Supporting Information

Achieving Chemical Accuracy in Cyclodextrin Host–Guest Binding via Integrative Atomistic Modelling

Fig. S1. Guest molecules binding to cyclodextrins. The experimental binding strengths on α-CD is given under the molecular graphs, in kcal/mol.

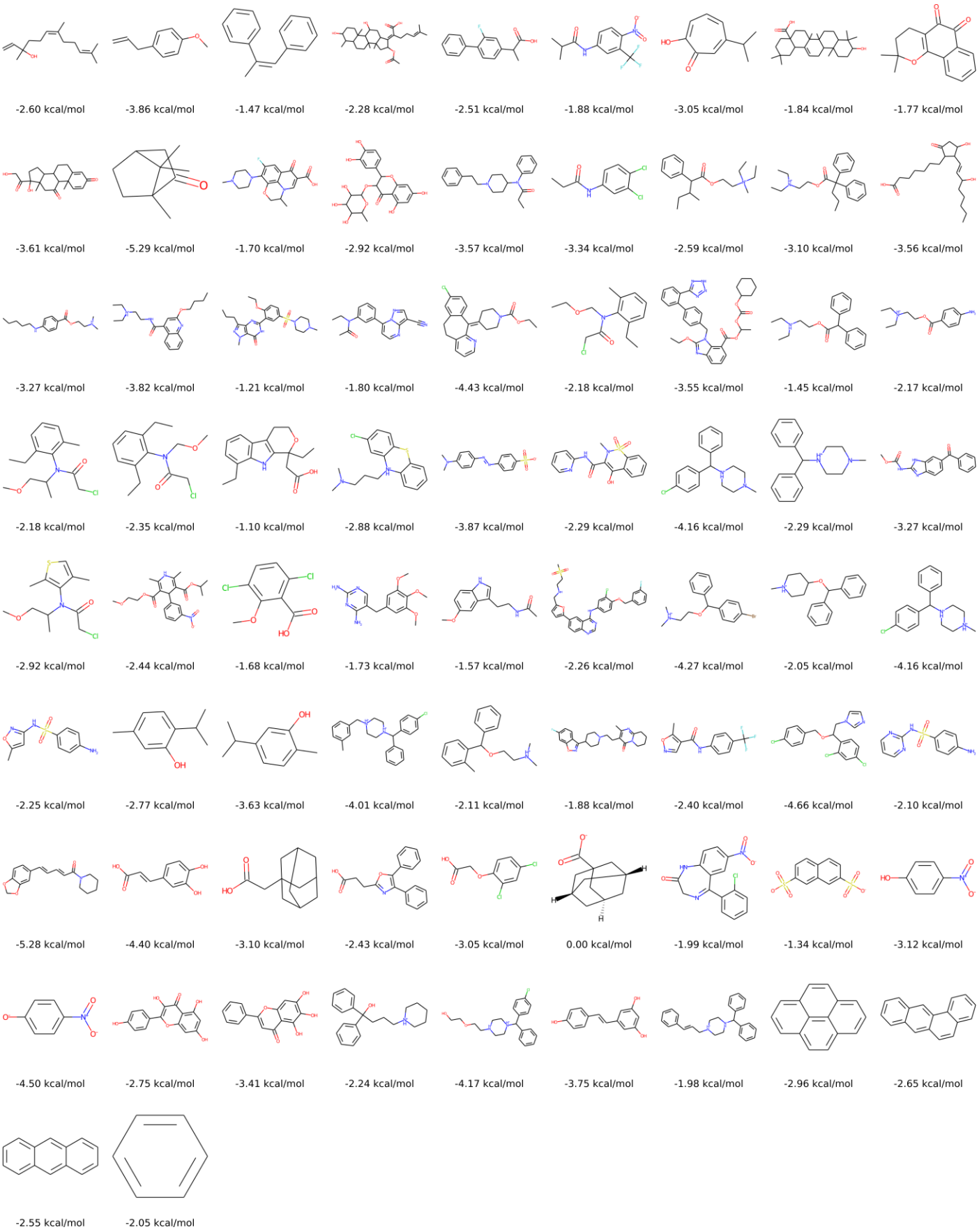


Fig. S2. Guest molecules binding to β-CD, with affinities shown in kcal/mol.

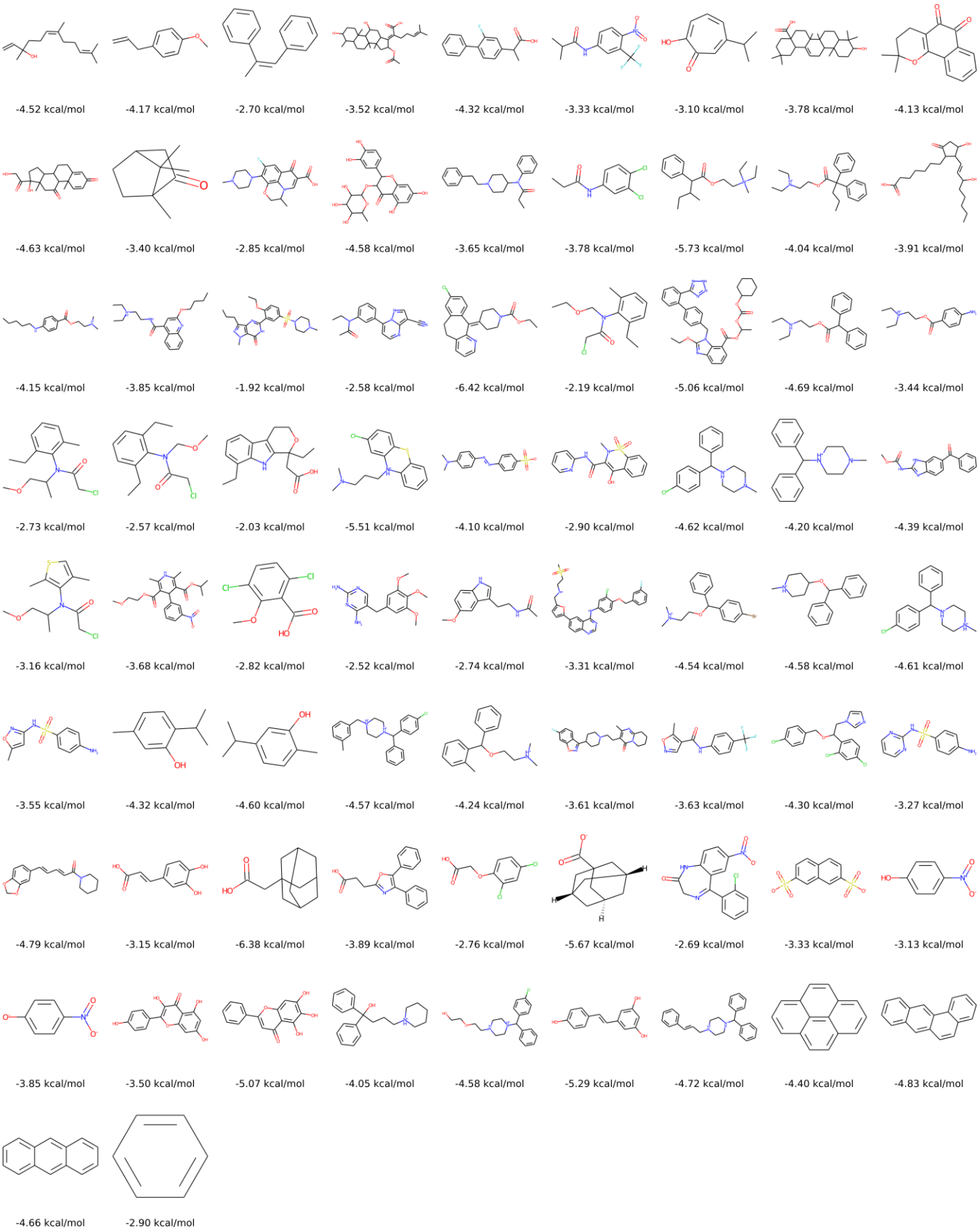


Fig. S3. Guest molecules binding to γ-CD, with affinities shown in kcal/mol.

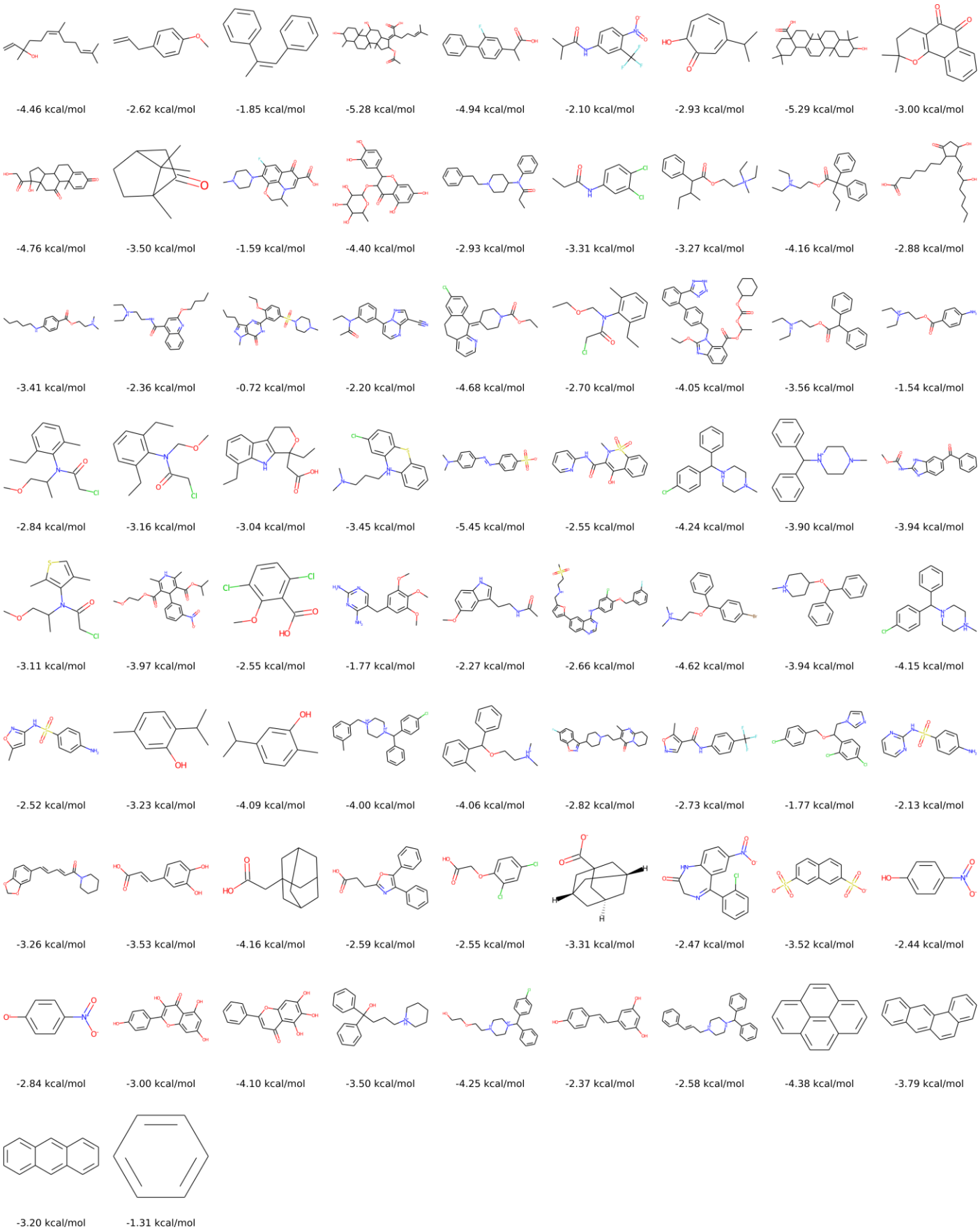


Fig. S4. Performance metrics for the α-CD host-guest dataset. MAE is in kcal/mol, while the other are dimensionless.

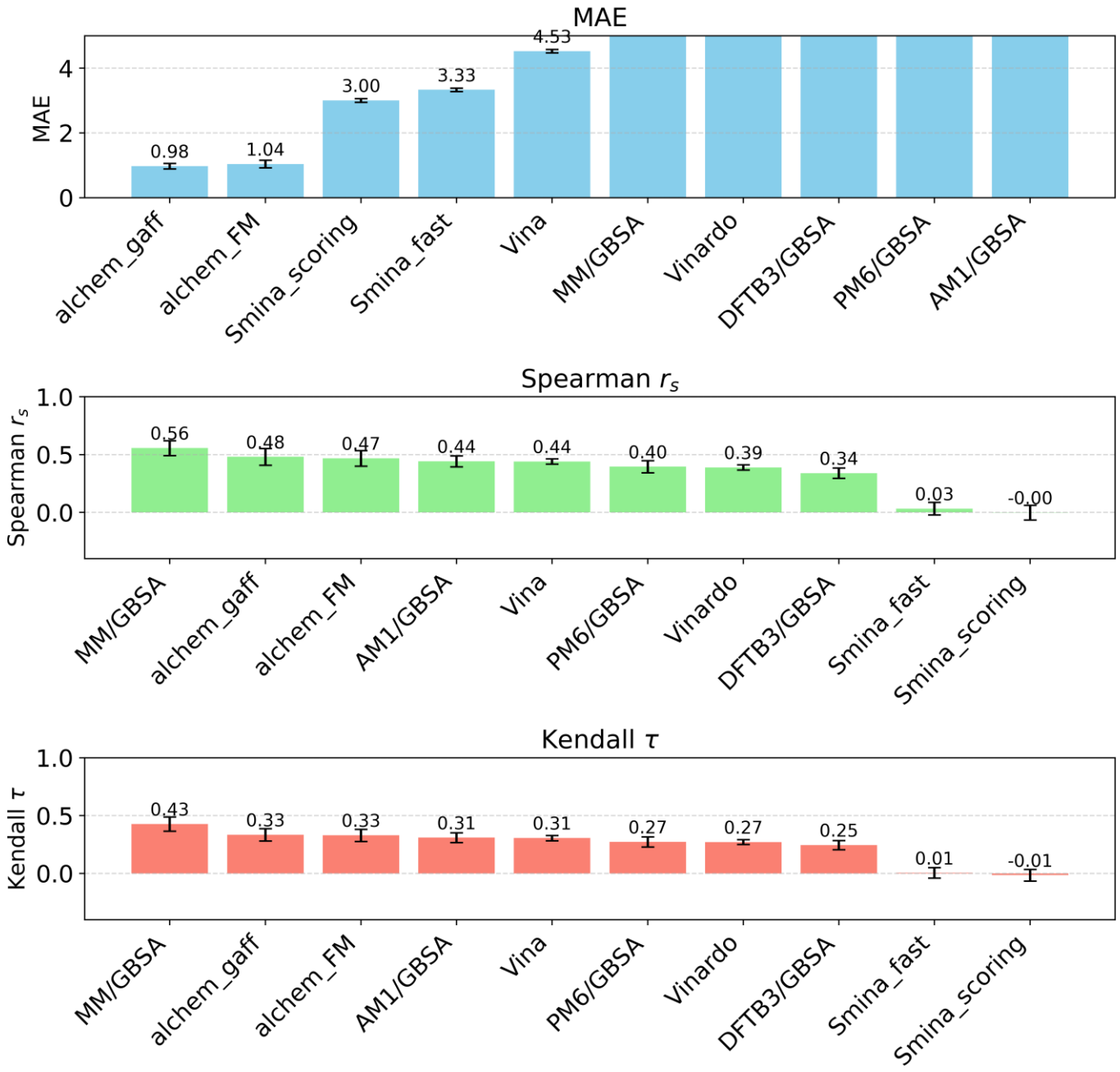


Fig. S5. Performance metrics for the β-CD host-guest dataset. MAE is in kcal/mol, while the other are dimensionless.

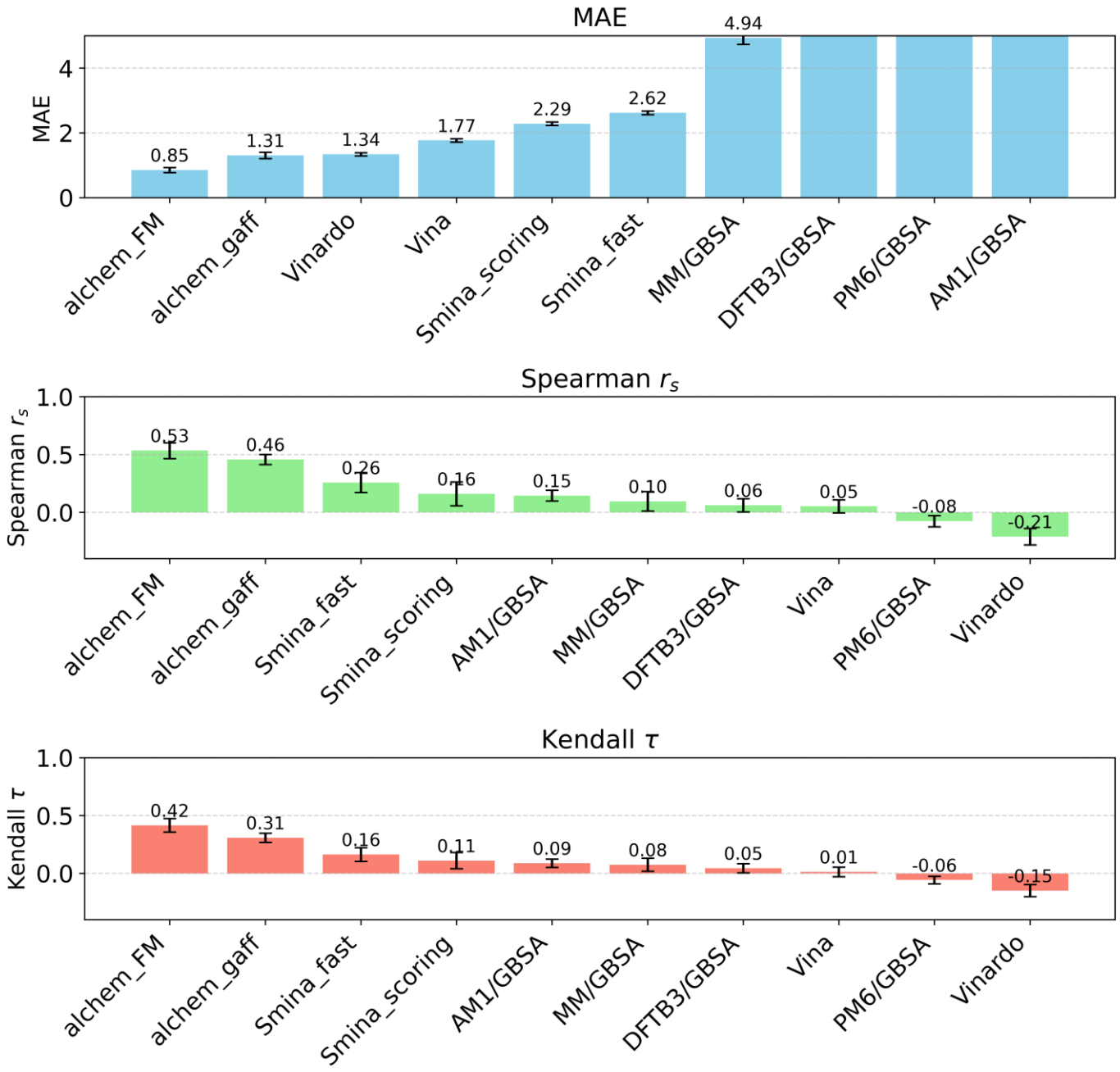
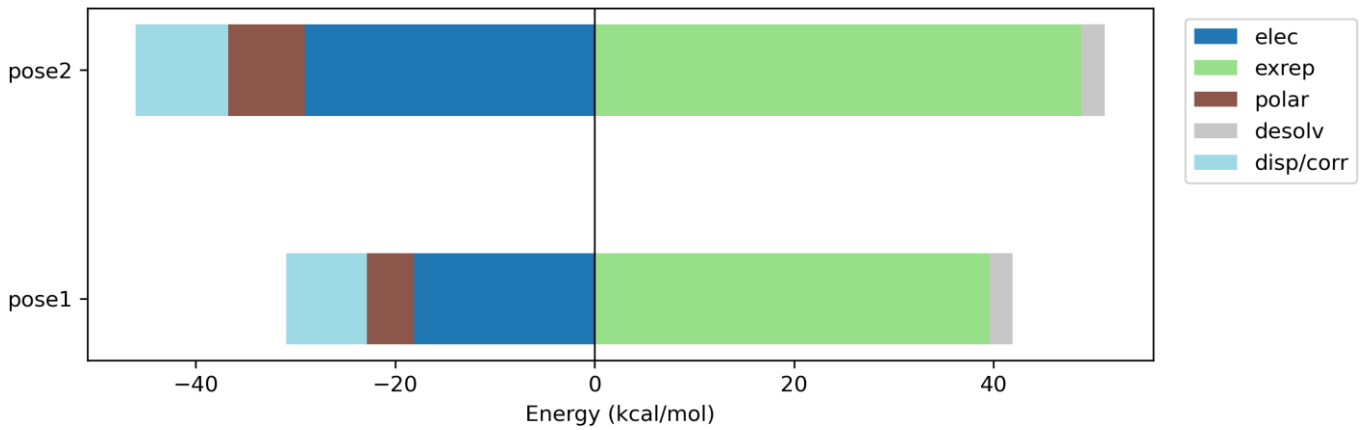


Fig. S6. Energy components from GKS-EDA analysis for the two binding poses shown in Fig. 3B.



Tab. S1. Comparison between the computational cost of the new alchemical-based protocol and the sampling strategy simulating the binding/unbinding event along the physical pathway. The GPU hardware is RTX 4090 and the simulation engine is GROMACS 2020.6 patched with PLUMED 2.7.4.

simulation cells		number of atoms	sampling time (ns)	GPU hours
Alchemical	gas-phase	~30	192	negligible
	unbound	~4000	90	0.83077
	bound	~8000	402	6.432
Physical		~30000	1000	32