During SAMPL4[1](#_ENREF_1) and SAMPL5[2](#_ENREF_2) we focused on two hosts: the octa-acid **1** (R = H) and another octa-acid derivative with four methyl groups positioned at the portal of the binding pocket (**1**, R = Me). These studies used Isothermal Titration Calorimetry (ITC) to measure the thermodynamics of respectively: **1** (R = H) complexing a range of carboxylate guests, and the binding of carboxylate and trimethylammonium guests to both hosts (**1**, H = H and Me). In both cases NMR was also used in a confirmatory role for free energy data. SAMPL5 emphasized that slight differences in the shape of the hydrophobic pocket of the host can in the case of some guests have a profound affect on affinity.

To continue with this work we will expand on the range of hosts by including **2** and **3** in our ITC studies. Like cavitand **1**, host **2** is an octa-acid derivative. However, the four benzoate groups are relocated from the extreme exterior in the case of **1**, to the rim of the binding pocket in **2**. We surmise that this will have a direct effect on the binding of charged guests, but more subtly, an indirect effect on guest complexation via changes to the solvation of the empty host. Octa-trimethylammonuim cavitand (“positand” **3**) has the same overall architecture as host **1**, but inverts the charges on the water solubilizing exterior coat. It is not entirely clear at this juncture if this switch in groups relatively remote from the pocket can directly affect guest complexation. However related (unpublished) results suggest that it can.



Guests for the five proposed ITC studies will be obtained from commercial sources and will be selected on both the limitations of force-fields available to the computationalists and new data as it is gathered. The PI (Mobley) will ratify each final list of guests.

SAMPL6 will involve hosts **1** and **2** with a set of five, previously uninvestigated guests. The principle aim for our group will be to examine how the location of the carboxylate affects guest binding. Building on what the computational chemists learn from this study, SAMPL7 will compare hosts **1** and **3** with a different set of five guests. We anticipate that because of the relative remoteness of the charged groups in these two hosts, the effects of switching charges will be subtler than the differences between **1** and **2**. SAMPL8 will switch gears and consider the effects salts have on guest binding. Thus, we will compare the effects of NaCl and NaI on the complexation of five guests to **1**. We have previously shown that iodide has a weak affinity for the binding pocket of **1**, whilst sodium ions have an affinity for the outer carboxylates,[3](#_ENREF_3) and this will be made clear to the participants. We will follow on from this with SAMPL9 looking at the affects of these same two salts on the complexation of five guests to **3**. We have not yet quantified the complexation of this salt to host **3**, but expect the iodide to have affinity for both the pocket and the positively charged solubilizing groups. Finally, for SAMPL10 we will consider the effects of co-solvents on the binding of five guests to **1** and **2**. This is for us an entirely new area, but we expect binding to be weaker because of co-solvent affinity for the binding pocket leading to competition; there will be an apparent weakening of the hydrophobic effect. However, the precise nature of this weakening phenomenon are unclear.

**References**

1. Gibb C. L. D., Gibb B. C. *Binding of cyclic carboxylates to octa-acid deep-cavity cavitand*. J. Comput. Aided Mol. Des., **2014**, *28*(4), 319-25. doi: 10.1007/s10822-013-9690-2. PubMed PMID: 24218290; PubMed Central PMCID: PMC4018434.

2. Sullivan M. R., Sokkalingam P., Nguyen T., Donahue J. P., Gibb B. C. *Binding of carboxylate and trimethylammonium salts to octa-acid and TEMOA deep-cavity cavitands*. J. Comput. Aided Mol. Des., **2016**, *SAMPL5 Special Issue*. doi: 10.1007/s10822-016-9925-0. PubMed PMID: 27432339.

3. Carnagie R., Gibb C. L. D., Gibb B. C. *Anion Complexation and The Hofmeister Effect*. Angew. Chem. Int. Ed., **2014**, *53*(43), 11498-500. doi: doi.org/10.1002/anie.201405796 PubMed PMID: 25196481.