Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Supplemental Information:

Cryptate Binding Energies Towards High Throughput Chelator Design: Metadynamics Ensembles with Cluster-Continuum Solvation

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While the xTB curves in Figure 3b are smooth, the subsequent r^{2}SCAN-3c[1] relaxation introduces some variance due to the variable degree of stabilization upon relaxation. The composite variance in the binding energy of the cluster vs. solvent molecules added is dominated by that of the cryptate complex rather than the aqueous metal ion. To examine this effect, we varied the energy cut-off, E_{win}, of the NCI-MTD steps for 2-30 water molecules added in increments of 2, with the results for Ca-cryptate shown in Figure 1. The green data represents the cryptate binding energy relative to the least-solvated case (with n, the number of water molecules, at just 2), while red is the convergence, quantified by the rate of change of the binding energy vs. n.

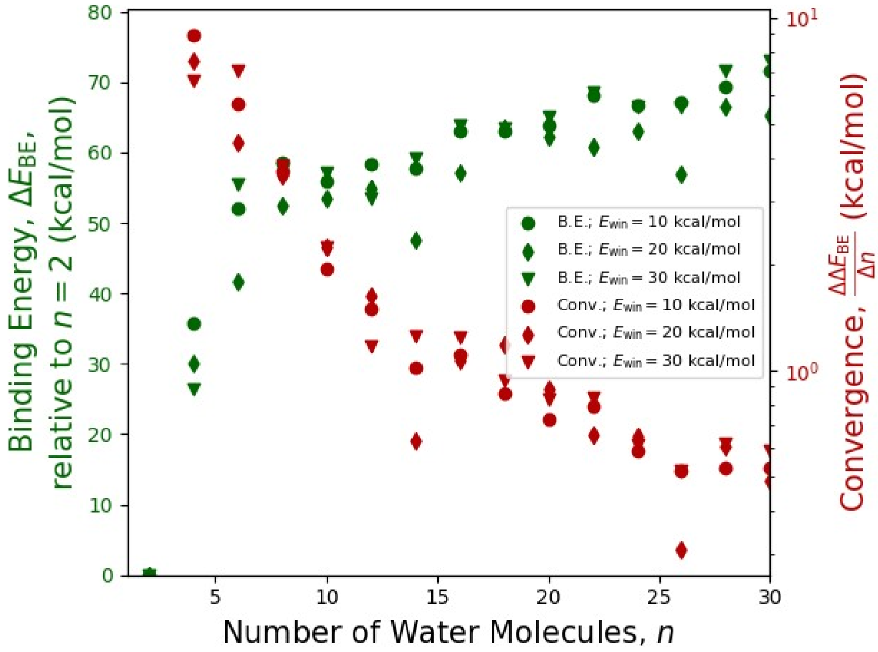

Figure S1: Convergence behavior of Ca-cryptate clusters as a function of added water molecules using CENSO/r^{2}SCAN-3c.[1,2], E_{win} is the CREST energy cutoff in kcal/mol.[3]

One observation is how minimal the impact of the energy window is for QCG for this system; however, relative to the computational expense of the entire scheme is much larger than that of the QCG solvation step, so the higher E_{win} setting is still recommended. Second, the variance for the binding energies here are much greater than for those in Figure 3b. It grows with n, likely a result of increasing unevenness of the PES. This can be mitigated by simply running the calculation multiple times, a feature of the computational efficiency of this scheme. This would be expected to lower the standard deviation by a factor of $\sqrt{s}$, s being the number of samples taken. We conclude that the number of solvent molecules should be chosen such that it is large enough that the difference in the interaction energies of the complex and lone metal ion with the solvent is well converged, but small enough so that variance is minimized in the relaxation and multiple runs can be conducted.

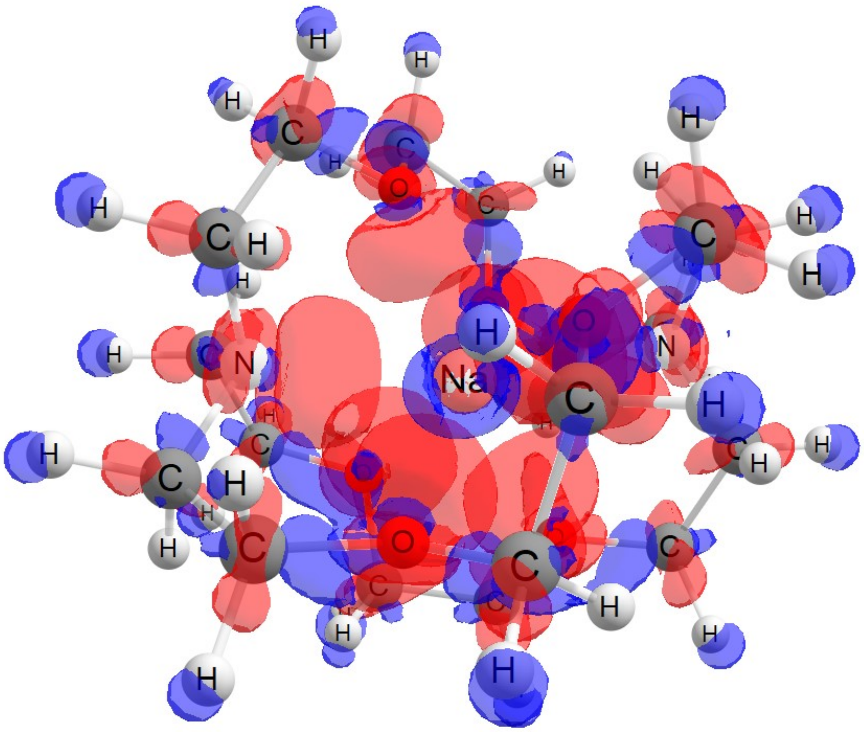

Figure S2: Na complex charge redistribution.

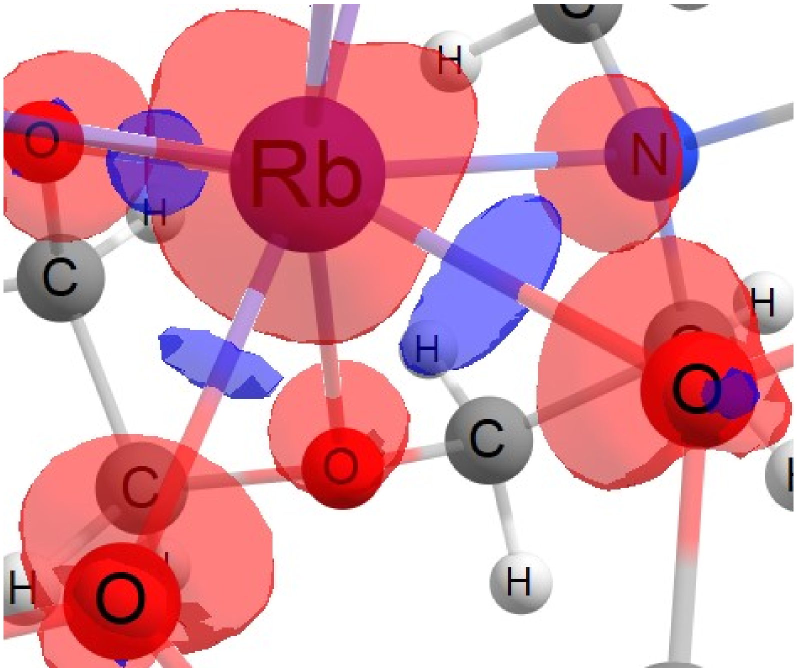

Figure S3: Rb complex charge redistribution.

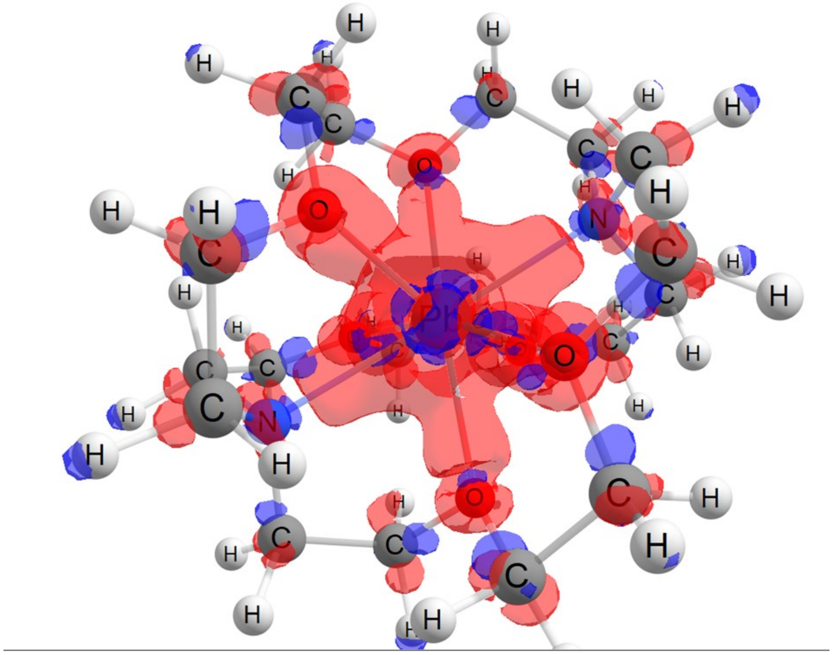

Figure S4: Pb complex charge redistribution.

Table S1: Metal-O/N distances for solvated complexes, calculated with GFN2-xTB and r^{2}SCAN-3c. The calculated % change is relative to the r^{2}SCAN-3c values.

	Average Metal-O/N Distance (Å)					
	GFN2-xTB		**r^{2}SCAN-3c**		**% Change**	
Metal	**N**	**O**	**N**	**O**	**N**	**O**
Ca	2.534	2.282	2.564	2.455	-1.19	-7.02
K	2.920	2.514	2.882	2.792	1.32	-9.98
Na	2.804	2.308	2.628	2.528	6.68	-8.71
Pb	2.689	2.675	2.740	2.704	-1.86	-1.07
Rb	3.080	2.707	3.003	2.894	2.56	-6.44
Zn	2.262	3.012	2.138	3.092	5.78	-2.59

Table S2: Standard deviations of ensemble energies across 10x runs apiece, in kcal/mol

	Ca(II)	**K(I)**	**Na(I)**	**Pb(II)**	**Rb(I)**	**Zn(II)**
Metal Ion	0.70	1.13	1.45	1.19	1.11	0.50
[2.2.2] Cryptate	1.81	3.63	3.87	2.15	4.31	3.11
[2.2.2] Cryptand	1.31					

References

(1) Grimme, S.; Hansen, A.; Ehlert, S.; Mewes, J.-M. r^{2}SCAN-3c: A "Swiss Army Knife" Composite Electronic-Structure Method. *Journal of Chemical Physics* **2021**, *154* (6). https://doi.org/10.26434/chemrxiv.13333520.v1.

(2) Grimme, S.; Bohle, F.; Hansen, A.; Pracht, P.; Spicher, S.; Stahn, M. Efficient Quantum Chemical Calculation of Structure Ensembles and Free Energies for Nonrigid Molecules. *J. Phys. Chem. A* **2021**, *125* (19), 4039–4054. https://doi.org/10.1021/acs.jpca.1c00971.

(3) Pracht, P.; Bohle, F.; Grimme, S. Automated Exploration of the Low-Energy Chemical Space with Fast Quantum Chemical Methods. *Phys. Chem. Chem. Phys.* **2020**, *22* (14), 7169–7192. https://doi.org/10.1039/C9CP06869D.