Supporting information

The Mechanism of Selective Binding Ability between Opiate Metabolites and Acyclic Cucurbit[4]uril: an MD/DFT Study

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1. Computational Details

MD simulations

Guests were located approximately 1.7 nm away from the host, using Packmol software.[1] Energy minimization was carried out, followed by 1 ns NVT (constant temperature/constant volume) simulations for thermal equilibration and 1 ns NPT (constant pressure/constant temperature) simulations for pressure equilibration. Subsequently, a periodic pulling simulation was carried out in GROMACS, which allowed the distance between the center of mass (COM) of the host and of the steroid ring of guests to be larger than half the box size, to form 1:1 host-guest complexes. The steroid ring of guests has pulled into the ACB[4] cavity with a harmonic force constant of 41840 kJ mol^{-1} nm^{-2} [2] and a pulling rate of 0.001 nm ps^{-1}. To obtain the potential of mean force (PMF) profiles during the binding process, these windows were then used to perform umbrella sampling simulations.[3] Each window was approximately run 30~50 ns.

After the simulation of each window converged, we constructed the PMFs with the weighted histogram analysis method (WHAM).[4-5] Statistical uncertainties of the PMFs were estimated using the Bayesian bootstrap of complete histograms.[5] The PMFs were defined to zero at ξ where host-guest interactions vanish. To reveal the essence of the formation of host-guest complexes in the binding process, the binding energy was analyzed through g_mmpbsa software package.[6-7] The VMD software was used to visualize structures and molecular surfaces.[8]

2. Analytical Data

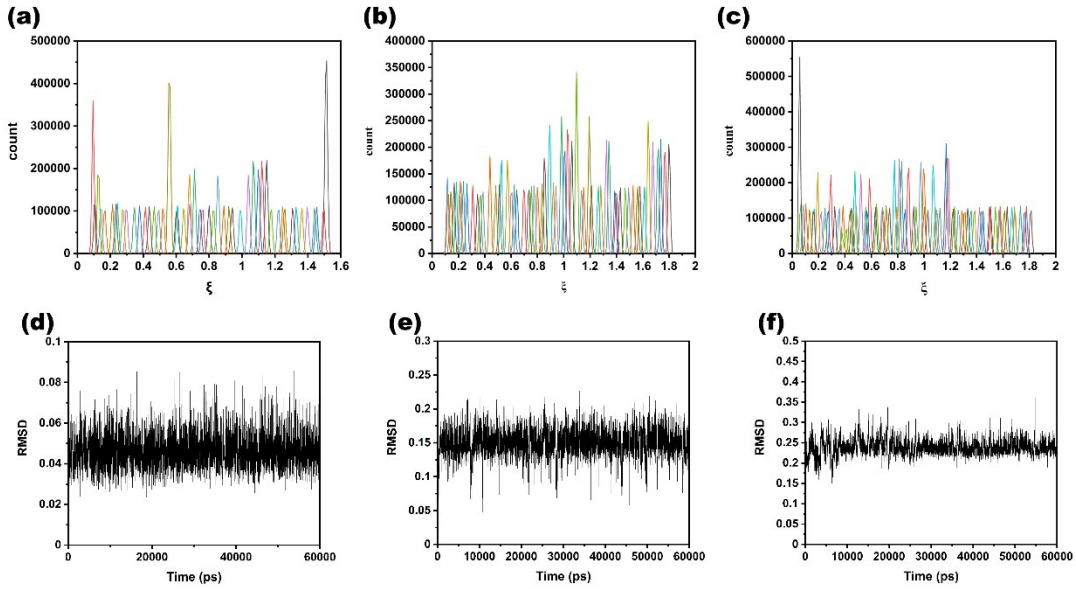

Fig. S1 Histogram of each configuration in the umbrella sampling window. (a), (d): NMOR@S1; (b), (e): MOR@S1; (c), (f): M3G@S1

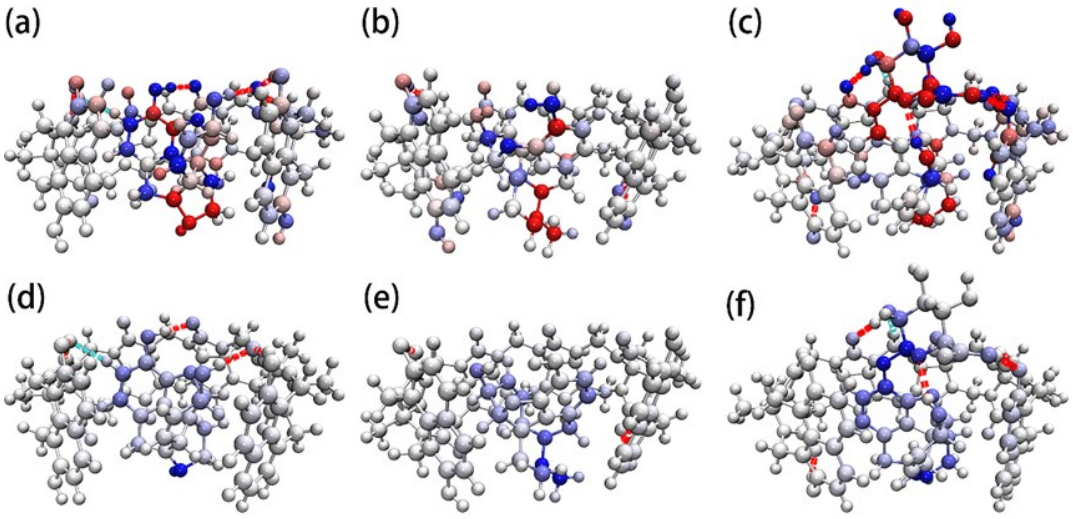

Fig. S2 Atomic coloring diagram of the complex for NMOR@S1, MOR@S1, M3G@S1. (a-c) are atomic contribution to total interaction energy; (d-f) are atomic contribution to dispersion interaction energy. Note: more blue the atoms color make a more negative contribution to interaction energy.

Table S1 QTAIM Parameters (in a.u.) Corresponding to the H---O BCP, the Electron Density at H---O BCP, ρ_{BCP}, its Laplacian, $-\nabla^2\rho_{BCP}$; the Kinetic Electron Energy Density, G_{BCP}; the Potential Electron Energy Density, V_{BCP}; the Total Electron Energy Density at BCP, H_{BCP}; Electron localization function, ELF; Cor-Valence Bifurcation Index, CVBI.

		ρ_{BCP}	$-\nabla^2\rho_{BCP}$	G_{BCP}	V_{BCP}	H_{BCP}	ELF	CVBI
NMOR@S1	O_{43}---H_{158}	0.0195	0.0772	0.0168	-0.0139	0.0027	0.0563	0.0362
	O_{8}---H_{157}	0.0371	0.1297	0.0330	-0.0335	-0.0005	0.1146	-0.0170
	O_{59}---H_{150}	0.0105	0.0327	0.0072	-0.0062	0.0010	0.0386	0.0482
	O_{56}---H_{152}	0.0073	0.0225	0.0049	-0.0042	0.0007	0.0219	0.0614
	O_{26}---H_{151}	0.0029	0.0100	0.0022	-0.0017	0.0005	0.0056	0.0831
	O_{4}---H_{160}	0.0096	0.0310	0.0068	-0.0058	0.0010	0.0327	0.0762
	O_{40}---H_{159}	0.0081	0.0247	0.0055	-0.0048	0.0007	0.0287	0.0544
MOR@S1	O_{56}---H_{151}	0.0088	0.0301	0.0065	-0.0055	0.0010	0.0270	0.0596
	O_{26}---H_{157}	0.0045	0.0148	0.0032	-0.0026	0.0005	0.0122	0.0731
	O_{5}---H_{157}	0.0089	0.0310	0.0066	-0.0054	0.0012	0.0274	0.0564
	O_{121}---H_{158}	0.0036	0.0126	0.0026	-0.0021	0.0005	0.0083	0.0733
	O_{43}---H_{158}	0.0040	0.0137	0.0029	-0.0024	0.0005	0.0101	0.0716
	O_{43}---H_{145}	0.0059	0.0205	0.0046	-0.0040	0.0006	0.0240	0.0594
	O_{8}---H_{145}	0.0074	0.0241	0.0053	-0.0046	0.0007	0.0224	0.0607
	O_{8}---H_{152}	0.0052	0.0177	0.0038	-0.0032	0.0006	0.0139	0.0732
	O_{29}---H_{152}	0.0066	0.0197	0.0044	-0.0039	0.0005	0.0220	0.0653
	O_{120}---H_{153}	0.0065	0.0210	0.0046	-0.004	0.0006	0.0193	0.0627
	O_{120}---H_{164}	0.0046	0.0137	0.0030	-0.0025	0.0004	0.0151	0.0665
M3G@S1	H_{98}---O_{156}	0.0106	0.0373	0.0080	-0.0066	0.0013	0.0327	0.0538
	O_{121}---H_{180}	0.0308	0.1062	0.0258	-0.0251	0.0007	0.1017	-0.0027
	O_{43}---H_{176}	0.0017	0.0069	0.0013	-0.0009	0.0004	0.0028	0.0224
	O_{8}---H_{175}	0.0141	0.0487	0.0105	-0.0089	0.0016	0.0482	0.0488
	O_{8}---H_{178}	0.0079	0.0280	0.0060	-0.0050	0.0010	0.0219	0.0660
	H_{35}---O_{159}	0.0102	0.0338	0.0072	-0.0060	0.0012	0.0346	0.0862
	O_{29}---H_{182}	0.0292	0.1127	0.0263	-0.0244	0.0019	0.0835	0.0114
	O_{59}---H_{163}	0.0055	0.0174	0.0037	-0.0031	0.0006	0.0172	0.0770
	O_{56}---H_{162}	0.0078	0.0250	0.0054	-0.0045	0.0009	0.0264	0.0609
	O_{26}---H_{165}	0.0087	0.0281	0.0062	-0.0053	0.0009	0.0283	0.0558
	O_{5}---H_{184}	0.0065	0.0202	0.0045	-0.0039	0.0006	0.0210	0.0608
	O_{5}---H_{172}	0.0086	0.0281	0.0061	-0.0051	0.0009	0.0284	0.0554
	O_{40}---H_{173}	0.0075	0.0252	0.0051	-0.0046	0.0008	0.0220	0.0645
	O_{40}---H_{171}	0.0049	0.0177	0.0037	-0.0029	0.0008	0.0122	0.0710

Table S2 Average hydrogen bond number and average hydrogen bond lifetime (ps) after trajectory convergence.

	S1	NMOR	NMOR@S1	MOR	MOR@S1	M3G	M3G@S1
Host-Water	16.58(4.94)		15.26(8.09)		15.49(5.02)		15.18(5.58)
Guest-Water		6.26(4.79)	3.74(9.72)	4.89(4.37)	2.90(4.38)	12.41(4.62)	9.08(4.44)
Host-Guest			2.19(74.46)		1.49(22.28)		0.93(76.34)
Complex-Water			19.00(8.37)		18.40(4.91)		24.26(5.10)

3. References

1 L. Martínez, R. Andrade, E. G. Birgin, J. M. Martínez, *Journal of Computational Chemistry*, 2009, 30, 2157-2164.

2 N. M. Henriksen, A. T. Fenley, M. K. Gilson, *Journal of Chemical Theory and Computation*, 2015, 11, 4377-4394.

3 H. -Y. Zhang, T. -W. Tan, C. Hetényi, D. van der Spoel, *Journal of Chemical Theory and Computation*, 2013, 9, 4542-4551.

4 S. Kumar, J. M. Rosenberg, D. Bouzida, R. H. Swendsen, P. A. Kollman, *Journal of Computational Chemistry*, 1992, 13, 1011-1021.

5 J. S. Hub, B. L. de Groot, D. van der Spoel, *Journal of Chemical Theory and Computation*, 2010, 6, 3713-3720.

6 N. A. Baker, D. Sept, S. Joseph, M. J. Holst, J. A. McCammon, *Proceedings of the National Academy of Sciences*, 2001, 98, 10037-10041.

7 R. Kumari, R.Kumar, A. Lynn, *Journal of Chemical Information and Modeling*, 2014, 54, 1951-1962.

8 W. Humphrey, A. Dalke, K. Schulten, *Journal of Molecular Graphics*, 1996, 14, 33-38.