Journal of Inclusion Phenomena and Macrocyclic Chemistry
https://doi.org/10.1007/s10847-019-00930-w

ORIGINAL ARTICLE

Enhanced host–guest complexation of short chain perfluoroalkyl substances with positively charged β-cyclodextrin derivatives

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Received: 17 April 2019 / Accepted: 12 June 2019

Abstract

Short chain perfluoroalkyl substances (PFAS), replacements for long chain legacy PFAS such as perfluorooctanoic acid (PFOA), have similar toxicity, negative health effects, and exceptional persistence as long chain PFAS. β-Cyclodextrin (β-CD) is a powerful host–guest complexing agent for a number of legacy PFAS, suggesting potential β-CD-based remediation processes. We report herein that the addition of charged functional groups at the perimeter of β-CD has a pronounced influence on the strength of the β-CD:PFAS complex. The presence of a positively charged amine functionality on the perimeter of β-CD significantly increases the complexation of legacy and short chain PFAS. We assigned the enhanced complexation to electrostatic attraction between the negatively charged PFAS head group and the positively charged β-CD derivative. In comparison to neutral β-CD, addition of a negative charge to β-CD decreases complexation to PFAS due to electrostatic repulsion between the negatively charged polar head group of PFAS and the negatively charged β-CD. ^{19}F NMR titration experiments illustrate the complexation of short chain PFAS by positive charged β-CDs over neutral β-CD, with increases up to 20 times depending on the PFAS guest. The results give further understanding to the nature of the β-CD:PFAS host–guest complex and the various intermolecular forces that drive complexation. Positively charged β-CDs appear to be potential complexing agents for remediation of short chain PFAS.

Keywords Perfluoroalkyl substance · PFAS · GenX · β-cyclodextrin · NMR spectroscopy

Introduction

Perfluoroalkyl substances (PFAS) are contaminants of emerging concern. "Legacy" PFAS have a fully fluorinated tail and a polar head group, rendering them extremely chemically and thermally stable, as well as both hydrophobic and lipophobic [1–4]. A lifetime advisory limit of 70 parts per trillion (ppt) was recently established by the US Environmental Protection Agency (EPA) for two legacy PFAS, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), due to increasing evidence of negative health effects stemming from PFOA and PFOS exposure [1, 3–8]. Due to the known negative environmental and health effects, chemical manufacturers have phased out production of long chain PFAS in favor of short chain PFAS, including perfluorobutanoic acid (PFBA) and perfluoropentanoic acid (PFPA) [4, 7]. Manufacture of "emerging" PFAS with ether functionalities, perfluoroethercarboxylic acids (PFECAs), has also increased, especially of short chain PFAS like perfluoro(2-methyl-3-oxahexanoic) acid, known as "GenX" [4, 9–11]. Short chain legacy and emerging PFAS were thought to be less persistent in the environment and thus less harmful to human health than long chain PFAS [9, 12]. Recent reports, however, suggest that short chain PFAS are as persistent as their legacy counterparts in the environment, with the same ability for long range transport as long chain PFAS [12, 13], and that short chain emerging PFAS like GenX may be just as toxic as PFOA and PFOS [14, 15]. Current effective remediation methods for long chain PFAS, such as activated carbon adsorption, however, are ineffective for short chain PFAS [16, 17], especially for ether-type short chain PFAS such as PFECAs [10, 11].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10847-019-00930-w) contains supplementary material, which is available to authorized users.

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Published online: 01 July 2019

β-Cyclodextrin (β-CD) has been proposed as a possible remediation strategy for PFAS contamination [18–23]. β-CD, a cyclic sugar composed of seven glucose monomers, has a truncated cone shape, with the smaller opening lined with seven primary hydroxyl groups and the larger opening lined with fourteen secondary hydroxyl groups, with numerous C–H bonds lining the interior of the cavity. The cavity interior is thus hydrophobic whereas the β-CD exterior is hydrophilic [24]. β-CD is ideal for engaging in host–guest chemistry of hydrophobic compounds in hydrophilic or aqueous solutions [25, 26]. Cucurbiturils have also received attention as fluorophilic receptors and have exhibited strong complexation of neutral highly fluorinated substrates; however, they are much less effective at complexing negatively charged fluorinated substrates such as legacy and emerging PFAS like PFOA or GenX compared with β-CD [22, 23, 27]. Furthermore, β-CD is non-toxic, water soluble, inexpensive, and synthesized from a renewable resource (starch), making it an environmentally friendly and economical alternative to current PFAS water treatment methods [24].

Our previous studies have elucidated the structure of the host–guest complex between parent β-CD and a variety of PFAS [22, 23]. The carboxylate head group of the PFAS orients towards the smaller opening of β-CD with the primary hydroxyl groups [23]. Three examples of potential complexes are shown in Fig. 1. The primary driving forces for host–guest complex formation is the van der Waals interactions between the interior hydrophobic cavity of β-CD and the aliphatic perfluorinated backbone of the PFAS paired with the displacement of water molecules from the cyclodextrin cavity [22, 25]. Insertion of an ether oxygen into the fluorinated chain weakens the attractive van der Waals interactions and thus a decrease in association constants is observed [23]. In addition to the hydrophobic interactions, hydrogen-bonding between the β-CD primary hydroxyl groups and the PFAS polar head group can influence complexation [28–31]. Long chain legacy PFAS with ionized head groups can have very strong (on the order of 10^5 M^{-1}) association constants with β-CD, compared with association constants between other guests and β-CD reported in the literature [22, 25]. Short chain legacy and emerging PFAS, however, have weak (on the order of 10^1–10^3 M^{-1}) association constants with β-CD [22, 23]. In a remediation application, the weaker complexation of short chain PFAS would be problematic for remediation because of the decreased selectivity for short chain PFAS over other environmental contaminants, which have similar association constants with β-CD, and increased equilibria between free and complexed PFAS [25]. Replacement of the primary hydroxyl groups with a positively charged group, such as an amino group, may enhance electrostatic attraction with the negatively charged PFAS carboxylate [32–35]. We chose to measure the complexation of short chain PFAS with positively charged amino β-CD derivatives due to potential increased association stemming from this electrostatic attraction.

In this study, ^{19}F NMR titration experiments have been conducted to determine the association constants of various charged β-CD derivatives with short chain PFAS to probe the effects of charge on the strength of the host–guest complex. Positively charged β-CD derivatives exhibit enhanced complexation of short chain PFAS and thus show promise for their remediation.

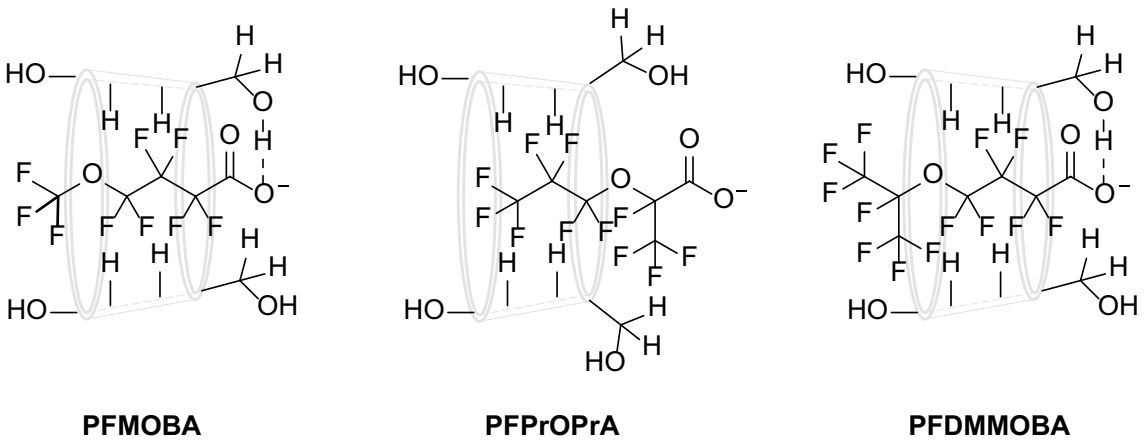

Fig. 1 The host–guest complexes between β-CD and PFMOBA, PFPrOPrA, and PFDMMOBA. Complex formation is driven by the favorable van der Waals interactions between the fluorines of the PFAS and the interior protons of β-CD. The host–guest complex formation is further driven by possible hydrogen-bonding between the carboxylate of the PFAS and the primary hydroxyl groups on β-CD, as shown in the cases of PFMOBA and PFDMMOBA; due to branching near the carboxylate, PFPrOPrA is less able to experience hydrogen-bonding, which is reflected in its weaker association constant with β-CD than PFMOBA and PFDMMOBA

Experimental methods

PFBA, PFPA, and hexafluorobenzene were purchased from Sigma-Aldrich. Perfluoro(3-oxabutanoic) acid (PFMOPrA), perfluoro(4-oxapentanoic) acid (PFMOBA), and perfluoro(5-oxa-6-dimethylhexanoic) acid (PFDMMOBA) were purchased from SynQuest Labs. Perfluoro(2-methyl-3-oxahexanoic) acid (PFPrOPrA, GenX) was purchased from Alfa Aesar. 6-Monodeoxy-6-monoamino-β-cyclodextrin hydrochloride (mono-am-β-CD), heptakis(6-deoxy-6-amino)-β-cyclodextrin heptahydrochloride (hepta-am-β-CD), (2-hydroxy-3-*N*,*N*,*N*-trimethylamino)propyl-β-cyclodextrin chloride (QACD; degree of substitution ~ 3–4), and sulfobutylated β-cyclodextrin sodium salt (SBECD; degree of substitution ~ 6.5) were purchased from Cyclolab Ltd. Deuterium oxide (99.9% D) was purchased from Sigma-Aldrich and stored at 4 °C. All chemicals were used without further purification.

Sample preparation

For the titration experiments, samples were prepared as previously described [22, 23]. The concentration of each PFAS was 2.42×10^{-3} M. The solution consisted of 50% D_2O and 50% DI H_2O, adjusted to pH 7 with 0.036 M NaOH. Hexafluorobenzene (1.44×10^{-3} M) was added as the ^{19}F NMR internal standard. Each β-cyclodextrin was added at various stoichiometric ratios and the solution was sonicated for 1 min to ensure dissolution and mixing of the compounds.

^{19}F NMR spectroscopy

^{19}F NMR spectroscopy was performed with a 400 MHz Bruker instrument with a quad probe (operating at 376.498 MHz for ^{19}F). Hexafluorobenzene was used as the internal standard with a reference chemical shift of − 164.9 ppm. For the titration experiments, the chemical shift of each peak was recorded, and the 1:1 β-CD:PFAS association constants were calculated in GraphPad Prism (version 5.03, La Jolla, CA) and Mathworks Matlab (version R2013b, Natick, MA) by Ramos Cabrer et al. method [22, 23, 36].

Results and discussion

The ^{19}F NMR chemical shift of the peaks corresponding to each fluorine changed as a function of β-CD concentration (see Supplementary Material Figs. S1–S6). The changes in chemical shifts were monitored and used to calculate the individual association constants experienced by each fluorine with the β-CD derivative (see Supplementary Material Tables S1–S6). The average from the sum of the calculated individual fluorine atom association constants is reported in Table 1 for each short chain PFAS with the different β-CD derivatives and the parent β-CD reported previously [22, 23].

In comparison to neutral β-CD, the negatively charged SBECD exhibited decreased complexation for all six of the short chain PFAS in this study. PFBA and PFMOPrA showed no measurable complexation with SBECD representing a decrease of ~ 100-fold compared to neutral β-CD, while the decreases for the other short chain PFAS varied

Table 1 Average association constants of short chain PFAS with β-CD derivatives

	β-CD	Mono-am-β-CD $^{+}NH_3$-β-CD	Hepta-am-β-CD $(^{+}NH_3)_7$-β-CD	QACD $(CH_3)_3N^{+}CH_2CH(OH)CH_2$-β-CD	SBECD $^{-}O_3S(CH_2)_4$ β-CD
PFBA $CF_3(CF_2)_2CO_2^-$	$2.90\ (0.24) \times 10^{2}$ [a]	$2.16\ (1.04) \times 10^{2}$	$1.02\ (0.40) \times 10^{3}$	$1.46\ (0.31) \times 10^{2}$	Not observed
PFPA $CF_3(CF_2)_3CO_2^-$	$7.60\ (0.44) \times 10^{2}$ [a]	$1.01\ (0.61) \times 10^{3}$	$2.62\ (0.79) \times 10^{3}$	$6.68\ (3.41) \times 10^{2}$	$1.07\ (0.18) \times 10^{2}$
PFMOPrA $CF_3O(CF_2)_2CO_2^-$	$1.54\ (0.52) \times 10^{2}$ [b]	$6.39\ (1.06) \times 10^{2}$	$3.06\ (1.33) \times 10^{3}$	$6.92\ (1.56) \times 10^{2}$	Not observed
PFMOBA $CF_3O(CF_2)_3CO_2^-$	$1.48\ (0.36) \times 10^{3}$ [b]	$1.76\ (1.02) \times 10^{3}$	$4.56\ (1.22) \times 10^{3}$	$3.29\ (0.63) \times 10^{3}$	$9.68\ (2.29) \times 10^{1}$
PFPrOPrA (GenX) $CF_3(CF_2)_2OCF(CF_3)CO_2^-$	$7.45\ (4.27) \times 10^{2}$ [b]	$1.55\ (0.62) \times 10^{4}$	$1.86\ (1.13) \times 10^{3}$	$4.43\ (1.66) \times 10^{2}$	$3.70\ (2.32) \times 10^{2}$
PFDMMOBA $(CF_3)_2CFO(CF_2)_3CO_2^-$	$2.66\ (0.61) \times 10^{4}$ [b]	$2.75\ (0.39) \times 10^{4}$	$2.12\ (0.49) \times 10^{5}$	$2.02\ (0.57) \times 10^{5}$	$6.49\ (2.79) \times 10^{3}$

All association constants listed are in units of M^{-1}. Standard deviations are listed in parentheses. Structures are listed for each compound

[a]From reference [22]

[b]From reference [23]

from ~0.50- to 6-fold. In general the pKa values for PFAS are low ($pK_a \leq 0$) and thus PFAS are largely deprotonated even under strongly acidic conditions [37]. Given the negatively charged PFAS and the negatively charged side chain of the potential host SBECD, electrostatic repulsion leads to weaker complexation with SBECD than neutral β-CD. In comparing the three positively charged β-CD derivatives (mono-am-β-CD, hepta-am-β-CD, and QACD) and neutral β-CD, the complexation of the six short chain PFAS complexation increased in most cases which we assign to the electrostatic attraction between the positively charged β-CD side chain and the negatively charged PFAS. The difference in the association constant of the positively charged β-CDs with the PFAS varied from almost no change to 20-fold increases depending on structural variations of the PFAS.

Our previous studies have confirmed the primary factors leading to the favorable encapsulation of PFAS by β-CD [22, 23]. PFAS have strong interactions with β-CD due to the cross-sectional sizes of the PFAS and β-CD (28.3 and 30.2 $Å^2$, respectively), leading to favorable van der Waals forces between the PFAS fluorinated chain and the β-CD cavity [38]. These hydrophobic interactions dominate the host–guest complex: legacy PFAS have stronger interactions with β-CD than PFECAs, which have ether oxygen atoms along the fluorinated backbone chain, leading to modest weakening of the van der Waals forces [23]. Secondary to the hydrophobic interactions is the hydrogen-bonding interactions between the PFAS head group (carboxylate, sulfonate, etc.) and the primary hydroxyl groups lining the perimeter of the smaller side of the β-CD cavity [23, 28–31]. When such hydrogen-bonding is prevented (as in the case of the β-CD:PFPrOPrA complex, due to branching of the PFAS next to the carboxylate), encapsulation is weakened; when it is forced (as in the case of the β-CD:PFDMMOBA complex, due to branching of the PFAS at the tail), encapsulation is strengthened [23].

The calculated association constants for the complexes between the β-CD derivatives and the short chain PFAS provide additional insight into the nature of β-CD:PFAS host–guest interactions. PFMOPrA, PFPrOPrA, and PFDMMOBA have the largest changes in association constants with the positively charged β-CD derivatives, as seen in Table 2. PFPrOPrA has increased complexation with mono-am-β-CD (20-fold), and PFDMMOBA has increased complexation with both QACD (8-fold) and hepta-am-β-CD (8-fold). PFMOPrA has increased complexation with all three studied positively charged β-CD derivatives, especially hepta-am-β-CD (20-fold).

The primary structural differences in the six studied PFAS are aliphatic versus ether backbones and linear versus branched backbones. PFDMMOBA, branched at the tail, must enter β-CD head first (threading the carboxylate through the β-CD cavity) [23, 38–41]. In native β-CD, once PFDMMOBA has threaded through the cavity, the primary hydroxyl groups will hydrogen-bond with the PFDMMOBA carboxylate, securing PFDMMOBA in place as illustrated in Fig. 1. For the mono-am-β-CD complex, there is no increase in association constant, suggesting that the complex with β-CD is significantly stable such that the presence of a single positive charge does not appreciably affect the strength of complexation. For the hepta-am-β-CD complex, the presence of seven positive charges increases the association constant relative to the β-CD complex by 8-fold. Thus, multiple positive charges can significantly strengthen the complex, whereas the presence of one positive charge has roughly the same effect as the hydrogen-bonding interactions. Furthermore, the QACD:PFDMMOBA association constant is also 8-fold stronger than the β-CD:PFDMMOBA complex. The QACD has a propyl linker between the β-CD cavity and the quaternary amine group. Compared with mono-am-β-CD or hepta-am-β-CD, the increased length of the linker may allow this side chain to fold back around the PFDMMOBA head group so that both the hydroxyl group in the middle of the linker and the positively charged quaternary amine group at the end of the linker can interact with the PFDMMOBA carboxylate through hydrogen-bonding and electrostatic interactions, respectively. These potential dual interactions could also be a great enough difference compared to the native β-CD neutral hydroxyl groups and the single amino group of the mono-am-β-CD to produce a noticeable increase in association.

Branching of the PFAS backbone chain also produces changes in the PFPrOPrA:β-CD complexes. PFPrOPrA can only enter the β-CD cavity tail first (threading the fluorinated tail through the β-CD cavity) due to this branching alpha to the carboxylate head group [23]. The amino groups of mono-am-β-CD and hepta-am-β-CD are substituted on the small side of β-CD, which is the opening that the fluorinated chain of PFPrOPrA must pass through to enter the β-CD cavity. Although the association constant for the hepta-am-β-CD:PFPrOPrA complex increased compared to the β-CD complex, the increase was smaller than all the other studied

Table 2 Changes in β-CD derivative:PFAS association constants compared with those measured for the parent β-CD:PFAS complex

PFAS	Mono-am-β-CD	Hepta-am-β-CD	QACD	SBECD
PFBA	0.7	3.5	0.5	*
PFPA	1.3	3.4	0.9	0.1
PFMOPrA	4.2	20	4.5	*
PFMOBA	1.2	3.1	2.2	0.08
PFPrOPrA	20	2.5	0.6	0.5
PFDMMOBA	1.0	8.0	8.0	0.2

*No complexation was observed

PFAS. Most likely this is observed because it is unfavorable for the fluorinated chain to pass through the ring of positively charged amino groups, whereas all the other studied PFAS can enter the β-CD cavity through the other opening (threading the carboxylate through the β-CD cavity) [23, 38]. The mono-am-β-CD:PFPrOPrA complex, however, is 20 times stronger than the complex with β-CD. For this complex, PFPrOPrA does not have to thread through a ring of multiple positive charges. From the previous results, the amino group is expected to be too far for effective hydrogen bonding with the carboxylate of PFPrOPrA in the complex, though potential electrostatic attraction may still lead to the large increase in association with mono-am-β-CD. Finally, a decrease in the association constant compared with native β-CD is exhibited for the complex with QACD. The addition of the bulky side-chain to the primary hydroxyl side, through which PFPrOPrA must thread to complex within the cavity, may make complex formation less favorable than with neutral β-CD.

Finally, PFMOPrA had dramatic increases in association constants with the three positively charged β-CD derivatives, especially for hepta-am-β-CD, compared with the other linear PFAS (PFBA, PFPA, and PFMOBA). PFMOPrA is the only PFAS studied that does not have the $–CF_2CF_2CF_2–$ subunit. From the molecular sizes of the PFAS and the β-CD cavity, three fluorinated carbons will be snugly encapsulated in the cavity [22, 38]. As this functionality is highly hydrophobic, its interactions with the hydrophobic β-CD cavity result in favorable van der Waals interactions and strong complexation of PFAS by β-CD. PFMOPrA does not possess $–CF_2CF_2CF_2–$ functionality; it has only two fluorinated carbons between the carboxylate and ether functionalities, with a $–CF_3$ group on the other side of the ether oxygen. Thus, the encapsulation of PFMOPrA by parent β-CD is in comparison weaker due to the substitution of a $–CF_2–$ group for the hydrophilic ether oxygen within the hydrophobic β-CD cavity during complexation. For the mono-am-β-CD:PFMOPrA and QACD:PFMOPrA complexes, the association constants are about four times the value of the association constant for the β-CD:PFMOPrA complex. Although the van der Waals interactions are often the driving force behind the host–guest complexation and the interactions between the PFAS carboxylate with the hydroxyl groups of the β-CD cavity perimeter are secondary, the change of one of the hydroxyl groups to a positively charged amino group, or the addition of the side chain with a quaternary amine, cause a larger change in the association constant than other PFAS due to the reduced van der Waals interactions in the β-CD cavity. The association constant is increased further (20-fold) by the replacement of all the primary hydroxyl groups by positively charged amino groups in hepta-am-β-CD. This result indicates that the presence of positively charged groups on the β-CD host become increasingly important for the strength of the β-CD:PFAS host–guest complexes in the absence of the $–CF_2CF_2CF_2–$ subunit present in the legacy PFAS structures. As the van der Waals forces are decreased, electrostatic interactions can help drive the host–guest interactions.

Analogous effects of charge and van der Waals forces can be employed to explain the observed behaviors of PFBA, PFPA, and PFMOBA in the complexation with different β-CD derivatives. These three PFAS have the favorable three-carbon subunit within their structure, despite PFMOBA having an ether functionality. Almost no increase in complexation is observed when only one or two positively charged groups are present (mono-am-β-CD and QACD), as the van der Waals forces are still the major driver of the host–guest complex, and the ionic bonding interactions play a minor role. In fact, a slight decrease in complexation is observed for the QACD complexes with PFBA and PFPA, suggesting that the addition of the bulky side chain hinders the equilibrium between free PFAS and complexed PFAS, or makes the process of complexation less favorable. A decrease in association constant is also observed between mono-am-β-CD and PFBA compared with β-CD complex; however, the error associated with the mono-am-β-CD complex renders the two association constants not significantly different. A slight increase (3-fold) in association constant occurs when the highly positively charged groups are present (hepta-am-β-CD), as the electrostatic interactions between the carboxylate and amino groups are more likely and thus become a greater factor in the overall strength of complexation.

Conclusions

Positively charged β-CD derivatives increased encapsulation of short chain PFAS relative to native β-CD. Linear PFAS with a $–CF_2CF_2CF_2–$ group had little or no increase with mono-am-β-CD and QACD, and moderate increase with hepta-am-β-CD, compared to β-CD. Favorable interactions between the hydrophobic fluorinated chain and the β-CD cavity dominate these complexes, while ionic bonding interactions between the PFAS carboxylate and the β-CD amino groups are secondary. A linear PFAS without the $–CF_2CF_2CF_2–$ group (PFMOPrA) had moderate increases in complexation with mono-am-β-CD and QACD and a large increase with hepta-am-β-CD compared to β-CD. PFMOPrA does not have strong van der Waals interactions between the PFAS chain and the β-CD cavity, and thus the electrostatic attraction due to addition of amino groups in the β-CD structure dominates the host–guest complex. PFDMMOBA, the PFAS branched at the tail, had moderate increases in association with QACD and hepta-am-β-CD compared with β-CD. The presence of a positively charged side chain (QACD) or multiple

positively charged amino groups (hepta-am-β-CD) can further lock PFDMMOBA into the β-CD cavity and hinder dissociation, increasing the strength of complexation beyond the base hydrophobic interactions. PFPrOPrA, the PFAS branched next to the carboxylate head group, had a large increase in association constant with mono-am-β-CD compared with β-CD, but not with the other positively charged β-CD derivatives. Since PFPrOPrA must enter the β-CD cavity through the narrow, and thus amino-substituted, side, the presence of the positively charged side chain (QACD) or multiple positively charged amino groups (hepta-am-β-CD) make the complex unfavorable, whereas the presence of one positively charged group (mono-am-β-CD) allows PFPrOPrA to enter the β-CD cavity leading to potential favorable electrostatic interactions.

The addition of positive groups on β-CD allows for greater complexation with short chain PFAS than neutral β-CD. A negatively charged β-CD derivative causes weaker complexation than neutral β-CD. Thus, the interaction between the PFAS carboxylate and the β-CD primary hydroxyl groups, or their substitutions, is important to the strength of the host–guest complex. This interaction, however, is secondary to the hydrophobic interactions between the PFAS fluorinated chain and β-CD cavity, which are the primary drivers of the host–guest complex. The ionic interactions with the positively charged amino groups are only important to the host–guest interactions (leading to large increases) when the hydrophobic interactions are unfavorable, such as in the case of PFMOPrA, or when branching has either hindered the host–guest complex originally (PFPrOPrA) or stabilized it (PFDMMOBA). These results give further insight into the host–guest chemistry between PFAS and CDs, and can be utilized in the design of β-CD-based remediation technologies for short chain and emerging PFAS.

Acknowledgements The authors gratefully acknowledge funding support from the National Science Foundation (Grants #1748752 and #1805718) and Florida International University's Dissertation Year Fellowship (DYF) Program. The authors would also like to thank Detlef Knappe of North Carolina State University for valuable feedback and providing the PFECA samples from SynQuest.

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