Computationally Modeling the Ability of Cyclodextrins to Bind Short-Chain PFAS

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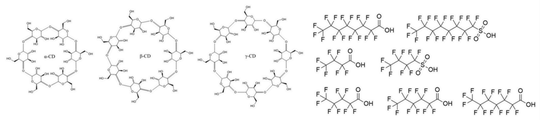
Background

- There are two main types of PFAS: long-chain and short-chain
- Existing adsorbents for PFAS **ineffective** for short-chain PFAS
- Cyclodextrins have been proposed as a novel solution
- Three main types of cyclodextrin depending on size (α, β, γ)
- Cyclodextrins form a ring; the interior surface is **hydrophobic** and the exterior surface is **hydrophilic**
- PFAS thread through cyclodextrin forming **hydrophobic interactions** with the inner surface and **hydrogen bonds** with the terminal hydroxyl groups
- H-bonds **compensate** for weak hydrophobic interactions

Introduction

- Per- and polyfluoroalkyl substances (PFAS) are a serious issue in water sources
- ~71 to 95 million people in the U.S. source their drinking water from PFAS-contaminated groundwater
- PFAS are endocrine disruptors and can increase the risk of certain cancers, and effects are still not fully known
- Further research is needed into the detection and removal of PFAS
- PFAS have a negatively charged hydrophilic (water-loving) head and hydrophobic tail

Methodology



- Acquired 3D structures of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin from PDBj and developed modifications replacing primary hydroxyls with quaternary nitrogens in Chem3D
- Acquired 3D structures of PFOA, PFOS (long-chain PFAS) and PFBA, PFBS, PFPeA, PFHxA, PFHpA (short-chain PFAS)
- Ran each combination of the six cyclodextrins and seven PFAS through AutoDock Vina to generate a docking score
- Analyzed with PyMOL and Excel

Tools

PDBj Protein Data Bank Japan

PubChem

Research Question

How do the type of cyclodextrin and modifications thereof affect the binding of PFAS to a cyclodextrin candidate?

Hypothesis

Beta-cyclodextrins and gamma-cyclodextrins with attached positive residues will bind short-chain PFAS better than alpha-cyclodextrins and unmodified gamma-cyclodextrins and beta-cyclodextrins.

Results

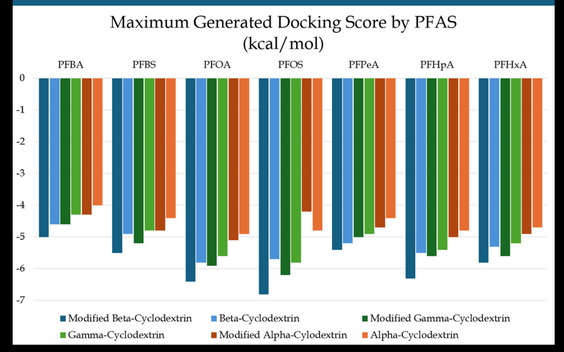


Figure 1: The docking scores for the most favorable pose generated with each cyclodextrin (grouped by PFAS).

Results

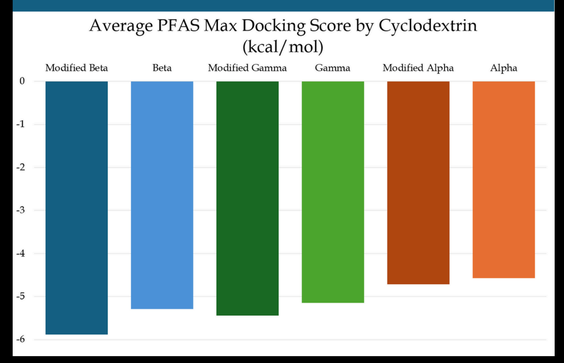


Figure 2: The average (by cyclodextrin) of the maximum docking scores for each PFAS in the sample.

Results

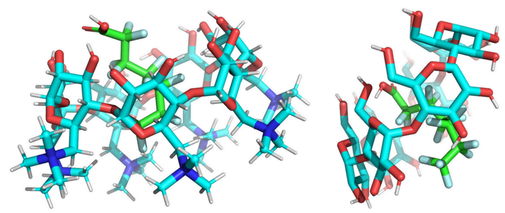


Figure 3: The optimal docking poses for modified β-CD and PFHpA (-6.3 kcal/mol) (left) and unmodified β-CD and PFHpA (-5.5 kcal/mol) (right)

Results

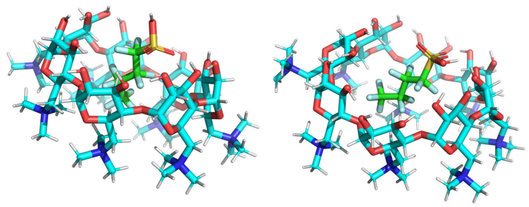


Figure 4: The optimal docking poses for modified β-CD and PFBS (-5.5 kcal/mol) (left) and modified γ-CD and PFBS (-4.9 kcal/mol) (right)

Analysis

- Matched-pairs t-testing used to confirm differences in average docking score between combinations of two cyclodextrins
- M = modified

	β-CD – α-CD	α-CD – γ-CD	β-CD – γ-CD	M-α-CD - α-CD	M-β-CD - β-CD	M-γ-CD - γ-CD	M-β-CD – M-γ-CD
H_A	$\mu \neq \mu_0$	$\mu \neq \mu_0$	$\mu \neq \mu_0$	$\mu > \mu_0$	$\mu > \mu_0$	$\mu > \mu_0$	$\mu > \mu_0$
t-score	12.01	-6.606	2.705	1.125	5.499	6.874	6.819
p-value	2.02×10^{-5}	5.79×10^{-4}	0.035	0.152	7.58×10^{-4}	2.34×10^{-4}	2.44×10^{-4}
reject H_0	yes at α=0.001	yes at α=0.001	yes at α=0.05, no at α=0.01	no at any α	yes at α=0.001	yes at α=0.001	yes at α=0.001

Table 1: Results of matched-pairs t-testing

Conclusion

- **No** evidence that modified α-cyclodextrins have higher docking scores than unmodified counterparts
- **Convincing** evidence that the average docking scores for modified β-cyclodextrins and γ-cyclodextrins are significantly higher than for their unmodified counterparts (***p<0.001), and the average docking score is higher for modified β-cyclodextrins than for modified γ-cyclodextrins (***p<0.001)
- **Modified β-cyclodextrins** had the highest generated docking scores for all PFAS tested – likely candidate for **further steps**

Future Work

- Creating additional modified cyclodextrins with positive groups
- Further modeling and analyzing the specific intermolecular attractions instead of relying on a scoring function
- Wet bench experiments to confirm results are outside the scope of this project but would be a goal for future research

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