

**Probing Phenylalanine/Adenine π -Stacking Interactions in Protein Complexes
with Explicitly Correlated and CCSD(T) Computations**

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To examine the effects of π -stacking interactions between aromatic amino acid side chains and adenine bearing ligands in crystalline protein structures, 26 toluene/(N9-methyl)adenine model configurations have been constructed from protein/ligand crystal structures. Full geometry optimizations with the MP2 method cause the 26 crystal structures to collapse to 6 unique structures. The complete basis set (CBS) limit of the CCSD(T) interaction energies have been determined for all 32 structures by combining explicitly correlated MP2-R12 computations with a correction for higher-order correlation effects from CCSD(T) calculations. The CCSD(T) CBS limit interaction energies of the 26 crystal structures range from -3.19 to -6.77 kcal mol $^{-1}$ and average -5.01 kcal mol $^{-1}$. The CCSD(T) CBS limit interaction energies of the optimized complexes increase by roughly 1.5 kcal mol $^{-1}$ on average to -6.54 kcal mol $^{-1}$ (ranging from -5.93 to -7.05 kcal mol $^{-1}$). Corrections for higher order correlation effects are extremely important for both sets of structures and are responsible for the modest increase in the interaction energy after optimization. The MP2 method overbinds the crystal by 2.31 kcal mol $^{-1}$ on average compared to 4.50 kcal mol $^{-1}$ for the optimized structures. This data indicates that CCSD(T) computations are still necessary to obtain reliable interaction energies for π -stacking systems even when they adopt the crystal structure geometry, where the fragments tend to be significantly further apart than at the gas-phase optimized geometry.