Supporting Information I for:

How are N-methylcarbamates encapsulated by β-cyclodextrin: Insight into binding mechanism

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Contents:

1. Initial structures for MD simulations

Due to the complexity of the conformation space of the four β-CD/N-methylcarbamate systems, we construct four different initial conformations for each system (Fig. S1). The four guest molecules, i.e. PC, BC, CY, CF, can enter β-CD cavity either from the secondary or primary rims of β-CD. The best initial conformations for these systems turn out to be (a1), (b1), (c1) and (d1).

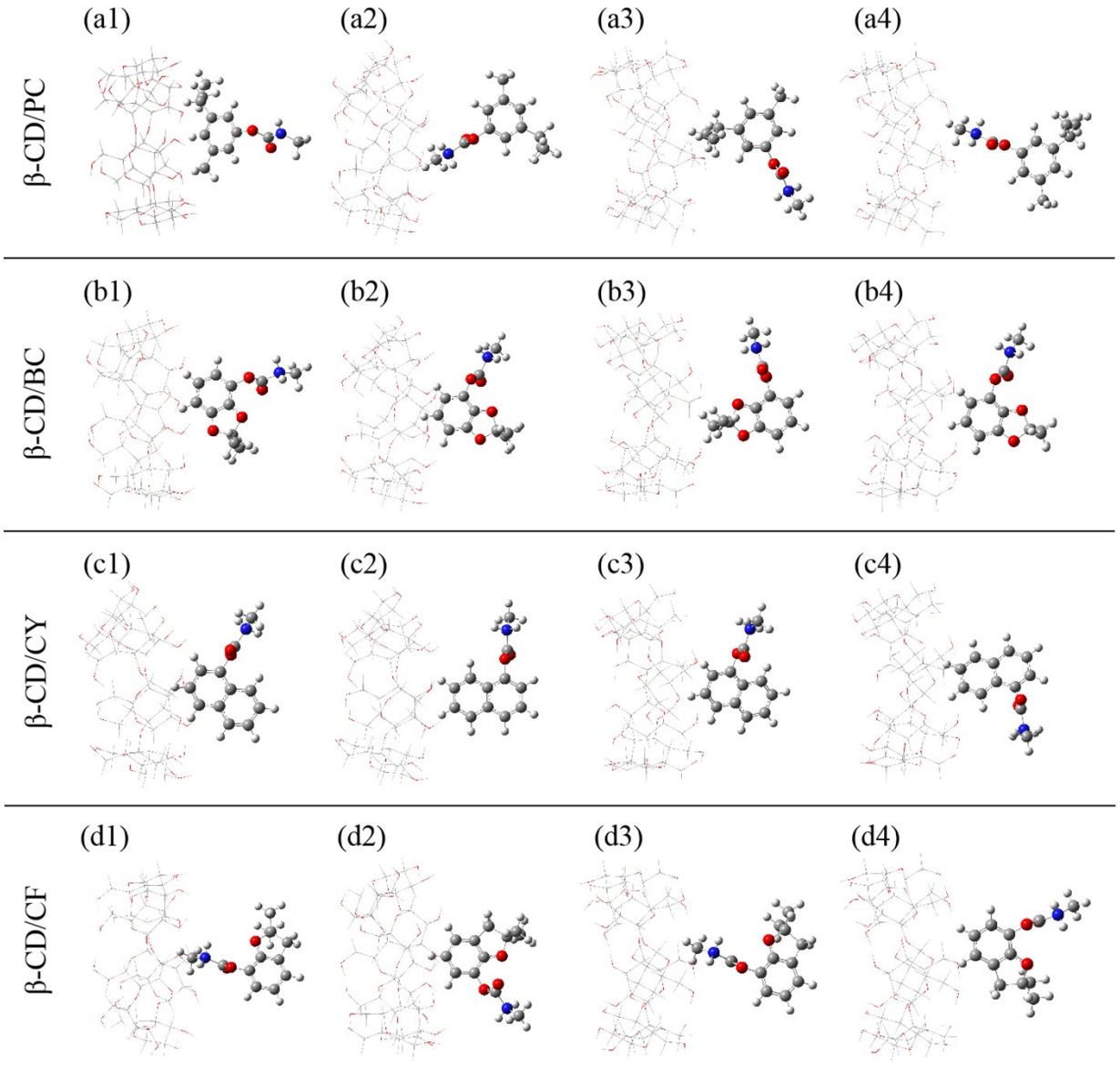

Fig. S1 The four initial structures used for MD simulations of each β-CD complex: (a) PC; (b) BC; (c) CY; (d) CF. The guest molecules in (1) and (2) is close to the secondary rim of β-CD, while those in (3) and (4) is close to the primary rim of β-CD.

2. The test of basis sets for ECD calculations

We perform additional tests using larger basis sets, i.e. 6-311G** and 6-311++G**, for ECD calculations using the four RC_{MM}. As illustrated in the Fig. S2, the three basis sets examined produce very close or similar ECD spectra. Considering the computational costs, we choose the 6-311G(d) basis set for ECD calculations in this study.

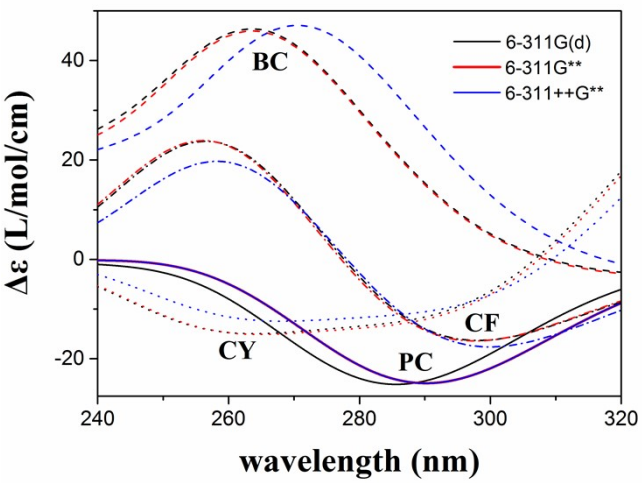

Fig. S2 Comparison of the ECD spectra computed from using B3LYP and three basis sets for the RC_{MM} of PC, BC, CY and CF.

3. The fluctuations of ECD and BA calculations

For each system, we extract RC candidates (RCC_i, i is the *i*th MD trajectory) from MD trajectories using cluster analysis and MM energy minimization. For each system, three $RCC_{i,j}$ are examined as shown in Fig. S3.

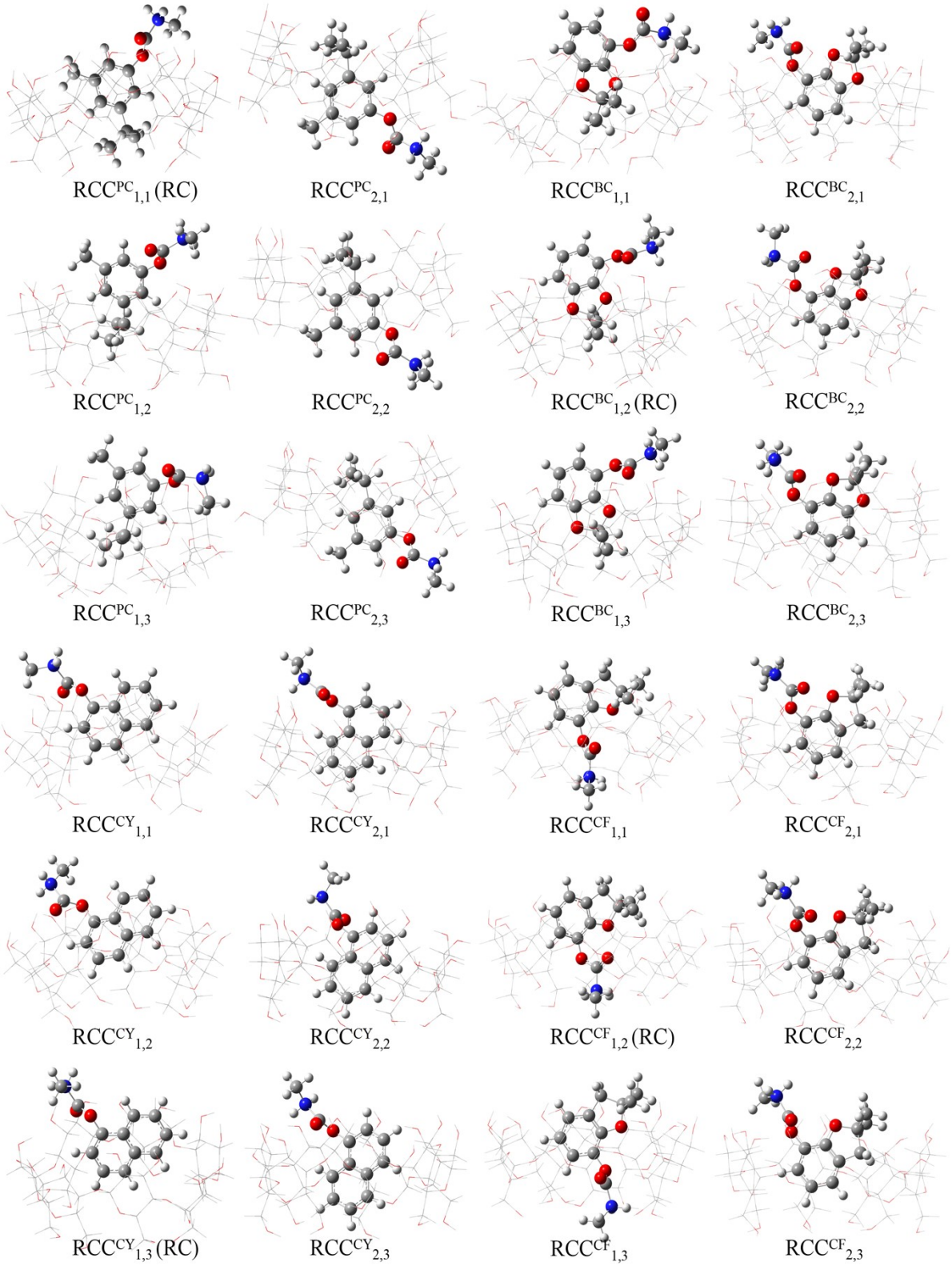

Fig. S3 The RCC$^{A}_{i,j}$ (A=PC, BC, CY, CF) for the four β-CD complexes.

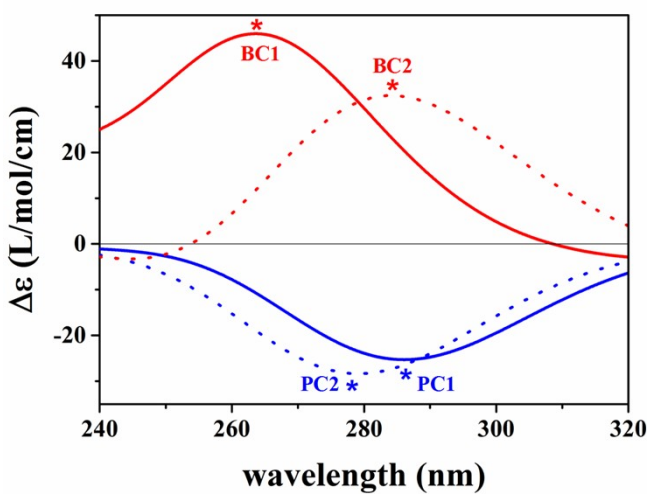

Fig. S4 Computed ECD spectra of β-CD/PC and β-CD/BC using RCC_1 (solid lines) and RCC_2 (dashed line) of. * corresponds the maximum of Δε.

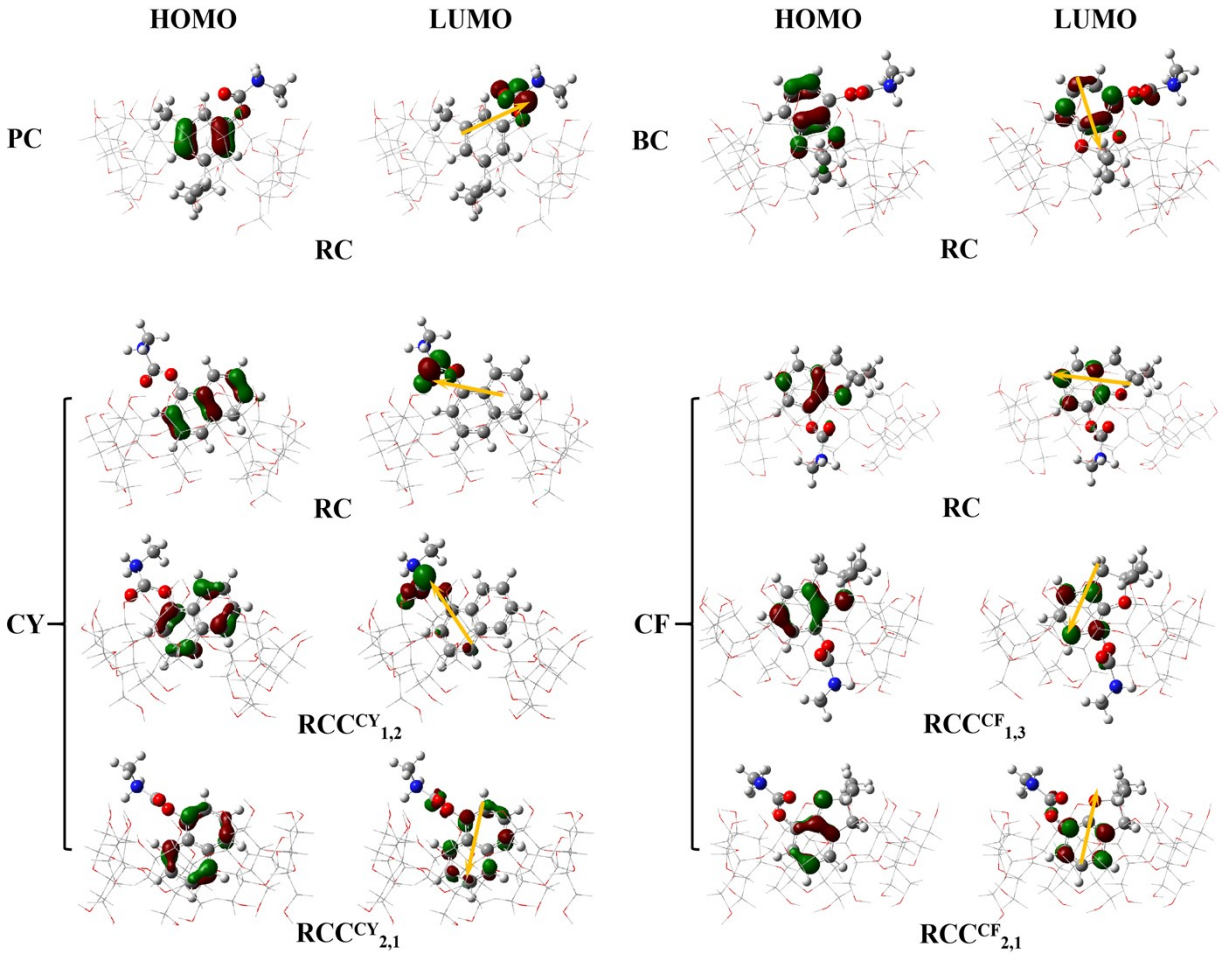

Fig. S5 The transition dipole moment of the host-guest system calculated by RCC_{MM}. The HOMO is on the left, and the LUMO is on the right. The arrows indicate the direction of the dipole moment of the electronic transition for each complex system. The secondary rim of the β-CD is located at the top.

Table S1 Computed BA in vacuum (ΔG_{bind}^{vacu}), solvent effect (ΔG_{bind}^{solv}) and BA (ΔG_{bind}^{aqu}) using $RCC^{A}{}_{i,j}$ (kcal·mol^{-1})

Systems		ΔG_{bind}^{vacu}	ΔG_{bind}^{solv}	ΔG_{bind}^{aqu}
PC	$RCC_{1,1}$	-20.0	6.1	-13.9
	$RCC_{1,2}$	-20.0	24.6	4.6
	$RCC_{1,3}$	-3.0	10.8	7.7
	$RCC_{2,1}$	-12.0	22.3	10.3
	$RCC_{2,2}$	-12.0	24.1	12.0
	$RCC_{2,3}$	-7.0	29.4	22.4
BC	$RCC_{1,1}$	-12.0	6.9	-5.1
	$RCC_{1,2}$	-20.0	19.2	-0.9
	$RCC_{1,3}$	-13.0	24.5	11.5
	$RCC_{2,1}$	-18.0	18.3	0.3
	$RCC_{2,2}$	-16.0	19.1	3.1
	$RCC_{2,3}$	-9.0	30.9	21.9
CY	$RCC_{1,1}$	-11.0	0.6	-10.4
	$RCC_{1,2}$	-1.0	5.0	4.0
	$RCC_{1,3}$	-22.0	33.9	11.9
CF	$RCC_{1,1}$	-23.0	34.4	11.3
	$RCC_{1,2}$	-23.0	37.2	14.2
	$RCC_{1,3}$	-21.0	41.0	20.0

4. Snap shots along optimal MD trajectories

Fig. S6 displays snapshots from the most successful MD trajectories of the β-CD inclusion process with BC, CY, and CF.

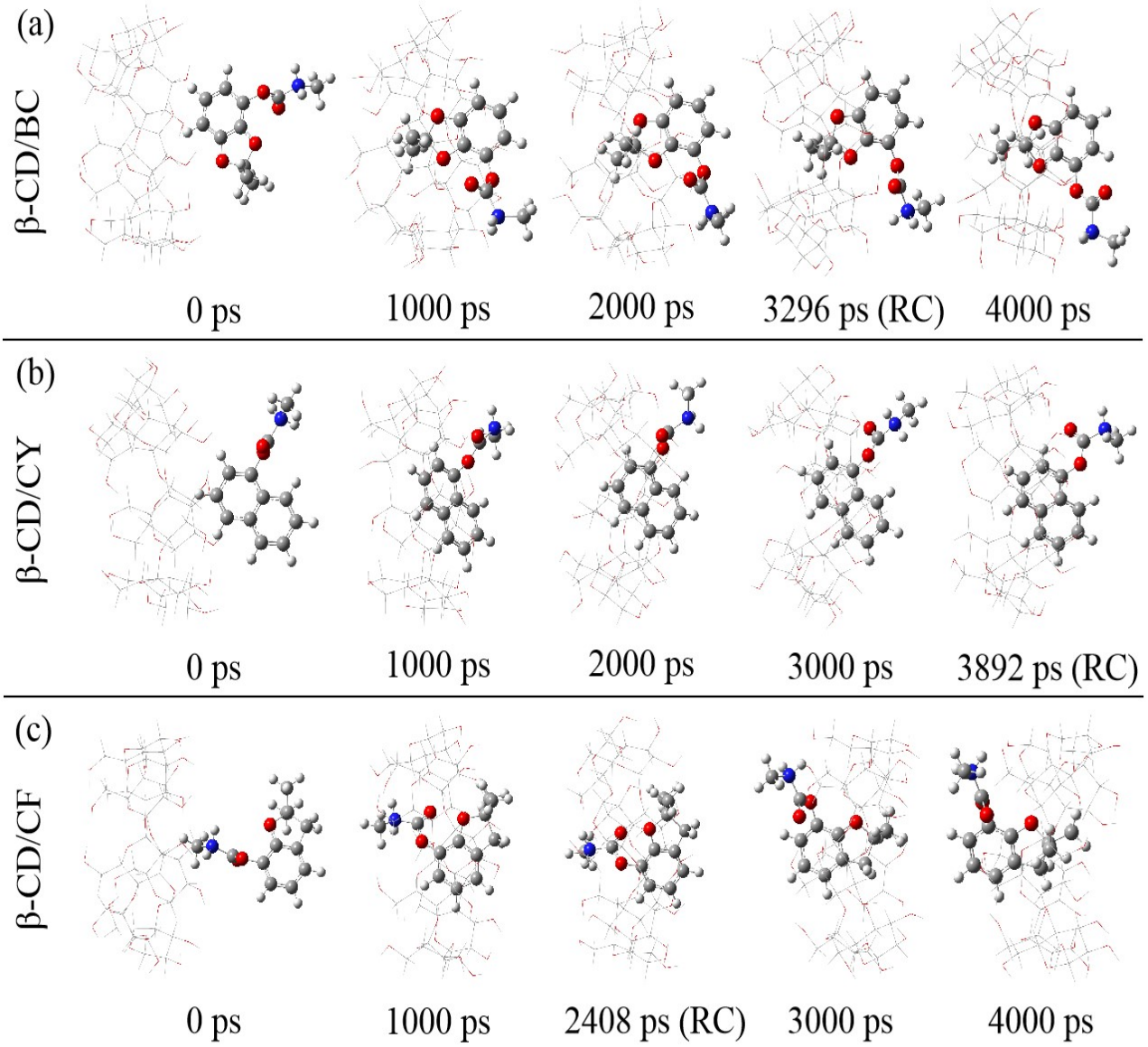

Fig. S6 The snapshots along the best MD trajectories showing the formation processes of the three host-guest systems: (a) β-CD/BC; (b) β-CD/CY; (c) β-CD/CF. The secondary rim of the β-CD is on the right.

5. Cluster analysis

Based on the structural similarity, cluster analysis is performed to classify the conformations along the MD trajectories of the host-guest systems. Those clusters from the optimal MD trajectories are shown in Fig. S7 for the β-CD/PC, β-CD/BC, β-CD/CY, and β-CD/CF systems.

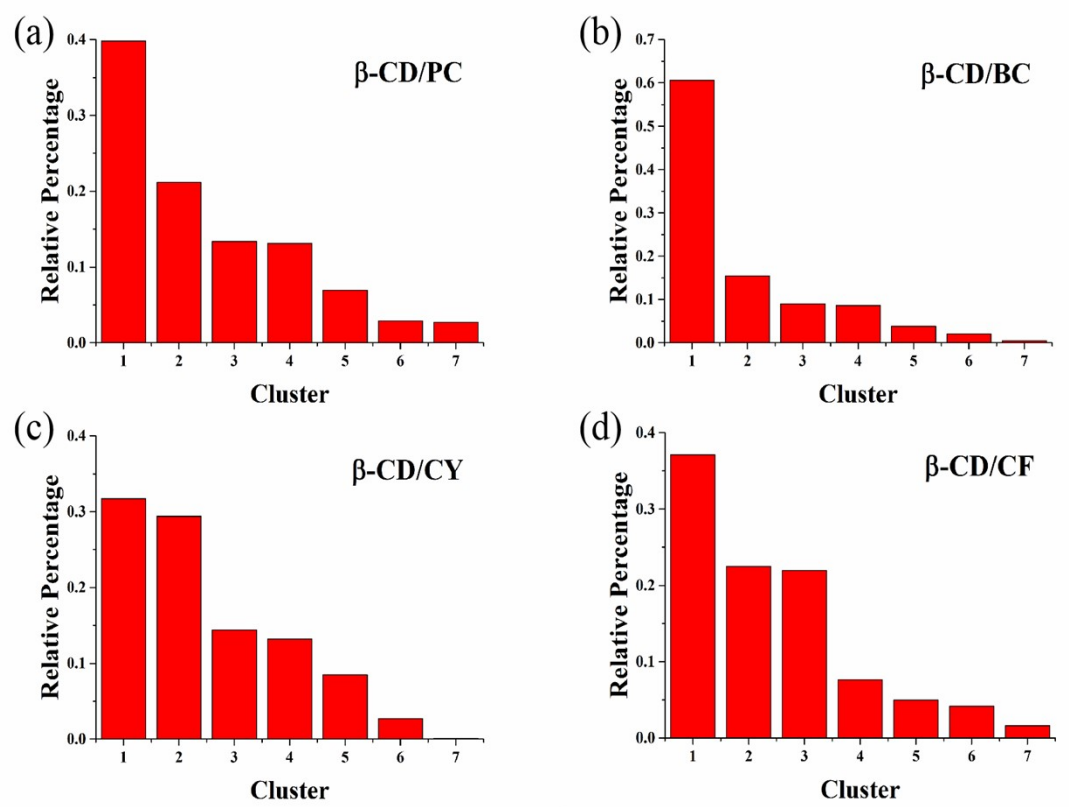

Fig. S7 The relative percentage of different clusters obtained from performing cluster analysis on the MD trajectories of the four inclusion systems.

6. **The computed thermodynamic quantities**

The non-covalent interaction is calculated by ONIOM2(B971/6-31G(d):PM6) method as follows:

$$\Delta E_{bind}^{vacu} = E_{comp,ONIOM2}^{vacu} - \left(E_{host,PM6}^{vacu} + E_{guest,B971}^{vacu}\right), \ [E = H, S, G].$$

The solvent effect is calculated by SMD method as:

$$G^{solv} = G^{elec} + G^{np}$$

$$\Delta G_{bind}^{solv} = G_{comp}^{solv} - (G_{host}^{solv} + G_{guest}^{solv})$$

Table S2 The computed thermodynamic data of β-CD, guest molecules and β-CD complexes (kcal·mol^{-1}).

		H_{bind}^{vacu}	$T \cdot S_{bind}^{vacu}$	G_{bind}^{vacu}	G^{elec}	G^{np}
PM6	β-CD	-846.8	127.1	-974.0	-139.1	16.7
B971/6-31G(d)	PC	-422051.5	40.7	-422092.2	-73.3	8.8
	BC	-491034.5	38.1	-491072.6	-74.1	8.6
	CY	-419828.6	34.9	-419863.6	-75.1	7.1
	CF	-468497.3	38.0	-468535.3	-73.2	8.2
ONIOM2(B971/6-31G(d):PM	β-CD/PC	-422940.9	145.3	-423086.2	-202.0	21.2
	β-CD/BC	-491921.7	145.3	-492067.1	-191.7	22.9
	β-CD/CY	-420717.0	143.0	-420860.0	-178.4	22.0
	β-CD/CF	-469386.7	145.0	-469531.8	-169.7	19.6