Supporting Information

Role of Donor Acceptor Macrocycles in Sequence Specific Peptide Recognition: A Detailed Computational Insight

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Conformational Analysis:

We have performed a detailed conformational analysis for the CPP-TCAQ system to show that the host-guest system is stable in different conformations and the binding energy trend also is followed for conformational changes in the system. We have carried out *Ab initio* molecular dynamics (AIMD) calculations using the QUICKSTEP module in the CP2K package, and we have considered the same set of parameters used for DFT calculations. Simulations are run at 300 K by using a Nose–Hoover thermostat.[1-2] The time step of 0.5 fs is used to integrate the equations of motion. The 20 ps trajectories are generated and used for analysis. First, we generated some structures from *ab-inito* MD and also rotated the peptide sequences inside the ring to create almost 50 random structures, and performed single point calculations. We found that tyr-leu-ala shows more affinity towards the ring.

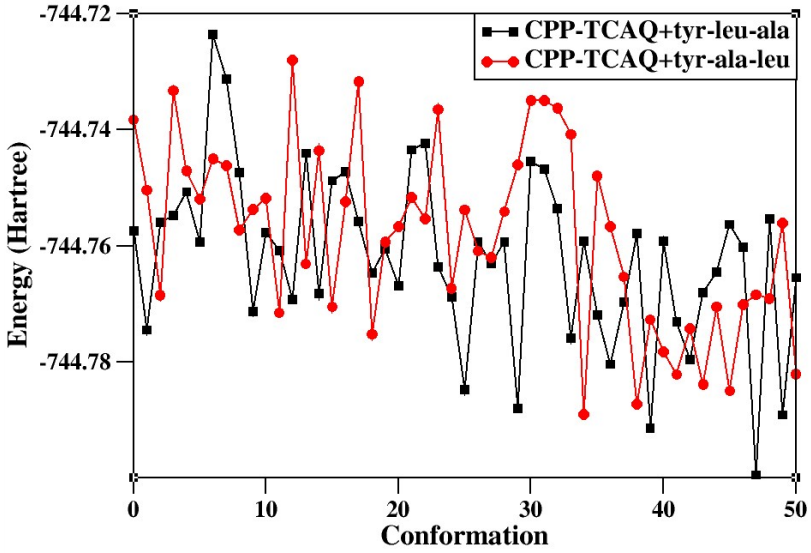
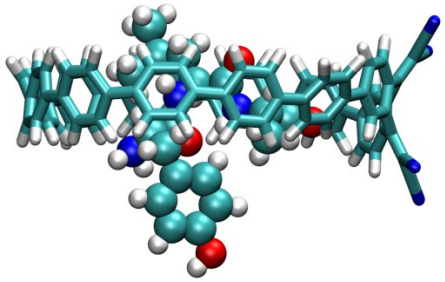
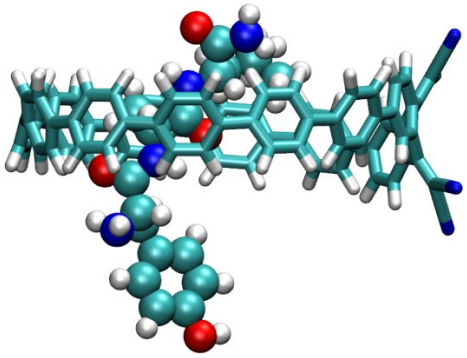
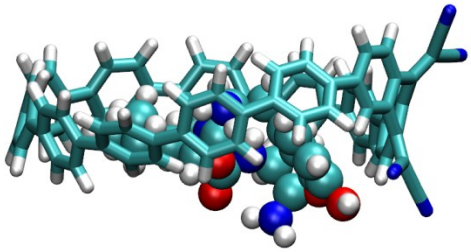
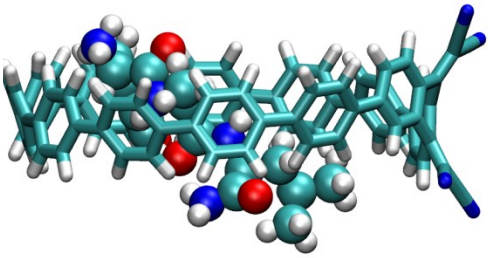


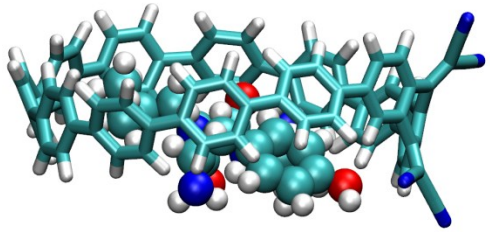
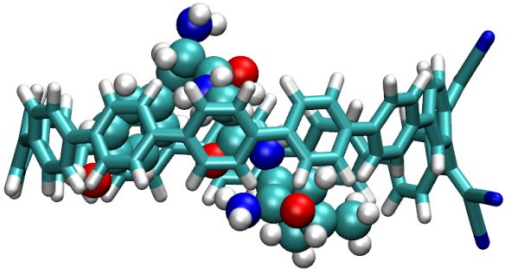
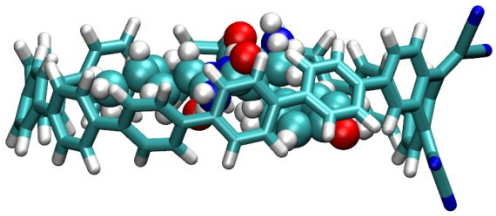
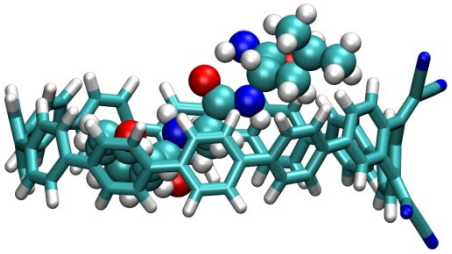
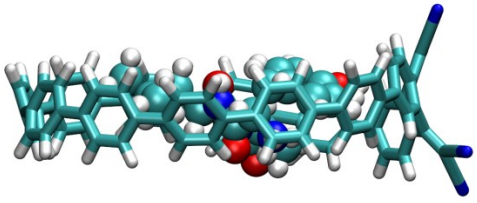
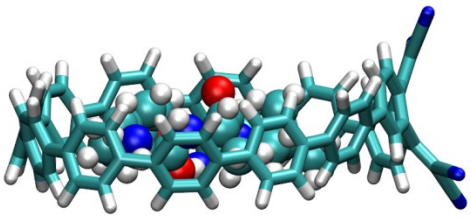
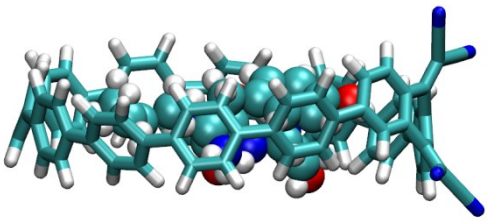
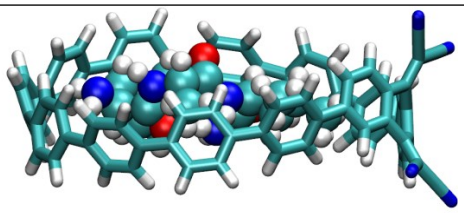
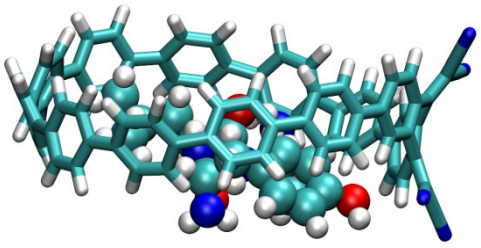
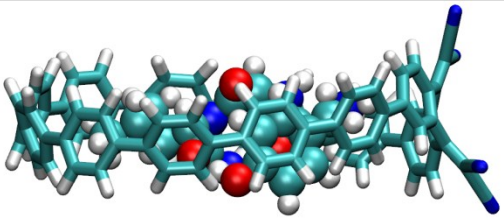
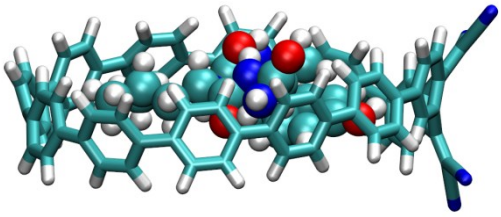
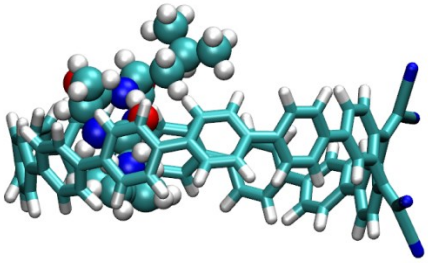
Figure S1: Energies of different conformations of the tripeptides inside the macrocycle CPP-TCAQ

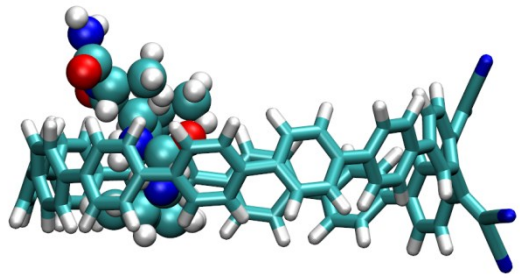
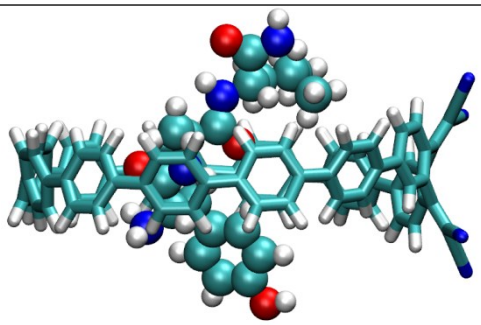
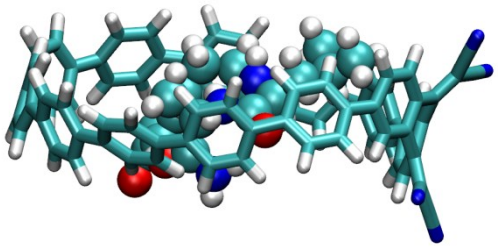
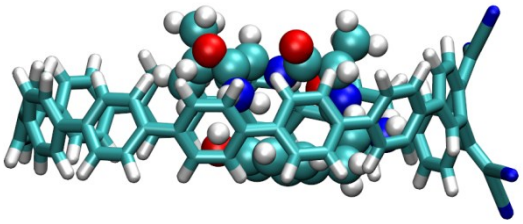
Finally, we took the low energy structures and optimized them using DFT. We present a set of quantum mechanically optimized low energy structures to show that still the most stable structure of CPP-TCAQ+tyr-leu-ala and CPP-TCAQ+tyr-ala-leu have an binding enery difference of 0.083 eV (table S1), where the former one is more stable. From the optimized energies of a number of CPP-TCAQ macrocycle with both the tripeptides, we find our conclusion to be correct, that is, tyr-leu-ala gets captured selectively than tyr-ala-leu. In presence of water also this remains same as anyway CPP-TCAQ macrocycle inner pore is hydro-phobic. For other complexes we studied a few conformers and found that still our result remains same.

It should be noted that, for the 1st row structures in table S1, there is a very weak non-covalent interaction present. Thus, these host-guest complexes are less stable. However, still tyr-leu-ala gets selectively recognized.

Table S1: DFT optimized structures and relative binding energies of the host-guest complexes of (i) CPP-TCAQ and tyr-leu-ala, (ii) CPP-TCAQ and tyr-ala-leu (iii) CPP-TCAQ and tyr-leu-ala in different conformations. Energies are given in eV.

CPP-TCAQ+tyr-leu-ala	**CPP-TCAQ+tyr-ala-leu**
 **0.94**	 **1.16**
 **0.18**	 **0.42**

 0.18	 0.66
 0.12	 0.43
 0.08	 0.08
 0.05	 0.14
 0.0	 0.095
 0.16	 0.12

 0.56	 0.89
 0.56	 0.32

Classical MD results:

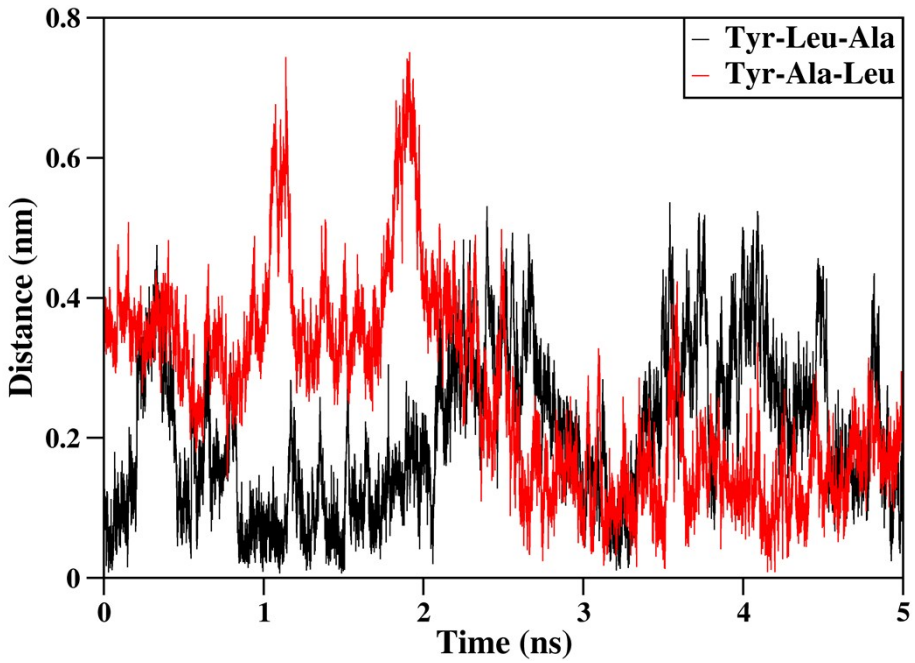


Figure S2: Plot of distance between the centre of masses of the tripeptides and the macrocycle evolving with time.

References:

1. Nosé, S., A Unified Formulation of the Constant Temperature Molecular Dynamics Methods. *The Journal of Chemical Physics* **1984**, *81*, 511-519.
2. Hoover, W. G., Canonical Dynamics: Equilibrium Phase-Space Distributions. *Physical Review A* **1985**, *31*, 1695.