Supplementary Materials

Supramolecular Complexes of β-Cyclodextrin with Clomipramine and Doxepin: Effect of the Ring Substituent and Component of Drugs on Their Inclusion Topologies and Structural Flexibilities

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References

1. Literature survey

Table S1. Summary of the CD–TCA inclusion complexes characterized by various techniques.

Host	Guest	Ratio	Inclusion mode [a]		K_a, M^{-1} (Tech.) [b]	Ref. [d]
			Aromatic	Side chain		
β-CD	CPM	1:1	✓ A		9.42×10^3 (U)	[1]
HP-β-CD	CPM	1:1	✓ A		9.58×10^3 (U)	[1]
α-CD	DXP	1:1		✓	140 (FI)	[2]
α-CD	DXP	2:1	✓ A+B		16.5×10^3 (U) 19.6×10^3 (F)	[3]
α-CD	DXP	1:1		✓	ND (Tg)	[3]
α-CD	DXP	1:1		✓	0.05×10^3 (I)	[4]
β-CD	DXP	1:1		✓	13.21×10^3 (I)	[4]
β-CD	DXP	1:1	✓ A+B		ND (N)	[5]
β-CD	DXP	3:1	✓ A+B	✓	ND (U, F)	[6]
β-CD	DXP	1:1	✓		397 (U), 624 (F)	[6]
β-CD	*E*-DXP	1:1		✓	36.0×10^3 (E)	[7]
β-CD	*Z*-DXP	1:1		✓	22.7×10^3 (E)	[7]
β-CD	DXP	1:1	✓ A		ND (Tg)	[8]
β-CD	DXP	2:1	✓ A+B		14.7×10^3 (U) 16.2×10^3 (F)	[3]
β-CD	DPM	1:1		✓	2.04×10^3 (C)	[9]
β-CD	DPM	2:1	✓ A+B		ND (F)	[10]
β-CD	DPM	1:1	✓		8.92×10^3 (U)	[11]
β-CD	DPM	1:1	✓	✓	42.2 (U), 32.0 (F)	[12]
β-CD	DPM	1:1	✓ A		ND (X)	[13]
β-CD	DPM	1:1	✓ A	✓	ND (Tg)	[13]
α-CD	IPM	1:1		✓	130 (FI)	[2]
α-CD	IPM	1:1		✓	0.08×10^3 (I)	[4]
β-CD	IPM	1:1		✓	8.70×10^3 (I)	[4]
β-CD	IPM	1:1		✓	1.50×10^3 (C)	[9]
HP-β-CD	IPM	1:1	ND [c]		0.82×10^3 (C)	[14]
β-CD	IPM	1:1 1:2 2:1	✓ ✓ A/B ✓ A+B	✓	ND (N, L)	[15]
β-CD	IPM	2:1	✓ A+B		ND (Tgl)	[15]
β-CD	IPM	1:1	✓ A		ND (Tg)	[8]
β-CD	IPM	1:1		✓	16.7 (U), 808 (F)	[16]
β-CD	IPM	1:1	✓ A		ND (X)	[13]
β-CD	IPM	1:1	✓ A	✓	ND (Tg)	[13]
α-CD	NRT	1:1		✓	70 (FI)	[2]
α-CD	NRT	1:1		✓	0.09×10^3 (I)	[4]
β-CD	NRT	1:1		✓	16.77×10^3 (I)	[4]
β-CD	NRT	1:1	✓	✓	235 (U), 211 (F)	[17]
β-CD	NRT	1:1	✓ A		ND (X)	[18]
β-CD	NRT	1:1		✓	ND (Tgl)	[18]
α-CD	AMT	1:1		✓	113 (FI)	[2]
α-CD	AMT	1:1		✓	0.06×10^3 (I)	[4]
β-CD	AMT	1:1		✓	23.90×10^3 (I)	[4]
β-CD	AMT	1:1		✓	3.19×10^3 (C)	[9]
HP-β-CD	AMT	1:1	ND		1.03×10^3 (C)	[14]
β-CD	AMT	1:1	✓ A		ND (X)	[19]
β-CD	AMT	1:1	✓ A		ND (X)	[18]
β-CD	NRT	1:1		✓	ND (Tgl)	[18]

[a] TCA moiety included in CD cavity: aromatic rings A, B or side chain.

[b] Binding constant (K_a) at 298 K derived from different techniques, mostly in solution: flow injection (FI); fluorescence (F); UV-vis (U); ion-selective electrode (I); capillary electrophoresis (E); light scattering (L); nuclear magnetic resonance (N); theoretical calculation in gas phase or solution (Tgl); single-crystal X-ray analysis (X); conductivity (C)

[c] ND – not determined

[d] Full reference list is given on pages 15–16.

2. Crystallographic data

Table S2. X-ray single crystal data collection and refinement statistics of **1** and **2**.

	1 β-CD–Clomipramine HCl	**2** β-CD–Doxepin HCl
Abbreviated formula	β-CD·CPM·HCl·9.6H_2O	β-CD·DXP·HCl·0.7EtOH·11.3H_2O
Chemical formula	$(C_6H_{10}O_5)_7 \cdot C_{19}H_{23}ClN_2 \cdot HCl \cdot 9.6H_2O$	$(C_6H_{10}O_5)_7 \cdot C_{19}H_{21}NO \cdot HCl \cdot 0.7(C_2H_6O) \cdot 11.3H_2O$
Formula weight	1645.32	1679.38
Crystal habit, color	Thin plate, colorless	Hexagonal, colorless
Crystal size [mm]	0.04 × 0.26 × 0.38	0.30 × 0.42 × 0.42
Crystal system, space gr.	Orthorhombic, $P2_12_12_1$ (No. 19)	Orthorhombic, $P2_12_12_1$ (No. 19)
a, *b*, *c* [Å]	15.2643(6), 18.7352(7), 29.5743(10)	15.1521(4), 18.4814(4), 29.6212(9)
α, β, γ [°]	90, 90, 90	90, 90, 90
V [Å^3]	8457.7(5)	8294.9(4)
Z	4	4
D_c [g cm^{-3}]	1.292	1.328
μ [mm^{-1}]	0.171	0.147
F(000)	3481	3576
Diffractometer	APEXII Kappa CCD (Bruker)	APEXII Kappa CCD (Bruker)
Wavelength [Å]	MoKα, 0.71073	MoKα, 0.71073
T [K]	296	296
Data collection	ω–ϕ scan, 0.4° step, 8 s expose	ω–ϕ scan, 0.4° step, 8 s expose
Frames collected	658	659
θ range [°]	1.38–25.42	1.74–30.61
Resolution [Å]	0.83	0.70
Completeness [%], R_{int}	99.7, 0.0592	99.8, 0.0350
Reflns collected / unique / observed	43530 / 15560 / 7967	55043 / 25417 / 16493
Data / restraints / parameters	15560, 59, 956	16493, 44, 939
R_1 [a], wR_2 [$I > 2\sigma(I)$] [b]	0.1032, 0.2676	0.0825, 0.2235
R_1, wR_2 [all data], GoF	0.1772, 0.3218, 1.005	0.1219, 0.2554, 1.026
$\Delta\rho_{min}$, $\Delta\rho_{max}$ [e Å^{-3}]	–0.60, 0.82	–0.50, 0.93
CCDC number	2011745	2011746

[a,b] $R = \sum||F_o| - |F_c||/\sum|F_o|$; $wR = \sum\{w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2\}^{1/2}$.

Table S3. Selected geometrical parameters of two β-CD macrocycles of **1** and **2**, in comparison with those of β-CD–(–)-epicatechin and β-CD·12H_2O.

Residue	Puckering Q [Å] [a], θ [°] [b]				Tilt angle [°] [c]				O4 deviation [Å] [d]				O4(n)···O4(n – 1), O4(n)···centroid [Å]			
n	**1**	**2**	**β-CD–EC** [e]	**β-CD·12W** [f]	**1**	**2**	**β-CD–EC**	**β-CD·12W**	**1**	**2**	**β-CD–EC**	**β-CD·12W**	**1**	**2**	**β-CD–EC**	**β-CD·12W**
1	0.571(11)	0.593(4)	0.561(2)	0.570									4.573(8)	4.528(4)	4.403(2)	4.489
	9.4(11)	8.3(5)	6.7(2)	7.6	21.5(4)	19.8(1)	19.7(1)	15.0	–0.218(5)	–0.222(2)	–0.180(1)	0.192	4.713(5)	4.781(3)	5.171	4.981
2	0.566(10)	0.589(4)	0.545(2)	0.583									4.419(9)	4.410(4)	4.263(2)	4.392
	2.9(10)	1.8(5)	5.6(2)	3.0	23.4(2)	22.5(1)	4.6(1)	26.2	0.069(5)	0.013(2)	–0.084(1)	0.091	5.255(5)	5.272(3)	5.397	5.153
3	0.540(11)	0.566(4)	0.574(2)	0.559									4.166(9)	4.199(4)	4.278(2)	4.286
	7.7(12)	5.8(4)	3.7(2)	3.9	5.2(2)	9.3(1)	6.9(1)	10.8	0.270(6)	0.254(3)	0.325(1)	–0.195	5.231(6)	5.216(3)	4.581	5.122
4	0.556(10)	0.579(5)	0.557(2)	0.596									4.418(8)	4.435(4)	4.498(2)	4.443
	5.7(10)	3.3(5)	4.9(3)	1.4	8.3(2)	6.6(1)	33.7(1)	7.9	–0.285(6)	–0.176(3)	–0.199(1)	–0.053	4.664(6)	4.640(3)	4.827	4.856
5	0.557(11)	0.571(5)	0.578(2)	0.579									4.463(9)	4.472(4)	4.322(2)	4.452
	5.3(10)	4.0(5)	3.2(2)	2.0	26.5(4)	26.4(2)	1.9(1)	10.7	–0.053(5)	–0.127(3)	–0.073(1)	0.276	4.892(5)	5.006(3)	5.435	5.054
6	0.552(11)	0.552(4)	0.565(2)	0.571									4.283(8)	4.244(4)	4.209(2)	4.247
	5.7(11)	7.1(4)	4.9(2)	3.9	3.9(2)	9.8(1)	14.6(1)	20.3	0.236(6)	0.184(2)	0.087(1)	–0.115	5.416(6)	5.390(3)	5.075	5.184
7	0.545(10)	0.560(5)	0.582(2)	0.567									4.197(8)	4.308(4)	4.626(2)	4.338
	5.7(11)	2.2(5)	8.8(2)	3.7	3.9(2)	1.9(1)	30.6(1)	6.4	–0.020(5)	0.074(2)	0.124(1)	–0.196	4.896(6)	4.862(3)	4.632	4.913
													0.407 [g]	*0.329*	*0.417*	*0.242*
													0.752 [g]	*0.750*	*0.854*	*0.328*
													0.874 [g]	*0.873*	*0.876*	*0.870*

[a,b] A perfect cyclohexane chair (for R(C–C) = 1.54 Å) has puckering amplitude Q = 0.63 Å and angle describing the polar position θ = 0° [20].

[c] Interplanar angle of the plane through C1(n), C4(n), O4(n) and O4(n – 1) against the O4 plane.

[d] Deviation of glycosidic O4 atoms from the least-squares plane through the seven O4 atoms.

[e] β-CD–(–)-epicatechin(EC) [21].

[f] β-CD·12H_2O [22].

[g] Ranges of the O4(n)···O4(n – 1), O4(n)···centroid distances and the average of their ratios are in *italics*; for an ideal heptagon, the ratio is 0.868.

[h] Endocyclic torsion angles ϕ and ψ at glycosidic O4, defined as O5(n + 1)–C1(n + 1)–O4(n)–C4(n) and C1(n + 1)–O4(n)–C4(n)–C5(n), respectively.

[i] Averages of ϕ and ψ are in *italics*; for the β-CD roundness, the sum of averages should be zero [23].

[j] Exocyclic torsion angles χ and ω are defined as C4–C5–C6–O6 and O5–C5–C6–O6, respectively.

[k,m] Doubly disordered O63–H group with occupancy factors 0.44 and 0.56 for respective sites A and B.

Table S3. Continued.

Residue	O3(*n*)···O2(*n* + 1) distance [Å]				Torsion angles ϕ [h], ψ [h] [°]				Torsion angles χ [j], ω [j] [°]			
n	**1**	**2**	**β-CD–EC**	**β-CD·12W**	**1**	**2**	**β-CD–EC**	**β-CD·12W**	**1**	**2**	**β-CD–EC**	**β-CD·12W**
1	2.877(11)	2.838(5)	2.924(2)	2.957	116.6(9)	116.0(4)	100.7(2)	119.3	54.4(13)	48.5(6)	53.5(2)	–169.4
					–100.2(10)	–99.8(4)	–121.5(2)	–95.9	–64.1(11)	–69.5(6)	–66.8(2)	70.5
2	2.885(10)	2.905(5)	2.765(2)	2.875	107.0(10)	108.7(4)	111.6(2)	110.5	56.1(17)	175.5(5)	58.7(3)	–173.9
					–111.3(10)	–115.1(4)	–118.1(2)	–106.6	–66.1(16)	57.1(6)	–62.7(2)	71.0
3	2.917(11)	2.924(6)	2.762(2)	2.902	105.3(8)	103.9(4)	129.1(2)	102.5	–172.3(38) [k] 61.6(43) [m]	58.2(5)	48.9(2)	58.7
					–120.3(8)	–118.3(4)	–97.4(2)	–121.1	66.4(51) [k] –73.9(36) [m]	–63.9(5)	–72.5(2)	–60.8
4	2.782(12)	2.870(7)	3.346(3)	2.783	105.7(9)	104.3(4)	90.1(2)	107.7	56.3(11)	56.2(5)	55.7(3)	57.0
					–108.9(10)	–113.4(4)	–131.9(2)	–109.4	–63.6(10)	–63.5(5)	–64.5(2)	–61.0
5	2.767(12)	2.794(5)	2.828(3)	2.770	122.9(9)	120.9(4)	117.1(2)	110.7	63.3(11)	64.7(6)	60.7(2)	50.7
					–104.1(10)	–101.0(5)	–105.9(2)	–114.1	–57.6(11)	–55.6(6)	–60.9(2)	–71.0
6	2.862(13)	2.850(6)	3.246(3)	2.855	105.8(9)	104.9(4)	105.9(2)	120.0	–176.0(8)	–173.9(4)	–167.8(2)	–175.4
					–129.6(8)	–123.1(4)	–96.5(2)	–109.8	63.8(10)	65.2(6)	69.8(2)	64.7
7	2.867(12)	2.874(5)	2.833(3)	2.862	114.3(9)	108.4(4)	102.7(2)	103.0	53.0(11)	54.7(5)	54.2(3)	52.1
					–111.8(9)	–119.0(4)	–118.4(2)	–125.7	–69.3(10)	–66.3(5)	–64.7(3)	–62.9
					111.1 [i]	*109.6*	*108.2*	*110.5*				
					–112.3 [i]	*–112.8*	*–112.8*	*–111.8*				
					–1.2 [i]	*–3.2*	*–4.6*	*–1.3*				

[a,b] A perfect cyclohexane chair (for *R*(C–C) = 1.54 Å) has puckering amplitude Q = 0.63 Å and angle describing the polar position θ = 0° [20].

[c] Interplanar angle of the plane through C1(*n*), C4(*n*), O4(*n*) and O4(*n* – 1) against the O4 plane.

[d] Deviation of glycosidic O4 atoms from the least-squares plane through the seven O4 atoms.

[e] β-CD–(–)-epicatechin(EC) [21].

[f] β-CD·12H_2O [22].

[g] Ranges of the O4(*n*)···O4(*n* – 1), O4(*n*)···centroid distances and the average of their ratios are in *italics*; for an ideal heptagon, the ratio is 0.868.

[h] Endocyclic torsion angles ϕ and ψ at glycosidic O4, defined as O5(*n* + 1)–C1(*n* + 1)–O4(*n*)–C4(*n*) and C1(*n* + 1)–O4(*n*)–C4(*n*)–C5(*n*), respectively.

[i] Averages of ϕ and ψ are in *italics*; for the β-CD roundness, the sum of averages should be zero [23].

[j] Exocyclic torsion angles χ and ω are defined as C4–C5–C6–O6 and O5–C5–C6–O6, respectively.

[k,m] Doubly disordered O63–H group with occupancy factors 0.44 and 0.56 for respective sites A and B.

Table S4. (a) Hydrogen bond parameters in β-CD·CPM·HCl·9.6H_2O (**1**) [Å, º].

D–H···A	D–H	H···A	D···A	∠(DHA)	D–H···A	D–H	H···A	D···A	∠(DHA)
β-*CD*–β-*CD*									
O31–H···O22	0.82	2.10	2.877(11)	158.5	O25–H···O6W	0.82	2.14	2.84(2)	143.4
O22–H···O66 [ii b]	0.82	2.53	3.043(11)	122.0	O35–H···O6W	0.82	2.52	3.31(2)	164.4
O32–H···O66 [ii]	0.82	2.22	2.860(10)	134.7	O26–H···O7W	0.82	2.28	3.08(4)	164.1
O33–H···O24	0.82	2.12	2.917(11)	163.6	O66–H···Cl2B	0.82	1.93	2.736(12)	165.5
O34–H···O25	0.82	2.01	2.782(12)	157.5	O27–H···O8W	0.82	2.43	3.24(2)	166.7
O36–H···O27	0.82	2.26	2.862(13)	130.2	O4W–H2···O27 [vi]	0.96	2.30	3.147(13)	146.7
O37–H···O21	0.82	2.21	2.867(12)	137.4	β-*CD*–*CPM*				
O67–H···O33 [v]	0.82	1.98	2.753(11)	157.5	O22–H···Cl1	0.82	2.72	3.504(10)	159.5
β-*CD*–H_2O/*Cl* [a]					C18M–H2···O34	0.97	2.40	3.36(2)	170.2
O21–H···O1W	0.82	2.48	2.91(2)	113.7	N5'M–H···O61 [ii]	0.98	1.82	2.73(2)	152.7
O61–H···O3W	0.82	2.36	3.17(2)	172.4	C31–H···*Cg*1 [d]	0.98	3.11	4.021	155.9
O4W–H1···O22 [v]	0.96	2.65	3.139(11)	112.0	C51–H···*Cg*2	0.98	3.75	4.542	139.5
O62–H···O6W [i]	0.82	2.19	2.90(3)	144.8	C55–H···*Cg*2	0.98	3.49	4.431	162.2
O23–H···Cl2A	0.82	2.05	2.773(10)	146.1	H_2O–H_2O				
O63B–H···O7W [i c]	0.82	2.44	2.93(4)	119.3	O1W–H2···O9W	0.96	2.33	3.12(3)	140.0
O24–H···O9W [iii]	0.82	2.04	2.81(2)	157.4	O8W–H1···O10W	0.96	1.88	2.81(3)	162.3
O64–H···Cl2A [iv]	0.82	1.91	2.674(9)	155.2	O8W–H2···O9W	0.96	1.99	2.87(3)	152.4

[a] Site occupancy factors (SOFs) are as follows
9.6 water molecules are distributed over 13 sites: 1.0 (O4W, O8W, O9W, O11W); 0.8 (O2W, O3W, O6W); 0.7 (O1W); 0.6 (O7W, O10W); 0.5 (O5W, O12W); 0.3 (O13W)
One twofold disordered chloride: 0.5 (Cl2A, Cl2B)

[b] Equivalent positions: (i) $-x + 1.5, -y + 1, z + 0.5$; (ii) $-x + 1, y + 0.5, -z + 1.5$; (iii) $x + 1, y, z$; (iv) $-x + 2, y - 0.5, -z + 1.5$; (v) $-x + 1, y - 0.5, -z + 1.5$; (vi) $x + 0.5, -y + 0.5, -z + 1$.

[c] Twofold disordered O63–H group with occupancy factors 0.44 and 0.56 for respective sites A and B.

[d] *Cg*1 = A-ring (C1M–C2M–C3M–C4M–C13M–C12M), *Cg*2 = B-ring (C6M–C7M–C8M–C9M–C15M–C14M)

(b) π···π interactions in β-CD·DPM·HCl·0.8EtOH·9.4H_2O (**1**) [Å, º].

Cg(*I*)	*Cg*(*J*)	*Cg*–*Cg*	Alpha	*CgI*_Perp	*CgJ*_Perp	Type
*Cg*1	*Cg*2($-x + 1, y + 0.5, -z + 1.5$)	5.877(5)	118.7(5)	2.209(4)	3.654(4)	Edge-to-face

Note:
- *Cg*(*I*) = Plane number *I*
  *Cg*1 = A-ring (C1M–C2M–C3M–C4M–C13M–C12M), *Cg*2 = B-ring (C6M–C7M–C8M–C9M–C15M–C14M)
- Alpha = Interplanar angle between planes *I* and *J* [°]
- *Cg*–*Cg* = Distance between ring centroids [Å]
- *CgI*_Perp = Perpendicular distance of *Cg*(*I*) on ring *J* [Å]
- *CgJ*_Perp = Perpendicular distance of *Cg*(*J*) on ring *I* [Å]

Table S5. (a) Hydrogen bond parameters in β-CD·DXP·HCl·0.7EtOH·11.3H_2O (**2**) [Å, º].

D–H···A	D–H	H···A	D···A	∠(DHA)	D–H···A	D–H	H···A	D···A	∠(DHA)
β-*CD*–β-*CD*									
O31–H···O22	0.82	2.06	2.838(5)	158.1	O65–H···O8WB	0.82	2.55	3.12(2)	126.7
O22–H···O66 [i b]	0.82	2.47	3.066(5)	130.8	O26–H···O9WA	0.82	2.00	2.808(11)	167.5
O32–H···O23	0.82	2.10	2.905(5)	169.1	O26–H···O9WB	0.82	2.00	2.80(2)	164.3
O33–H···O67 [i]	0.82	2.28	2.828(5)	124.2	O27–H···O1E	0.82	2.40	3.041(14)	136.0
O24–H···O33	0.82	2.14	2.924(6)	160.4	β-*CD*–*DXP*				
O25–H···O34	0.82	2.29	2.870(7)	128.2	N5'X–H···O52 [i]	0.98	2.42	3.167(6)	132.3
O35–H···O26	0.82	1.98	2.793(5)	170.7	N5'X–H···O62 [i]	0.98	2.20	3.011(9)	139.2
O66–H···O32 [iv]	0.82	2.07	2.782(5)	144.3	C31–H···*Cg*2 [c]	0.98	3.14	4.007	149.0
O37–H···O21	0.82	2.22	2.874(5)	137.3	C31–H···*Cg*3	0.98	2.95	3.837	150.7
O67–H···O64 [v]	0.82	2.13	2.920(6)	161.1	C51–H···*Cg*1	0.98	3.65	4.524	149.3
β-*CD*–H_2O/*EtOH*/*Cl* [a]					C55–H···*Cg*1	0.98	3.32	4.244	146.9
O21–H···O1W	0.82	2.03	2.785(7)	152.0	C51–H···*Cg*4	0.98	3.75	4.600	157.8
O61–H···O3W	0.82	2.21	2.955(7)	150.8	C55–H···*Cg*4	0.98	3.46	4.400	162.7
O62–H···O4W	0.82	1.92	2.722(7)	167.5	H_2O–H_2O/*EtOH*/*Cl*				
O23–H···Cl1 [i]	0.82	1.97	2.779(5)	168.3	O3W–H1···O12W	0.96	1.88	2.81(2)	161.7
O63–H···Cl2 [ii]	0.82	2.05	2.816(6)	154.1	O3W–H2···Cl2	0.96	2.32	3.234(9)	158.9
O11W–H2···O24 [v]	0.96	2.03	2.941(10)	158.5	O4W–H1···O11W [iv]	0.96	1.90	2.786(10)	152.5
O34–H···O13W [iii]	0.82	2.38	2.97(2)	129.4	O4W–H2···O13W	0.96	1.95	2.78(2)	143.7
O64–H···Cl1 [ii]	0.82	2.00	2.739(5)	149.2	O6W–H2···O12W [i]	0.96	2.20	2.94(2)	132.5
O1E–H···O25 [v]	0.82	2.41	2.939(13)	123.5	O7W–H1···Cl1 [ii]	0.96	2.06	2.906(8)	146.1
O6W–H1···O35	0.96	2.34	2.819(10)	110.4	O11W–H1···O1W	0.96	2.14	2.830(11)	127.5
O7W–H2···O65	0.96	1.87	2.807(8)	164.0	O13W–H1···O1E [iv]	0.96	2.31	3.03(2)	131.4
O65–H···O8WA	0.82	2.09	2.740(8)	136.4	O13W–H2···O5W	0.96	1.92	2.82(2)	155.5

[a] Site occupancy factors (SOFs) are as follows
11.3 water molecules distributed over 15 sites: 1.0 (O1W–O4W, O6W, O7W, O11W); 0.7 (O5W, O8WA, O13W); 0.6 (O9WA, O12W); 0.4 (O9WB), 0.3 (O8WB, O10W);
EtOH: 0.7 (O1E); one twofold disordered chloride: 0.5 (Cl1, Cl2)

[b] Equivalent positions: (i) $–x + 1, y + 0.5, –z + 1.5$; (ii) $x + 1, y, z$; (iii) $–x + 2, y + 0.5, –z + 1.5$; (iv) $–x + 1, y – 0.5, –z + 1.5$; (v) $x – 1, y, z$; $–x + 1.5, –y + 1, z – 0.5$.

[c] *Cg*1 = A-ring (C1A–C2A–C3A–C4A–C13A–C12A), *Cg*2 = B-ring (C6A–C7A–C8A–C9A–C15A–C14A) for *E*-DXP
*Cg*3 = A-ring (C1B–C2B–C3B–C4B–C13B–C12B), *Cg*4 = B-ring (C6B–C7B–C8B–C9B–C15B–C14B) for *Z*-DXP

(b) π···π interactions in β-CD·DXP·HCl·0.7EtOH·11.3H_2O (**2**) [Å, º].

- *E*-DXP (DXP site A with SOF = 0.63)

Cg(*I*)	*Cg*(*J*)	*Cg*–*Cg*	Alpha	*CgI*_Perp	*CgJ*_Perp	Type
*Cg*2	*Cg*1($–x + 1, y + 0.5, –z + 1.5$)	5.461(5)	108.5(5)	2.136(3)	4.074(3)	Edge-to-face

- *Z*-DXP (DXP site B with SOF =0.37)

Cg(*I*)	*Cg*(*J*)	*Cg*–*Cg*	Alpha	*CgI*_Perp	*CgJ*_Perp	Type
*Cg*3	*Cg*4($–x + 1, y + 0.5, –z + 1.5$)	5.575(8)	117.5(8)	1.496(5)	4.054(5)	Edge-to-face

Note:
- *Cg*(*I*) = Plane number *I*
*Cg*1 = A-ring (C1A–C2A–C3A–C4A–C13A–C12A), *Cg*2 = B-ring (C6A–C7A–C8A–C9A–C15A–C14A)
*Cg*3 = A-ring (C1B–C2B–C3B–C4B–C13B–C12B), *Cg*4 = B-ring (C6B–C7B–C8B–C9B–C15B–C14B)
- Alpha = Interplanar angle between planes *I* and *J* [°]
- *Cg*–*Cg* = Distance between ring centroids [Å]
- *CgI*_Perp = Perpendicular distance of *Cg*(*I*) on ring *J* [Å]
- *CgJ*_Perp = Perpendicular distance of *Cg*(*J*) on ring *I* [Å]

Table S6. Structural parameters of CPM, DXP, DPM, IPM, AMT and NRT in free HCl salt form and in complex with proteins.

(a) Free HCl salt form

CSD/PDB code [d]	CIMPRA [e]		PUKGEI [f]				IMIPRC [g]		JINGIW [h]	YOVZEO [i]
	CPM		DPM				IPM		NRT	AMT
	7-Cl [j]	3-Cl [j]	Mol 1 [k]	Mol 2	Mol 3	Mol 4	Mol 1	Mol 2		
1) [6-7-6]-Tricyclic core										
Butterfly angle [°] [a]	123.2	123.2	122.5	122.2	124.2	122.8	123.0	130.2	124.3	129.6
Annellation angle [°] [b]	32.5	32.5	32.0	31.1	32.0	31.8	26.6	32.5	29.6	25.7
Twist angle [°] [c]	−15.5	15.5	−13.3	13.7	13.9	−13.5	7.4	15.2	13.8	7.2
C15–C10–C11–C12 torsion angle [°]	−63.2	63.2	−60.4	59.8	60.9	−59.8	49.2	70.1	64.3	58.9
A-centroid–B-centroid distance d_{AB} [Å]	4.867	4.867	4.857	4.863	4.889	4.866	4.790	4.965	4.963	4.973
2) Side chain at N5/C5										
C13–C5/N5–C16–C17 torsion angle [°]	−142.5	−71.2	−142.3	−69.5	−70.4	−141.3	−159.7	−68.5	179.1	−174.3
C5/N5–C16–C17–C18 torsion angle [°]	71.1	−71.2	−177.8	178.1	177.1	−176.5	160.5	−179.6	–113.0	121.2
N5'–A-ring centroid distance d_{NA} [Å]	6.553	6.107	6.197	6.541	6.533	6.176	6.537	6.248	7.330	7.301
N5'–B-ring centroid distance d_{NB} [Å]	6.107	6.553	6.495	6.106	6.088	6.488	6.076	7.219	5.955	5.765

(b) Complex with proteins

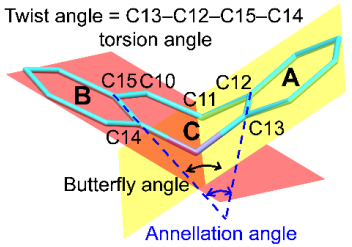
CSD/PDB code [d]	2Q6H [l]		2QEI [m]		4MMA [n]	6G9I [p]	3RZE [q]	
	CPM		CPM		CPM	CPM	DXP	
	7-Cl	3-Cl	7-Cl	3-Cl	3-Cl	3-Cl	*E* form	*Z* form
1) [6-7-6]-Tricyclic core								
Butterfly angle [°] [a]	128.6	120.7	126.4	120.7	136.0	130.2	123.3	123.7
Annellation angle [°] [b]	28.9	30.6	29.1	30.6	30.6	32.5	24.4	25.8
Twist angle [°] [c]	10.6	7.4	9.6	7.4	−13.5	15.5	−10.7	13.5
C15–C10–C11–C12 torsion angle [°]	54.3	42.0	47.4	42.0	−76.9	76.8	−66.1	69.3
A-centroid–B-centroid distance d_{AB} [Å]	5.037	4.881	4.988	4.881	5.037	4.947	4.910	4.923
2) Side chain at N5/C5								
C13–C5/N5–C16–C17 torsion angle [°]	179.1	−131.2	−160.4	−131.2	−90.0	−135.2	1.0	−179.4
C5/N5–C16–C17–C18 torsion angle [°]	92.9	85.2	59.6	85.2	167.7	−145.0	112.8	99.11
N5'–A-ring centroid distance d_{NA} [Å]	7.446	5.927	7.150	5.927	6.207	7.274	6.256	6.997
N5'–B-ring centroid distance d_{NB} [Å]	5.303	5.406	5.408	5.406	5.281	5.577	6.918	6.089

Table S6. Continued.

(b) Complex with proteins

CSD/PDB code [d]	2QB4 [r]		2QJU [s]	2Q72 [t]		6G9B [u]		4M48 [v]	3APV [w]	
	DPM		DPM	IPM		IPM		NRT	AMT	
	Mol 1	Mol 2		Mol 1	Mol 2	Mol 1	Mol 2		Mol 1	Mol 2
1) [6-7-6]-Tricyclic core										
Butterfly angle [°] [a]	127.5	129.3	120.5	129.2	126.0	111.6	110.1	124.2	122.8	120.5
Annellation angle [°] [b]	28.3	28.5	29.2	29.1	29.0	32.4	33.5	29.1	27.6	27.7
Twist angle [°] [c]	10.8	−8.7	9.7	−9.2	11.2	−14.4	−12.1	14.7	9.6	11.8
C15–C10–C11–C12 torsion angle [°]	57.9	−50.8	54.5	−48.9	55.8	−62.8	−61.5	72.0	59.8	62.9
A-centroid–B-centroid distance d_{AB} [Å]	5.016	5.036	4.855	5.021	5.101	4.781	4.757	4.950	4.920	4.878
2) Side chain at N5/C5										
C13–C5/N5–C16–C17 torsion angle [°]	−168.1	68.7	179.5	73.0	−167.6	−144.7	−138.3	–0.1	−178.8	179.2
C5/N5–C16–C17–C18 torsion angle [°]	77.0	89.4	81.4	85.8	69.8	165.2	145.9	162.1	128.7	128.7
N5'–A-ring centroid distance d_{NA} [Å]	7.331	6.697	7.767	6.722	7.293	7.297	7.012	6.571	6.152	6.188
N5'–B-ring centroid distance d_{NB} [Å]	5.373	6.014	5.170	5.949	5.430	6.508	6.714	6.307	5.153	5.224

[a,b,c] Angle between aromatic planes A and B; Angle between C13–C12 and C14–C15; C13–C12–C15–C14 torsion angle (see inset for atom numbering).



[d] For the β-CD encapsulation of DPM, IPM [13] and NRT, AMT [18], see Table 1 and Figure 3.

[e,f,g,h,i] CSD codes: CIMPRA [24]; PUKGEI [25]; IMIPRC [26]; JINGIW [27]; YOVZEO [28]; none of free DXP HCl or DXP in complex with small molecule has been reported.

[j] Two CPM molecules are inversion-symmetry-related, i.e., crystals belong to monoclinic, space group $P2_1/c$.

[k] Number of molecules in the asymmetric unit.

[l] CPM in complex with bacterial leucine transporter (LeuT), L-leucine and sodium (PDB code: 2Q6H) [29].

[m] CPM in complex with LeuT, L-alanine and sodium (PDB code: 2QEI) [29].

[n] CPM in complex with biogenic leucine transporter (LeuBAT) (PDB code: 4MMA) [30].

[p] CPM in complex with ebolavirus glycoprotein (PDB code: 6G9I) [31].

[q] DXP in complex with human histamine H_1 (PDB code: 3RZE) [32].

[r] DPM in complex with LeuT, L-leucine and sodium (PDB code: 2QB4) [29].

[s] DPM in complex with LeuT and L-leucine (PDB code: 2QJU) [33].

[t] IPM in complex with LeuT, L-leucine and sodium (PDB code 2Q72) [29].

[u] IPM in complex with ebolavirus glycoprotein (PDB code: 6G9B) [31].

[v] NRT in complex with dopamine transporter(DAT), NaCl and cholesterol (PDB code: 4M48) [34].

[w] AMT in complex with human alpha1-acid glycoprotein (PDB code: 3APV) [35].

3. Computational data

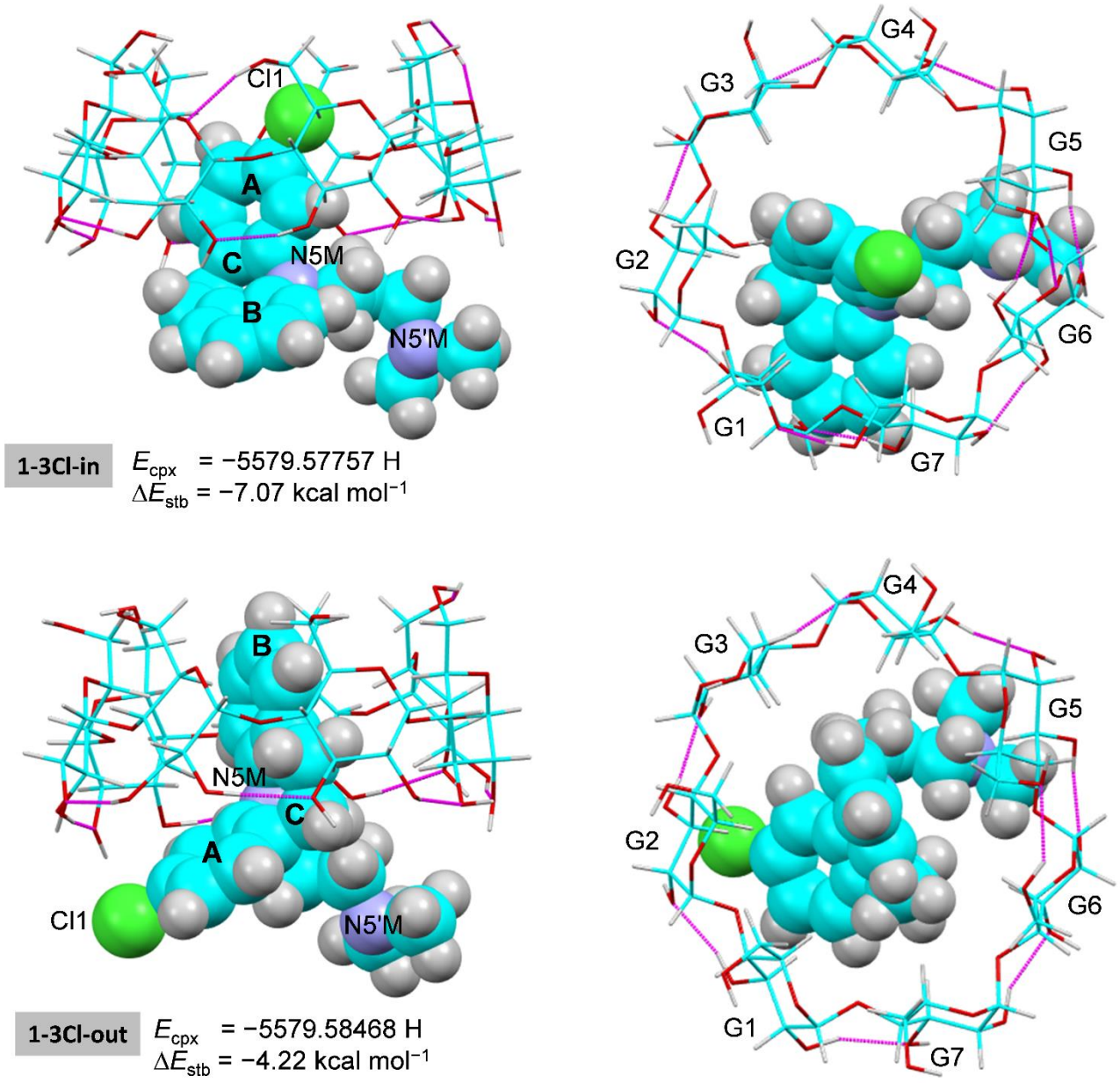
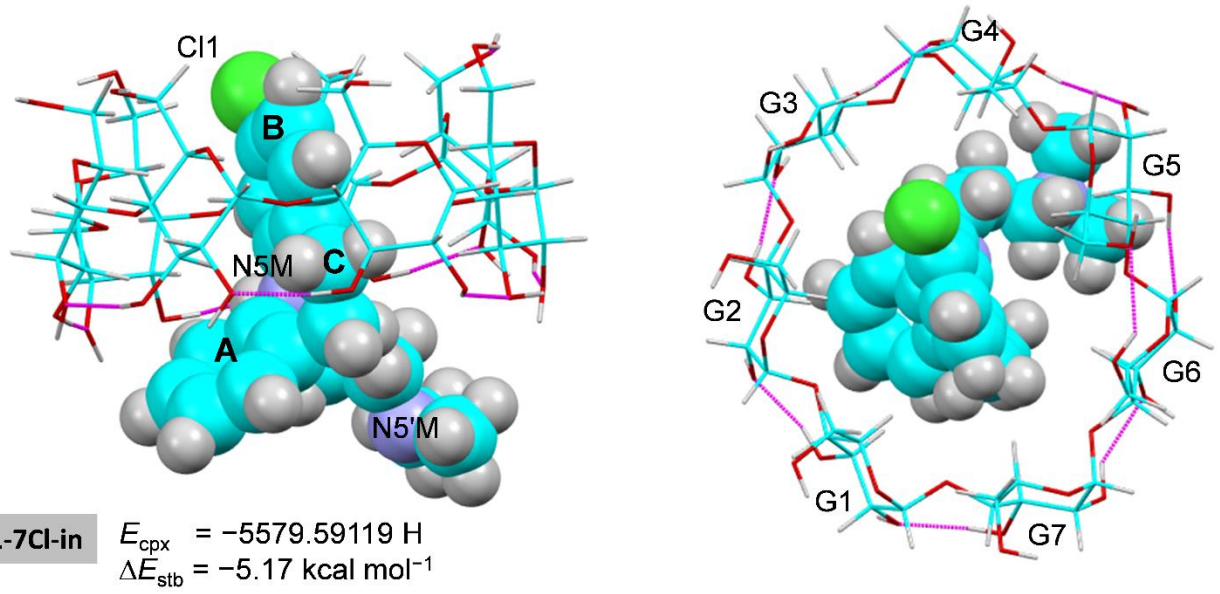
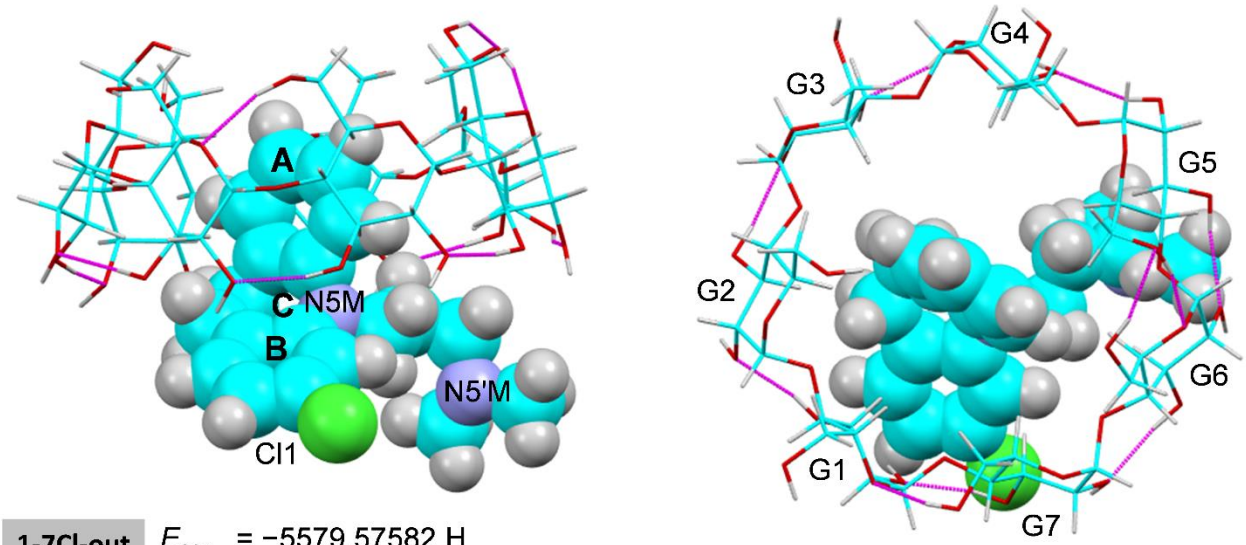


Figure S1. Inclusion complexes of (a) β-CD−CPM(Cl on C3), (b) β-CD−CPM(Cl on C7) with Cl inside and outside the β-CD cavity, and (c) β-CD−*E*/*Z*-DXP, derived from DFT complete-geometry optimization in the gas phase; side view (left) and top view (right). For better comparison, the energy of complex (E_{cpx}) and stabilization energy (ΔE_{stb}) are given; see also Tables S7 and 3. The H-bonding interactions are indicated by magenta lines.



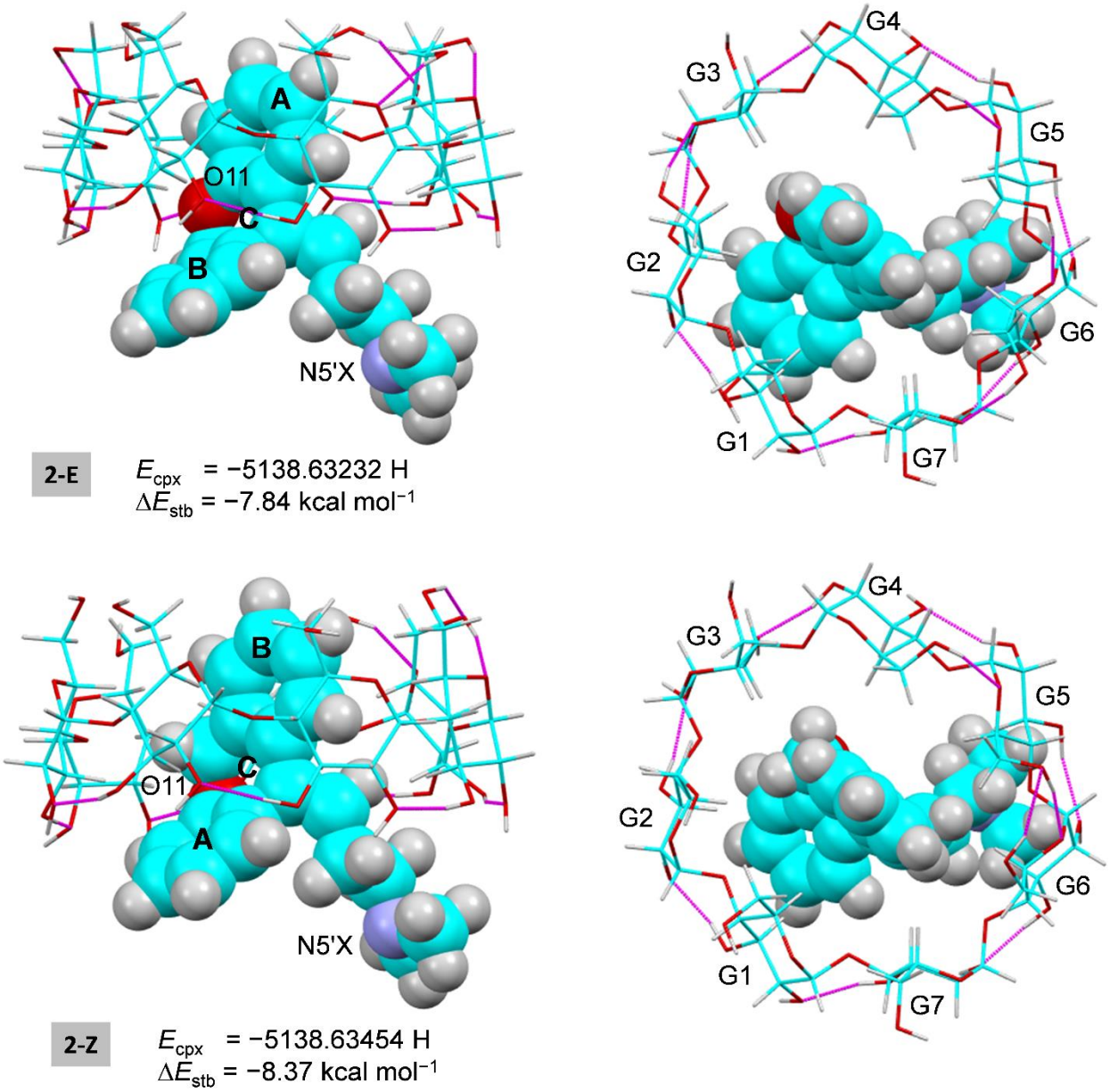
1-7Cl-in E_{cpx} = −5579.59119 H
ΔE_{stb} = −5.17 kcal mol^{-1}



1-7Cl-out E_{cpx} = −5579.57582 H
ΔE_{stb} = −5.62 kcal mol^{-1}

(b) β-CD–CPM(Cl on C7)

Figure S1. Continued.



(c) β-CD–DXP

Figure S1. Continued.

Table S7. Hydrogen bond parameters in β-CD–CPM (4 modes) and β-CD–DXP (2 modes) inclusion complexes from DFT full-geometry optimization [Å, º]. [a]

D–H···A	D–H	H···A	D···A	∠(DHA)	D–H···A	D–H	H···A	D···A	∠(DHA)
β-CD·CMP [b]									
1-3Cl-in			β–CD	conformation					
β-*CD*–β-*CD*			Distorted	round	β-*CD*–*CMP*				
O31–H···O22	0.98	1.95	2.91	167.4	C31–H···*Cg*1 [c]	1.10	3.55	4.62	163.7
O32–H···O23	0.98	1.91	2.87	167.3	O21–H···*Cg*2 [c]	0.98	2.84	3.47	123.1
O24–H···O33	0.98	1.99	2.93	162.4					
O25–H···O34	0.98	2.12	3.05	158.8					
O35–H···O26	0.98	2.12	3.07	165.3					
O65–H···O56	0.98	1.88	2.85	166.5					
O36–H···O27	0.98	1.93	2.90	168.2					
O66–H···O65	0.97	2.28	3.12	143.4					
O37–H···O21	0.98	1.92	2.88	164.6					
O67–H···O51	0.98	2.06	3.01	163.7					
1-3Cl-out									
β-*CD*–β-*CD*			Distorted	round	β-*CD*–*CMP*				
O21–H···O37	0.98	2.07	2.99	157.4	C52–H···*Cg*2	1.10	3.46	4.50	157.7
O31–H···O22	0.98	1.98	2.93	164.6	C55–H···*Cg*2	1.10	3.36	4.36	151.6
O32–H···O23	0.98	1.96	2.92	164.1					
O33–H···O24	0.98	1.96	2.92	168.2					
O34–H···O25	0.98	1.94	2.91	166.8					
O35–H···O26	0.98	1.98	2.93	163.4					
O66–H···O65	0.98	2.29	3.11	140.9					
O27–H···O36	0.98	2.05	2.96	153.7					
1-7Cl-in									
β-*CD*–β-*CD*			Distorted	round	β-*CD*–*CMP*				
O31–H···O22	0.98	1.91	2.86	164.6	C52–H···*Cg*2	1.10	3.59	4.67	167.5
O32–H···O23	0.98	1.94	2.91	166.7	C55–H···*Cg*2	1.10	3.48	4.43	145.6
O33–H···O24	0.98	1.95	2.92	168.3	C32–H···*Cg*1	1.10	3.57	4.55	150.2
O34–H···O25	0.98	1.94	2.91	168.0					
O35–H···O26	0.98	1.96	2.91	164.0					
O66–H···O65	0.97	2.41	3.22	140.0					
O27–H···O36	0.98	2.18	3.02	143.6					
O37–H···O21	0.98	1.94	2.91	170.2					
1-7Cl-out									
β-*CD*–β-*CD*			Distorted	round	β-*CD*–*CMP*				
O31–H···O22	0.98	1.93	2.90	168.2	O21–H···*Cg*2	0.98	3.11	3.69	119.9
O32–H···O23	0.98	1.91	2.87	168.2					
O24–H···O33	0.98	1.98	2.93	162.6					
O25–H···O34	0.98	2.13	3.07	160.1					
O35–H···O26	0.98	2.14	3.10	164.4					
O65–H···O56	0.98	1.89	2.85	164.9					
O36–H···O27	0.98	1.92	2.89	168.6					
O66–H···O65	0.97	2.19	3.05	146.2					
O37–H···O21	0.98	1.93	2.88	164.7					
O67–H···O51	0.98	2.04	2.99	162.5					

Table S7. Continued.

D–H···A	D–H	H···A	D···A	∠(DHA)	D–H···A	D–H	H···A	D···A	∠(DHA)
β-CD·DXP [b]									
2-E									
β-*CD*–β-*CD*			Distorted	round	β-*CD*–*E-DXP*				
O31–H···O22	0.98	1.88	2.84	167.1	C31–H···*Cg*2	1.10	3.75	4.62	137.8
O32–H···O23	0.98	2.04	2.98	161.0					
O62–H···O53	0.98	2.02	2.96	159.7					
O24–H···O33	0.98	2.01	2.97	164.1					
O64–H···O55	0.98	1.97	2.88	155.4					
O25–H···O34	0.98	2.11	3.03	156.9					
O35–H···O26	0.98	2.03	2.99	164.8					
O65–H···O56	0.98	2.00	2.93	158.3					
O36–H···O27	0.98	1.97	2.94	166.8					
O66–H···O57	0.98	2.04	2.98	161.6					
O37–H···O21	0.98	1.88	2.86	168.9					
2-Z									
β-*CD*–β-*CD*			Distorted	round	β-*CD*–*Z-DXP*				
O31–H···O22	0.98	1.90	2.86	164.8	C51–H···*Cg*2	1.10	3.41	4.46	167.5
O32–H···O23	0.98	1.98	2.95	167.2	C55–H···*Cg*2	1.10	3.64	4.57	145.6
O24–H···O33	0.98	2.02	2.97	162.6	C31–H···*Cg*1	1.10	3.50	4.62	137.8
O64–H···O55	0.98	1.97	2.89	155.0	C32–H···*Cg*1	1.10	3.62	4.55	150.2
O25–H···O34	0.98	2.07	2.99	156.8					
O35–H···O26	0.98	2.07	3.02	163.7					
O65–H···O56	0.98	1.91	2.87	167.2					
O36–H···O27	0.98	1.88	2.85	168.7					
O66–H···O65	0.97	2.37	3.21	143.2					
O37–H···O21	0.98	1.92	2.89	167.1					

[a] DFT energy minimization in vacuum at the B3LYP/6–31+G(d)/4–31G level, see also Figure S1 and Table 3.
[b] X-ray-derived structures are used as starting models.
[c] C/O–H···π interactions with *Cg*1 and *Cg2* as the centroids of A-ring (C1–C2–C3–C4–C13–C12) and B-ring (C6–C7–C8–C9–C15–C14), respectively.

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