, each CD, namely, α-, β-, and γ-CD, can be selectively obtained in high yields in the presence of sodium dodecyl sulfate, 1-adamantane carboxylic acid, and $NaBPh_4$, respectively, as templating guest molecules of the amphiphilic or hydrophobic ionic type. Interestingly, large ring CDs (δ-CD and ε-CD) could also be synthesized by treating smaller CD homologues, such as α-CD with cyclodextrin glycosyl transferase (CGTase) in the presence of dodecaborate anions (*e.g.* $Cs_2B_{12}I_{12}$), where they serve as a template (Fig. 9), owing to their high affinity to large-ring CDs.[44] In this manner, halogenated dodecaborate cluster anions serve as templates for the practical synthesis of these precious large-ring CD homologues.

The largest dodecaborate anion, $B_{12}I_{12}^{2-}$, is also a promising X-ray contrast agent for medical diagnostics (owing to the heavy-atom content) but it is known to induce hemolysis at high mM concentrations.[160,161] Hollow and Johnstone have recently reported that the complexation of the iodinated

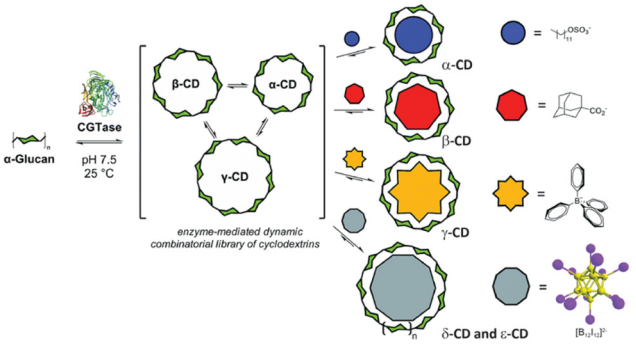

Fig. 9 Template-selective synthesis of CDs in the presence of differently sized anionic guest molecules. Reproduced from ref. 49 with permission from the Royal Society of Chemistry.

cluster with a permethylated γ-CD derivative prevents hemolysis, due to complexation.[160] The authors also reported the XRD structure of the $B_{12}I_{12}^{2-}$·γ-CD complex which bears close similarity to that of $B_{12}Br_{12}^{2-}$·γ-CD (Fig. 3a).

CDs have also been used as templates for the synthesis of polyoxometalates. The Lindqvist $M_6O_{19}^{2-}$ ions (M = Mo or W) were found to be formed in the presence of γ-CD, despite their low aqueous solubility.[80] Recently, Falaise *et al.* have shown that the Mo_{154} polyoxometalate can readily be made in the presence of γ-CD as a templating agent.[27] Host–guest complexation between the host and molybdenum-halide anionic clusters in aqueous solution was successfully applied to generate luminescent and redox-active materials.[162] In detail, $[Mo_6X^i{}_8Cl_6]^{2-}$ ions with X^i = Cl, Br or I are known to undergo hydrolysis in aqueous solution, and consequently form precipitates. This, however, could be suppressed, in particular for the brominated and iodinated clusters, upon complexation with γ-CD due to the formation of stable host–guest inclusion complexes, as indicated by ^{1}H NMR experiments.[162] Furthermore, the host–guest complexes were assembled in the presence of Al^{3+}-based polycations, which did not affect the structure of the γ-CD/$[Mo_6X^i{}_8Cl_6]^{2-}$ complex, and showed no effect on the optical and electrochemical properties of the $[Mo_6X^i{}_8Cl_6]^{2-}$ clusters.[162] Similarly, the hydrolytic stability of $[W_6X_8Cl_6]^{2-}$ (X = Br and I) was enhanced upon encapsulation inside two γ-CD rings.[163]

Another application has recently been reported using bambusuril functionalized with an aza-crown ether, which can be utilized for the extraction of simple inorganic salts from aqueous solution to organic solvents (chloroform).[164] Dodecaborate anions were found to facilitate the preparation of stable and dispersed gold nanoparticles (AuNPs), which allowed for the further fabrication of the nanoparticle surface through supramolecular host–guest complexation.[41] For example, gold nanoparticles stabilized by $B_{12}H_{11}SH^{2-}$ anions were functionalized by an amphiphilic calixarene macrocycle (Fig. 8).[41] The cationic calixarene derivative forms a stable complex with $B_{12}H_{11}SH^{2-}$ clusters, which allowed for the assembly of mono- and bilayers of calixarene on the surface of AuNPs in a controlled manner (Fig. 10a). Zhang and co-

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workers have also reported on the ability of the CB7-$B_{12}H_{12}^{2-}$ assembly to reduce noble metals, for example Pt^{4+}, to the zero-valent form, and subsequently the formation of nanoparticles which can be used for applications in catalysis.[165] Similarly, Qi *et al.* prepared metal nanomaterials based on the assembly of $B_{12}H_{12}^{2-}$-capped nanoparticles with CD-functionalized Fe_3O_4 (Fig. 10b). The new nano-composites showed remarkable catalytic activity and recyclability in the selective reduction of nitroaromatic compounds.[166]

The propensity of large anions to associate with the exterior of macrocyclic hosts (see above) leads to the formation of higher-order aggregates (precipitation) and, thus, enables applications in the direction of separation and isolation. CB*n*/dodecaborate assemblies have been used as adsorbent materials for the preferential removal of organic dyes from aqueous solution.[167] Qi *et al.* used the CB*n*/$B_{12}H_{12}^{2-}$ assembly to prepare metal-cluster supramolecular composites as catalysts for Suzuki reactions.[168] Heptamolybdate ($Mo_7O_{24}^{6-}$) showed a preferential association with the outer surface of CB*n*.[135] In detail, the $Mo_7O_{24}^{6-}$ anion forms an exclusion complex with CB7 in aqueous solution, which precipitates out. The finding has led to a new strategy for the separation of ^{99m}Tc from ^{99}Mo solutions.

The propensity of superchaotropic anions to form precipitates with CB*n* macrocycles by outer-wall binding has been initially described for dodecaborate clusters as a manifestation of the chaotropic effect.[134] Since then, this macrocycle-induced precipitation has been exploited for the separation of different precious metal complexes.[169–171] For example, gold can be separated through the high binding of $[AuBr_4]^-$ and $[AuCl_4]^-$ to CB6 as well as α-CD, while $PtCl_6^{2-}$ forms also an exclusion complex with CB6. The resulting complexes immediately precipitate, allowing their separation. The superchaotropic anions thereby act as a "supramolecular glue",[134] made possible by their large size and external binding. Interestingly, the binding shows high selectivity, because $PtCl_6^{2-}$ can be separated from $PdCl_4^{2-}$ and $RhCl_6^{3-}$.[170] Very likely, this is related to the fact that $PtCl_6^{2-}$ is the anion with the highest chaotropicity in this large-anion set, because $PdCl_4^{2-}$ is less chaotropic on account of its smaller size, while $RhCl_6^{3-}$ is less chaotropic on account of its higher charge. These structure–activity relationships in large anion binding in water are emerging only now, and will help design refined applications in the future.

Recently, Wang *et al.* have explored the supramolecular assembly of CB8 with a dodecaborate derivative for image-guided photodynamic therapy applications (Fig. 11).[172] The $B_{12}H_{12}^{2-}$ cluster was monofunctionalized with an RGD cell-binding sequence through polyethylene glycol units for targeted therapy purposes. The modified cluster can assemble at the exterior of CB8, which is prefilled with methylene blue, in aqueous solution, to form nanoparticles. Methylene blue served as a photosensitizer dye. The nanoparticles were found to accumulate in the tumor region when injected in mice through the tail vein. The release of methylene blue from the cavity could then be triggered through competitive binding using a peptide with an aromatic N-terminus.

The self-assembly of β-CD with $SiW_{12}O_{40}^{4-}$ provides a versatile tool to prepare metal–organic frameworks (MOFs).[173] The structure of the $(KCl_4)Na_7[(\beta\text{-CD})_3(SiW_{12}O_{40})]\cdot 9H_2O$ composite indicated that the anionic polyoxometalate is captured by

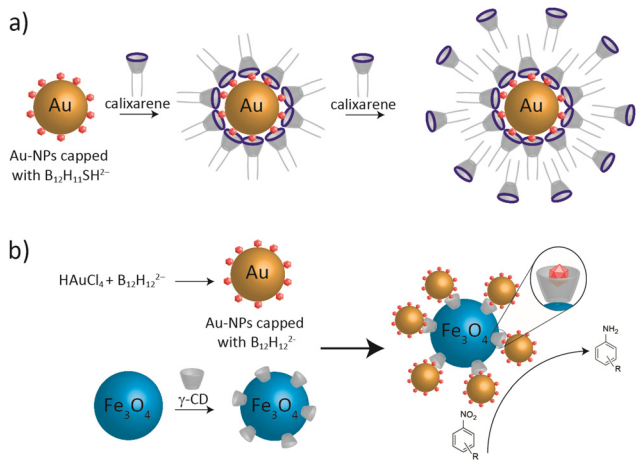

Fig. 10 (a) Assembly of a calixarene derivative on $B_{12}H_{11}SH^{2-}$ coated AuNPs.[41] (b) The preparation of $B_{12}H_{12}$-capped gold nanoparticles and CD-functionalized Fe_3O_4 and their assembly as a catalyst for the reduction of nitroaromatics.[166]

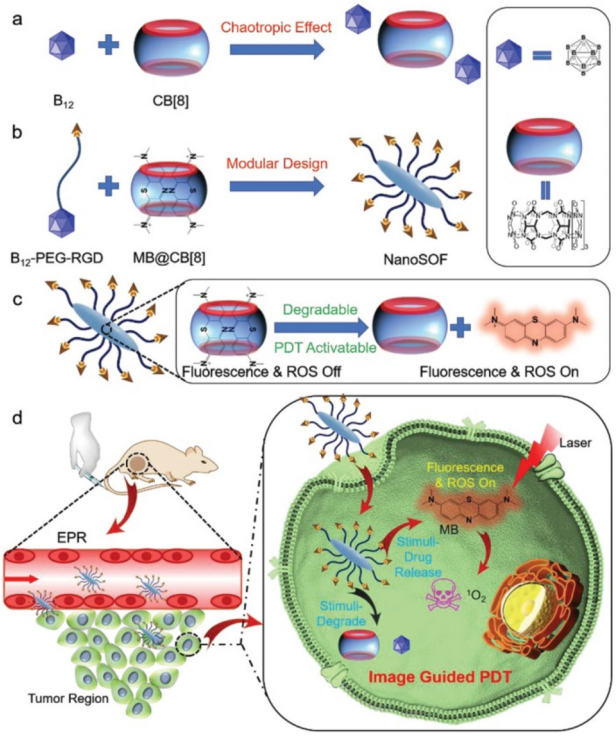

Fig. 11 Schematic illustration for the implementation of the chaotropic effect for the design of nano-carriers for image-guided photodynamic therapy application. (a) the association of the chaotropic $B_{12}H_{12}^{2-}$ anion to CB8, (b) molecular assembly of the functionalized $B_{12}H_{12}^{2-}$ cluster and CB8, (c) activation of supramolecular photosensitizer, and (d) the working principle of the assembly as smart drug carrier for image-guided photodynamic therapy *in vivo*. Reproduced with permission from ref. 172 Copyright 2020 John Wiley and Sons, Inc.

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three β-CD units. The new hybrid-MOF possesses high catalytic activity for the chemical oxidation of alcohols, alkenes, and thiophene to their corresponding products in the presence of H_2O_2.[173] MOFs have also been synthesized based on the interaction between the polyoxometalate $PW_{12}O_{40}^{3-}$ and α-CD as well as a polyoxopalladate ($P_{10}Pd_{15.5}O_{50}^{19-}$) and γ-CD.[174] Although the large size of the anionic clusters does not allow the formation of inclusion-type complexes, the propensity of the large ions to associate with the outer walls of CDs drives the assembly into MOFs.[174] Other examples have recently been reported.[175] The strong interaction between the native CDs and Anderson–Evans type polyoxometalates, namely $[AlMo_6O_{18}(OH)_6]^{3-}$, was used to design infinite CD-channels linked through a polyoxometalate.[175]

While the development of chemosensors for kosmotropic anions presents an important challenge in supramolecular chemistry,[2,176–182] sensing applications for large chaotropic and superchaotropic anions are of comparably lesser interest, because most of them are purely synthetic in nature (BF_4^-, PF_6^-, boron cluster anions, polyoxometalates), and therefore of limited environmental or biological concern. An exception is the perchlorate anion, ClO_4^-, which is formed as a by-product from oxidative processes of chloride ions or chlorinated hydrocarbons, and for which several specific receptors have been reported.[183]

Conclusions

The research field of anion recognition has experienced considerable developments in the past two decades. Despite a large number of reports on the binding of natural (small) inorganic anions by synthetic receptors, their relatively weak binding properties frequently limit the application potential to areas where the ions themselves serve either as analytes (ion sensing) or as cargos (ion transport) rather than as supramolecular building blocks on their own. The emergence of large cluster anions as tight binders for several macrocycles in 2015 has allowed their utilization as new assembly motifs in aqueous solution that have afforded, during the past 10 years, a wide spectrum of complex supramolecular architectures and several applications, ranging from the design of functional materials for catalysis to separation agents. Large anions, in particular those of the boron cluster and polyoxometalate type, display superchaotropic properties, which allow them to interact with extraordinary affinity with hydrophobic surfaces, and in particular with the hydrophobic cavity of macrocyclic hosts, which can be traced back to a combination of desolvation and dispersion effects. Since the two types of superchaotropic anions are emerging key ingredients for solid-state batteries[184,185] and photocatalytic water-splitting,[186] large anion binding could also become relevant for future energy-related applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work has been supported by the DFG through projects NA-868/14 (chaotropic effect of boron cluster anions) and NA-868/17 (chaotropic effect of polyoxometalates).

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