Supporting Information

Mechanistic and Dynamic Insights into Ligand Encapsulation by Helical Arylamide Foldamers

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All atom molecular dynamics (MD) simulations were performed on free **O1** and **O1**-H_2O, **O1**-H_2O_2, **O1**-N_2H_4, **O1**-HCOOH, **O1**-CH_3OH complexes using general AMBER force field (GAFF).[1] As aromatic rings and peptide bonds in the helical oligoamide, **O1**, are stabilized by electron delocalization, the flexibility in **O1** comes from the rotation around the aryl-amide ($C_{aromatic}$-$C_{peptide}$ and $C_{aromatic}$-$N_{peptide}$) bonds. Previous studies have shown that GAFF overestimates the torsional potential for the rotation around these bonds (the GAFF torsional barrier corresponds to 29 kcal/mol,[1] while quantum mechanically derived barriers are less than 10 kcal/mol[2]). Therefore, we reparametrized torsional parameters in GAFF using methodology described in our previous studies.[3,4] The modified torsional parameters ($V_{n/2}$)[a] are 3.6, 5.7, 4.3 and 4.2 kcal/mol for the torsions around the $C_{quinoline}$-$C_{peptide}$, $C_{quinoline}$-$N_{peptide}$, $C_{pyridine}$-$C_{peptide}$ and $C_{pyridine}$-$N_{peptide}$ bonds, respectively. The atomic charges were derived by the RESP[5] procedure.

The starting structure for **O1** was built using LEaP module in the AMBER 12 suite of programs.[6] The **O1**-ligand initial structure was constructed by placing the ligand, randomly orientated, in the center of a pre-equilibrated capsule **O1** using UCSF Chimera.[7] All MD starting structures were placed in three solvents – water (using ~3500 with TIP3P[8] water molecules and a box size of ~50 x 50 x 50 $Å^3$), methanol (using a box size of ~50 x 50 x 50 $Å^3$ with ~3300 molecules), and chloroform (using a box size of ~60 x 60 x 60 $Å^3$ with ~1300 molecules). The systems were simulated using SANDER module of the AMBER 12 package. Periodic boundary conditions were used with the particle mesh Ewald[9] (PME) procedure for the long-range electrostatic interactions in the periodic box systems. SHAKE[10] algorithm for constraining all bonds involving hydrogen atoms was applied with an integration time step of 1 fs. The simulations were first equilibrated for 500 ps in an NPT ensemble at constant temperature of 300 K and pressure of 1 atm. Production runs were then performed for 50 ns in an NVT ensemble.

The Ptraj module in the AMBER 12 package was used to analyze **O1**-ligand and solvent-**O1** hydrogen bonds. The **O1** conformational distributions were calculated using *in-house* Perl scripts. The central cavity volumes were measured using the SURFNET program.[11] The figures were generated using VMD[12] and the distributions were plotted using Origin.[12]

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[a] V_n in kcal/mol. $E_{torsion} = \frac{V_n}{2}(1+\cos(n\phi - f))$, n = 2 and $f = 180°$.

For selected systems, additional simulations from different **O1**-ligand initial structures were carried out. Our objective was to gain better statistics in capsule-ligand binding interactions as well as on stabilities of capsule-ligand complexes. Therefore, most of the additional simulations were carried out on systems with relatively short encapsulation durations. The initial structures of the additional runs were extracted from previous runs and the velocities were re-initialized. One exception is the **O1**-H_2O system in which one additional simulation was carried out from the crystal structure.

Table S1. Summary of initial conditions,[a] encapsulation durations, and departure mechanisms of all MD simulations.

	water	methanol	chloroform
H_2O	1 - ~23.5 ns, top 2 (crystal structure) - ~25 ns, top	x, (100 ns)[b]	x
H_2O_2	~6.2 ns, top	~6.3 ns, top	x, (80 ns)[b]
N_2H_4	1 - ~0.8 ns, top 2 - ~1.0 ns, top 3 - ~0.5 ns, top	~6.4 ns, side	~38.8 ns, top
HCOOH	1 - ~2.7 ns, top 2 (binding mode I)[c] - ~0.5 ns, top	~3.1 ns, side	x
CH_3OH	1 - ~0.3 ns, top 2 - ~0.8 ns, top 3 - ~0.1 ns, top	1 - ~0.4 ns, side 2 - ~0.5 ns, side 3 - ~0.2 ns, side	~12 ns, side

[a] For the first run, the **O1**-ligand initial structure was constructed by placing the ligand, randomly orientated, in the center of a pre-equilibrated capsule **O1.** The initial structures of the additional runs (if not specified) were extracted from previous runs in the same solvent and the velocities were re-initialized.
[b] Total simulation time is in parenthesis, it is 50 ns if not specified. x indicates cases where ligand did not leave during the whole simulation length.
[c] Since the first run gave exclusively binding mode II, the second one started from an initial **O1**-HCOOH structure in binding mode I, extracted from a previous run in chloroform.

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