# Supplementary Materials

## Distinctive Supramolecular Features of β-Cyclodextrin Inclusion Complexes with Antidepressants Protriptyline and Maprotiline: A Comprehensive Structural Investigation

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**References**

# 1. Literature survey

**Table S1.** Summary of the CD–3° amine TCA complexes characterized by various techniques.

| Host | Guest | Ratio | Inclusion mode [a] | | $K_a$, M$^{-1}$ (Tech.) [b] | Ref. [d] |
|---|---|---|---|---|---|---|
| | | | Aromatic | Side chain | | |
| α-CD | AMT | 1:1 | | ✓ | 113 (FI) | [1] |
| α-CD | AMT | 1:1 | | ✓ | 0.06×10$^3$ (I) | [2] |
| β-CD | AMT | 1:1 | | ✓ | 23.90×10$^3$ (I) | [2] |
| β-CD | AMT | 1:1 | | ✓ | 3.19×10$^3$ (C) | [3] |
| HP-β-CD | AMT | 1:1 | ND | | 1.03×10$^3$ (C) | [4] |
| β-CD | AMT | 1:1 | ✓ A/B | | 18.4×10$^3$ (H) | [5] |
| β-CD | AMT | 1:1 | ✓A/B | | 8.2×10$^3$ (N) | [6] |
| β-CD | AMT | 1:1 | ✓ A | | ND (X) | [7] |
| β-CD | AMT | 1:1 | ✓ A | | ND (X) | [8] |
| β-CD | AMT | 1:1 | | ✓ | ND (Tgl) | [8] |
| α-CD | IPM | 1:1 | | ✓ | 130 (FI) | [1] |
| α-CD | IPM | 1:1 | | ✓ | 0.08×10$^3$ (I) | [2] |
| β-CD | IPM | 1:1 | | ✓ | 8.70×10$^3$ (I) | [2] |
| β-CD | IPM | 1:1 | | ✓ | 1.50×10$^3$ (C) | [3] |
| β-CD | IPM | 1:1 | | ✓ | 16.7 (U), 808 (F) | [9] |
| HP-β-CD | IPM | 1:1 | ND [c] | | 0.82×10$^3$ (C) | [4] |
| β-CD | IPM | 1:1 | ✓ A/B | | 8.8×10$^3$ (H) | [5] |
| β-CD | IPM | 1:1 | ✓ | ✓ | ND (N, L) | [10] |
| | | 1:2 | ✓ A/B | | | |
| | | 2:1 | ✓ A+B | | | |
| β-CD | IPM | 2:1 | ✓ A+B | | ND (Tgl) | [10] |
| β-CD | IPM | 1:1 | ✓ A | | ND (Tg) | [11] |
| β-CD | IPM | 1:1 | ✓ A | | ND (X) | [12] |
| β-CD | IPM | 1:1 | ✓ A | ✓ | ND (Tg) | [12] |
| β-CD | CPM | 1:1 | ✓ A | | 9.42×10$^3$ (U) | [13] |
| HP-β-CD | CPM | 1:1 | ✓ A | | 9.58×10$^3$ (U) | [13] |
| β-CD | CPM | 1:1 | ✓ B | | ND (X) | [14] |
| β-CD | CPM | 1:1 | ✓ A+B | | ND (Tg) | [14] |
| α-CD | DXP | 1:1 | | ✓ | 140 (FI) | [1] |
| α-CD | DXP | 1:1 | | ✓ | 0.05×10$^3$ (I) | [2] |
| α-CD | DXP | 1:1 | | ✓ | ND (Tg) | [15] |
| α-CD | DXP | 2:1 | ✓ A+B | | 16.5×10$^3$ (U), 19.6×10$^3$ (F) | [15] |
| β-CD | DXP | 1:1 | | ✓ | 13.21×10$^3$ (I) | [2] |
| β-CD | *E*-DXP | 1:1 | | ✓ | 36.0×10$^3$ (E) | [16] |
| β-CD | *Z*-DXP | 1:1 | | ✓ | 22.7×10$^3$ (E) | [16] |
| β-CD | DXP | 3:1 | ✓ A+B | ✓ | ND (U, F) | [17] |
| β-CD | DXP | 1:1 | ✓ | | 397 (U), 624 (F) | [17] |
| β-CD | DXP | 1:1 | ✓ A/B | | 13.4×10$^3$ (H) | [5] |
| β-CD | DXP | 1:1 | ✓ A+B | | ND (N) | [18] |
| β-CD | DXP | 1:1 | ✓ A | | ND (Tg) | [11] |
| β-CD | DXP | 2:1 | ✓ A+B | | 14.7×10$^3$ (U), 16.2×10$^3$ (F) | [15] |
| β-CD | DXP | 1:1 | ✓ A+B | | ND (X) | [14] |
| β-CD | DXP | 1:1 | ✓ A+B | | ND (Tg) | [14] |

[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); high-performance liquid chromatography (H)
[c] ND – not determined.
[d] Full reference list is given on pages 11–12.

## 2. Crystallographic data

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

| | **1**<br>β-CD–Protriptyline HCl | **2**<br>β-CD–Maprotiline HCl |
|---|---|---|
| Abbreviated formula | β-CD·PRT·HCl<br>·0.4EtOH·12.9H$_2$O | β-CD·MPL·HCl<br>·0.7EtOH·10.4H$_2$O |
| Chemical formula | (C$_6$H$_{10}$O$_5$)$_7$·C$_{19}$H$_{21}$N·HCl<br>·0.4(C$_2$H$_6$O)·12.9H$_2$O | (C$_6$H$_{10}$O$_5$)$_7$·C$_{20}$H$_{23}$N·HCl<br>·0.7(C$_2$H$_6$O)·10.4H$_2$O |
| Formula weight | 1670.92 | 1657.55 |
| Crystal habit, color | Rod, colorless | Rod, colorless |
| Crystal size [mm] | 0.42 × 0.40 × 0.38 | 0.46 × 0.42 × 0.30 |
| Crystal system, space gr. | Monoclinic, $P2_1$ (No. 4) | Orthorhombic, $P2_12_12_1$ (No. 19) |
| $a$, $b$, $c$ [Å] | 15.6016(4), 18.9261(6), 16.4508(5) | 14.9858(5), 18.6252(5), 29.9133(8) |
| $\alpha$, $\beta$, $\gamma$ [º] | 90, 117.384(1), 90 | 90, 90, 90 |
| $V$ [Å$^3$] | 4313.2(2) | 8349.2(4) |
| $Z$ | 2 | 4 |
| $D_c$ [g cm$^{-3}$] | 1.287 | 1.319 |
| $\mu$ [mm$^{-1}$] | 0.141 | 0.143 |
| $F$(000) | 1774 | 3526 |
| Diffractometer | APEXII Kappa CCD (Bruker) | APEXII Kappa CCD (Bruker) |
| Wavelength [Å] | MoK$_\alpha$, 0.71073 | MoK$_\alpha$, 0.71073 |
| T [K] | 296(2) | 296(2) |
| Data collection | $\omega$–$\phi$ scan, 0.4° step, 8 s expose | $\omega$–$\phi$ scan, 0.5° step, 8 s expose |
| Frames collected | 910 | 966 |
| $\theta$ range [°] | 1.82–25.38 | 1.87–25.35 |
| Resolution [Å] | 0.83 | 0.83 |
| Completeness [%], $R_{int}$ | 99.9, 0.0354 | 99.8, 0.0284 |
| Reflns<br>  collected / unique / observed | 42205 / 15779 / 10114 | 53243 / 15279 / 11996 |
| Data / restraints / parameters | 15779, 5, 1007 | 15279, 29, 930 |
| $R_1$ [a], $wR_2$ [$I > 2\sigma(I)$] [b] | 0.0781, 0.2074 | 0.0768, 0.2127 |
| $R_1$, $wR_2$ [all data], GoF | 0.1181, 0.2443, 1.005 | 0.0948, 0.2329, 1.025 |
| $\Delta\rho_{min}$, $\Delta\rho_{max}$ [e Å$^{-3}$] | −0.42, 0.56 | −0.47, 0.69 |
| CCDC number | 2093556 | 2093557 |

[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$_2$O.

| Residue n | Puckering $Q$ [Å] $^a$, $\theta$[°] $^b$ | | | | Tilt angle [°] $^c$ | | | | O4 deviation [Å] $^d$ | | | | O4($n$)···O4($n$ – 1), O4($n$)···centroid [Å] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **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 | 0.569(9) | 0.569(6) | 0.561(2) | 0.570 | | | | | | | | | 4.498(7) | 4.504(5) | 4.403(2) | 4.489 |
| | 4.7(9) | 4.7(6) | 6.7(2) | 7.6 | 30.4(4) | 13.6(2) | 19.7(1) | 15.0 | 0.128(4) | –0.191(3) | –0.180(1) | 0.192 | 4.678(4) | 4.944(3) | 5.171 | 4.981 |
| 2 | 0.571(10) | 0.557(6) | 0.545(2) | 0.583 | | | | | | | | | 4.445(7) | 4.315(5) | 4.263(2) | 4.392 |
| | 1.5(10) | 3.4(6) | 5.6(2) | 3.0 | 12.1(5) | 18.8(1) | 4.6(1) | 26.2 | –0.251(4) | –0.053(3) | –0.084(1) | 0.091 | 5.119(4) | 5.262(3) | 5.397 | 5.153 |
| 3 | 0.557(9) | 0.566(6) | 0.574(2) | 0.559 | | | | | | | | | 4.280(7) | 4.303(5) | 4.278(2) | 4.286 |
| | 3.9(9) | 2.9(6) | 3.7(2) | 3.9 | 5.6(3) | 8.2(1) | 6.9(1) | 10.8 | –0.071(4) | 0.264(3) | 0.325(1) | –0.195 | 5.282(4) | 5.088(4) | 4.581 | 5.122 |
| 4 | 0.562(11) | 0.562(6) | 0.557(2) | 0.596 | | | | | | | | | 4.350(6) | 4.442(5) | 4.498(2) | 4.443 |
| | 1.4(11) | 4.0(6) | 4.9(3) | 1.4 | 12.3(5) | 6.6(1) | 33.7(1) | 7.9 | 0.336(4) | –0.133(4) | –0.199(1) | –0.053 | 4.852(4) | 4.735(4) | 4.827 | 4.856 |
| 5 | 0.577(8) | 0.558(8) | 0.578(2) | 0.579 | | | | | | | | | 4.419(6) | 4.468(6) | 4.322(2) | 4.452 |
| | 3.4(8) | 2.3(8) | 3.2(2) | 2.0 | 28.7(4) | 25.5(3) | 1.9(1) | 10.7 | –0.117(4) | –0.136(4) | –0.073(1) | 0.276 | 4.715(4) | 5.130(3) | 5.435 | 5.054 |
| 6 | 0.552(8) | 0.537(6) | 0.565(2) | 0.571 | | | | | | | | | 4.359(6) | 4.203(6) | 4.209(2) | 4.247 |
| | 2.7(8) | 7.9(6) | 4.9(2) | 3.9 | 5.6(4) | 11.2(2) | 14.6(1) | 20.3 | –0.279(4) | 0.128(3) | 0.087(1) | –0.115 | 5.311(4) | 5.286(4) | 5.075 | 5.184 |
| 7 | 0.561(8) | 0.557(6) | 0.582(2) | 0.567 | | | | | | | | | 4.171(6) | 4.405(5) | 4.626(2) | 4.338 |
| | 6.9(9) | 0.0(6) | 8.8(2) | 3.7 | 12.1(3) | 0.4(1) | 30.6(1) | 6.4 | 0.253(4) | 0.122(3) | 0.124(1) | –0.196 | 5.091(4) | 4.797(4) | 4.632 | 4.913 |
| | | | | | | | | | | | | | *0.327* $^g$ | *0.301* | *0.417* | *0.242* |
| | | | | | | | | | | | | | *0.633* $^g$ | *0.551* | *0.854* | *0.328* |
| | | | | | | | | | | | | | *0.873* $^g$ | *0.871* | *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 $\theta$ = 0° [19].

$^c$ 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) [20].

$^f$ β-CD·12H$_2$O [21].

$^g$ 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 $\phi$ and $\psi$ 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 $\phi$ and $\psi$ are in *italics*; for the β-CD roundness, the sum of averages should be zero [22].

$^j$ Exocyclic torsion angles $\chi$ and $\omega$ are defined as C4–C5–C6–O6 and O5–C5–C6–O6, respectively.

$^{k,m}$ Doubly disordered O64–H group with occupancy factors 0.77 and 0.23 for respective sites A and B.

| Residue | O3(n)···O2(n + 1) distance [Å] | | | | Torsion angles $\phi$[h], $\psi$[h] [°] | | | | Torsion angles $\chi$[j], $\omega$[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 | 2.866(10) | 2.811(7) | 2.924(2) | 2.957 | 116.3(7) | 114.1(5) | 100.7(2) | 119.3 | 59.5(11) | 48.5(9) | 53.5(2) | −169.4 |
| | | | | | −100.4(6) | −105.3(5) | −121.5(2) | −95.9 | −60.8(10) | −71.4(7) | −66.8(2) | 70.5 |
| 2 | 2.918(9) | 2.816(7) | 2.765(2) | 2.875 | 103.1(7) | 112.2(5) | 111.6(2) | 110.5 | 54.6(10) | 179.8(6) | 58.7(3) | −173.9 |
| | | | | | −123.3(7) | −112.9(5) | −118.1(2) | −106.6 | −65.9(9) | 60.2(8) | −62.7(2) | 71.0 |
| 3 | 2.890(10) | 2.888(7) | 2.762(2) | 2.902 | 104.3(7) | 107.7(5) | 129.1(2) | 102.5 | 58.4(9) | 56.2(7) | 48.9(2) | 58.7 |
| | | | | | −114.4(6) | −118.6(5) | −97.4(2) | −121.1 | −64.4(10) | −65.4(7) | −72.5(2) | −60.8 |
| 4 | 2.853(7) | 2.898(9) | 3.346(3) | 2.783 | 109.7(8) | 105.7(5) | 90.1(2) | 107.7 | 47.7(15)[k] 77.7(49)[m] | 55.2(7) | 55.7(3) | 57.0 |
| | | | | | −110.3(8) | −112.4(5) | −131.9(2) | −109.4 | −68.9(13)[k] −60.7(50)[m] | −64.6(7) | −64.5(2) | −61.0 |
| 5 | 2.851(8) | 2.817(7) | 2.828(3) | 2.770 | 119.4(6) | 118.5(6) | 117.1(2) | 110.7 | 56.1(9) | 65.0(9) | 60.7(2) | 50.7 |
| | | | | | −101.7(7) | −100.6(7) | −105.9(2) | −114.1 | −63.5(8) | −56.6(8) | −60.9(2) | −71.0 |
| 6 | 2.926(9) | 2.844(7) | 3.246(3) | 2.855 | 99.1(6) | 104.9(6) | 105.9(2) | 120.0 | 56.9(7) | −175.8(7) | −167.8(2) | −175.4 |
| | | | | | −134.9(5) | −119.5(6) | −96.5(2) | −109.8 | −66.2(7) | 62.9(10) | 69.8(2) | 64.7 |
| 7 | 2.919(9) | 2.829(7) | 2.833(3) | 2.862 | 111.3(6) | 108.3(6) | 102.7(2) | 103.0 | −169.2(6) | 56.2(7) | 54.2(3) | 52.1 |
| | | | | | −103.8(6) | −118.5(6) | −118.4(2) | −125.7 | 68.7(8) | −65.1(6) | −64.7(3) | −62.9 |
| | | | | | *109.0*[i] | *110.2* | *108.2* | *110.5* | | | | |
| | | | | | *−112.7*[i] | *−112.5* | *−112.8* | *−111.8* | | | | |
| | | | | | *−3.7*[i] | *−2.3* | *−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 $\theta$ = 0° [19].

[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) [20].

[f] β-CD·12H$_2$O [21].

[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 $\phi$ and $\psi$ 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 $\phi$ and $\psi$ are in *italics*; for the β-CD roundness, the sum of averages should be zero [22].

[j] Exocyclic torsion angles $\chi$ and $\omega$ are defined as C4–C5–C6–O6 and O5–C5–C6–O6, respectively.

[k,m] Doubly disordered O64–H group with occupancy factors 0.77 and 0.23 for respective sites A and B.

**Table S4.** (a) Hydrogen bond parameters in β-CD·PRT·HCl·0.4EtOH·12.9H$_2$O (**1**) [Å, °].

| D–H···A | D–H | H···A | D···A | ∠(DHA) | D–H···A | D–H | H···A | D···A | ∠(DHA) |
|---|---|---|---|---|---|---|---|---|---|
| *β-CD–β-CD* | | | | | | | | | |
| O21–H···O37 | 0.82 | 2.13 | 2.919(9) | 162.4 | O26–H···O3W | 0.82 | 2.42 | 3.064(14) | 135.8 |
| O31–H···O22 | 0.82 | 2.11 | 2.866(10) | 153.1 | O36–H···O11WA | 0.82 | 2.53 | 3.28(4) | 151.6 |
| O32–H···O23 | 0.82 | 2.15 | 2.918(9) | 156.5 | O36–H···O11WB | 0.82 | 1.94 | 2.71(4) | 155.1 |
| O24–H···O33 | 0.82 | 2.18 | 2.890(10) | 145.0 | O37–H···O8W | 0.82 | 1.97 | 2.77(3) | 166.1 |
| O34–H···O25 | 0.82 | 2.18 | 2.853(7) | 139.6 | O1W–H2···O67 [iii] | 0.96 | 2.01 | 2.664(14) | 123.1 |
| O64A–H···O61 [iii b c] | 0.82 | 2.04 | 2.747(19) | 144.7 | O3W–H1···O33 [vi] | 0.97 | 2.55 | 3.091(14) | 115.6 |
| O25–H···O62 [iii] | 0.82 | 2.08 | 2.728(8) | 135.9 | *PRT–β-CD/Cl* | | | | |
| O35–H···O26 | 0.82 | 2.04 | 2.851(8) | 171.1 | N5'P–H1···O21 [viii] | 0.89 | 2.41 | 3.087(10) | 133.1 |
| O66–H···O63 [vi] | 0.82 | 2.21 | 2.878(9) | 138.9 | N5'P–H1···O31 [viii] | 0.89 | 2.06 | 2.856(11) | 148.6 |
| O27–H···O36 | 0.82 | 2.35 | 2.926(8) | 128.3 | N5'P–H2···Cl2 | 0.89 | 2.07 | 2.934(15) | 162.3 |
| O67–H···O35 [vii] | 0.82 | 2.06 | 2.733(9) | 138.9 | C51–H···*Cg*2 [d] | 0.98 | 3.69 | 4.461 | 137.8 |
| *β-CD–H$_2$O/EtOH/Cl* [a] | | | | | C55–H···*Cg*2 | 0.98 | 3.39 | 4.239 | 146.3 |
| O61–H···O12WB [i] | 0.82 | 1.69 | 2.48(4) | 161.5 | C32–H···*Cg*1 | 0.98 | 3.21 | 4.135 | 158.9 |
| O22–H···Cl1 | 0.82 | 2.41 | 3.097(11) | 142.0 | *H$_2$O–H$_2$O* | | | | |
| O62–H···O7W | 0.82 | 1.90 | 2.67(2) | 155.6 | O1E–H···O7W | 0.82 | 2.14 | 2.70(5) | 125.1 |
| O23–H···O10WA | 0.82 | 2.05 | 2.85(3) | 163.5 | O1W–H1···O12WA | 0.96 | 1.98 | 2.93(3) | 172.9 |
| O23–H···O10WB | 0.82 | 2.25 | 2.82(4) | 127.2 | O2W–H1···O6W [vii] | 0.96 | 1.99 | 2.70(3) | 129.1 |
| O33–H···O3W [ii] | 0.82 | 2.43 | 3.091(14) | 138.2 | O3W–H2···O1W [vi] | 0.98 | 2.39 | 3.00(3) | 120.3 |
| O63–H···O12WA | 0.82 | 2.33 | 2.74(2) | 112.4 | O4W–H1···O2W [vii] | 0.96 | 2.35 | 2.83(3) | 110.4 |
| O64B–H···O8W [iv] | 0.82 | 2.62 | 3.16(6) | 124.7 | O4W–H2···O7W [vi] | 0.96 | 1.62 | 2.53(4) | 157.1 |
| O65–H···Cl1 [v] | 0.82 | 2.26 | 3.073(12) | 174.0 | O5W–H1···O1E [ix] | 0.96 | 2.23 | 2.99(5) | 135.5 |
| O26–H···Cl1 [viii] | 0.82 | 2.78 | 3.403(12) | 133.7 | O6W–H1···O12WA [iii] | 0.96 | 1.84 | 2.72(2) | 151.9 |

[a] Site occupancy factors (SOFs) are as follows:

12.9 water molecules are distributed over 20 sites: 1.0 (O1W, O3W, O5W, O6W); 0.8 (O2W, O4W); 0.7 (O7W, O8W, O10WA, O12WA); 0.6 (O9WA); 0.5 (O10WB, O11WA/B, O12WB/C); 0.4 (O9WB, O14W); 0.3 (O13W, O15W)

EtOH: 0.4 (O1E); one twofold disordered chloride: 0.5 (Cl1, Cl2)

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

[c] Twofold disordered O64–H group with occupancy factors 0.77 and 0.23 for respective sites A and B.

[d] *Cg*1 = A-ring (C1P–C2P–C3P–C4P–C13P–C12P), *Cg*2 = B-ring (C6P–C7P–C8P–C9P–C15P–C14P)

(b) π···π interactions in β-CD·PRT·HCl·0.4EtOH·12.9H$_2$O (**1**) [Å, °].

There is no π···π interaction in **1**.

**Table S5.** (a) Hydrogen bond parameters in β-CD·MPL·HCl·0.7EtOH·10.4H$_2$O (**2**) [Å, °].

| D–H···A | D–H | H···A | D···A | ∠(DHA) | D–H···A | D–H | H···A | D···A | ∠(DHA) |
|---|---|---|---|---|---|---|---|---|---|
| *β-CD–β-CD* | | | | | O3W–H2···O66 | 0.96 | 2.06 | 2.888(11) | 143.2 |
| O22–H···O31 | 0.82 | 2.11 | 2.811(7) | 143.4 | O4W–H2···O37 | 0.96 | 1.89 | 2.832(7) | 166.8 |
| O32–H···O23 | 0.82 | 2.00 | 2.816(7) | 171.8 | O67–H···Cl2 | 0.82 | 2.04 | 2.833(9) | 163.7 |
| O24–H···O33 | 0.82 | 2.08 | 2.888(7) | 166.2 | *MPL–β-CD/H$_2$O* | | | | |
| O64–H···O67 [i b c] | 0.82 | 2.15 | 2.945(8) | 164.8 | O61–H···N5'M [ii] | 0.82 | 2.44 | 3.159(12) | 146.4 |
| O25–H···O34 | 0.82 | 2.10 | 2.898(9) | 164.2 | N5'M–H1···O52 [iv] | 0.89 | 2.50 | 3.141(8) | 129.2 |
| O66–H···O32 [ii] | 0.82 | 2.04 | 2.805(8) | 154.2 | N5'M–H1···O62 [iv] | 0.89 | 2.10 | 2.930(11) | 155.7 |
| O26–H···O35 | 0.82 | 2.01 | 2.817(7) | 167.7 | N5'M–H2···O61 [iv] | 0.89 | 2.60 | 3.159(12) | 121.7 |
| O27–H···O36 | 0.82 | 2.23 | 2.844(7) | 132.4 | N5'M–H2···O13W | 0.89 | 2.33 | 3.09(6) | 143.3 |
| O37–H···O21 | 0.82 | 2.17 | 2.829(7) | 137.6 | C51–H···Cg1 [c] | 0.98 | 3.577 | 4.515 | 161.1 |
| *β-CD–H$_2$O/EtOH/Cl* [a] | | | | | C55–H···Cg1 | 0.98 | 3.843 | 4.782 | 161.4 |
| O21–H···O6WA | 0.82 | 2.12 | 2.825(11) | 144.6 | C31–H···Cg2 | 0.98 | 3.018 | 3.903 | 150.9 |
| O21–H···O6WB | 0.82 | 2.09 | 2.90(2) | 170.5 | O21–H···Cg2 | 0.82 | 4.394 | 4.499 | 92.1 |
| O31–H···O6WB | 0.82 | 2.29 | 3.07(2) | 159.5 | O37–H···Cg2 | 0.82 | 3.930 | 4.520 | 132.0 |
| O1E–H···O22 [ii] | 0.82 | 2.07 | 2.81(2) | 150.2 | *H$_2$O–H$_2$O/EtOH* | 0.96 | 1.88 | 2.81(2) | 161.7 |
| O62–H···O4W [ii] | 0.82 | 1.92 | 2.743(9) | 175.3 | O1W–H1···O11W [ii] | 0.96 | 2.11 | 2.96(2) | 146.3 |
| O23–H···Cl1 | 0.82 | 1.96 | 2.768(7) | 170.5 | O1W–H2···O12W | 0.96 | 2.36 | 3.32(4) | 172.2 |
| O33–H···O6WA [i] | 0.82 | 2.22 | 2.972(12) | 152.3 | O2W–H1···O6WA [ii] | 0.96 | 1.90 | 2.785(13) | 151.5 |
| O63–H···Cl2 [i] | 0.82 | 2.03 | 2.846(7) | 170.5 | O2W–H1···O6WB [ii] | 0.96 | 2.26 | 3.02(2) | 136.2 |
| O5W–H2···O24 [iii] | 0.96 | 2.20 | 2.872(11) | 126.2 | O3W–H1···O1E | 0.96 | 1.88 | 2.75(2) | 149.1 |
| O34–H···O1W [iv] | 0.82 | 2.52 | 3.120(15) | 131.0 | O4W–H1···O10W | 0.96 | 2.04 | 2.79(2) | 134.2 |
| O35–H···O11W | 0.82 | 2.06 | 2.87(2) | 175.6 | O5W–H1···O4W | 0.96 | 2.06 | 2.784(13) | 131.0 |
| O65–H···O3W | 0.82 | 2.23 | 2.824(12) | 129.8 | | | | | |
| O2W–H2···O65 | 0.96 | 2.19 | 2.859(11) | 125.5 | | | | | |

[a] Site occupancy factors (SOFs) are as follows:
  10.4 water molecules distributed over 16 sites: 1.0 (O1W–O5W); 0.8 (O7W); 0.7 (O6WA, O8WA);
  0.6 (O10W, O11W), 0.4 (O9W, O12W), 0.3 (O6WB, O8WB, O13W, O14W);
  EtOH: 0.7 (O1E); one twofold disordered chloride: 0.5 (Cl1, Cl2)
[b] Equivalent positions: (i) $x + 1$, $y$, $z$; (ii) $-x + 1$, $y - 0.5$, $-z + 1.5$; (iii) $x - 1$, $y$, $z$; (iv) $-x + 1$, $y + 0.5$, $-z + 1.5$.
[c] $Cg1$ = A-ring (C1M–C2M–C3M–C4M–C13M–C12M), $Cg2$ = B-ring (C6M–C7M–C8M–C9M–C15M–C14M)

(b) π···π interactions in β-CD·MPL·HCl·0.7EtOH·10.4H$_2$O (**2**) [Å, °].

| $Cg(I)$ | $Cg(J)$ | $Cg–Cg$ | Alpha | $CgI$_Perp | $CgJ$_Perp | Type |
|---|---|---|---|---|---|---|
| $Cg2$ | $Cg1$ | 4.482(3) | 61.4(3) | 2.241(2) | 2.331(2) | Edge-to-face |
| $Cg2$ | $Cg1(-x + 1, y + 0.5, -z + 1.5)$ | 5.587(3) | 60.4(3) | 1.280(2) | 4.076(2) | Edge-to-face |

Note:
- $Cg(I)$ = Plane number $I$
  $Cg1$ = A-ring (C1M–C2M–C3M–C4M–C13M–C12M), $Cg2$ = 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]

## 3. Computational data

**Table S6.** Hydrogen bond parameters in β-CD–PRT and β-CD–MPL 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·PRT [b] | | | β–CD | conformation | | | | | |
| *β-CD–β-CD* | | | Distorted | round | *β-CD–PRT* | | | | |
| O21–H···O37 | 0.98 | 2.09 | 3.00 | 155.8 | C52–H···*Cg*2 [c] | 1.10 | 3.75 | 4.80 | 162.2 |
| O31–H···O22 | 0.98 | 1.96 | 2.91 | 163.5 | C55–H···*Cg*2 | 1.10 | 4.61 | 3.56 | 161.6 |
| O32–H···O23 | 0.98 | 1.90 | 2.86 | 165.8 | C31–H···*Cg*1 [c] | 1.10 | 4.49 | 3.46 | 157.1 |
| O24–H···O33 | 0.98 | 2.11 | 2.95 | 143.6 | | | | | |
| O34–H···O25 | 0.98 | 1.95 | 2.91 | 167.0 | | | | | |
| O35–H···O26 | 0.98 | 1.91 | 2.87 | 167.2 | | | | | |
| O27–H···O36 | 0.98 | 1.95 | 2.92 | 167.0 | | | | | |
| β-CD·MPL [b] | | | | | | | | | |
| *β-CD–β-CD* | | | Distorted | round | *β-CD–MPL* | | | | |
| O21–H···O37 | 0.98 | 2.05 | 2.98 | 158.3 | C51–H···*Cg*1 [c] | 1.10 | 3.93 | 4.98 | 160.7 |
| O61–H···O52 | 0.98 | 2.03 | 2.93 | 151.4 | C31–H···*Cg*2 [c] | 1.10 | 3.37 | 4.30 | 143.5 |
| O22–H···O31 | 0.98 | 1.95 | 2.90 | 160.6 | | | | | |
| O32–H···O23 | 0.98 | 1.91 | 2.88 | 167.0 | | | | | |
| O24–H···O33 | 0.98 | 2.01 | 2.90 | 151.2 | | | | | |
| O25–H···O34 | 0.98 | 1.98 | 2.93 | 163.5 | | | | | |
| O65–H···O56 | 0.98 | 2.12 | 2.97 | 144.5 | | | | | |
| O26–H···.O35 | 0.98 | 1.98 | 2.94 | 165.9 | | | | | |
| O27–H···O36 | 0.98 | 2.05 | 3.00 | 162.5 | | | | | |
| O67–H···O51 | 0.98 | 1.99 | 2.90 | 153.8 | | | | | |

[a] DFT energy minimization in vacuum at the B3LYP/6−31+G(d)/4−31G level, see also Figure 8 and Table 3.

[b] X-ray-derived structures are used as starting models.

[c] C/O–H···π interactions with *Cg*1 and *Cg*2 as the centroids of A-ring (C1−C2−C3−C4−C13−C12) and B-ring (C6−C7−C8−C9−C15−C14), respectively.

**Table S7.** Stabilization and interaction energies of β-CD–PRT and β-CD–MPL, in comparison to other β-CD–TCA inclusion complexes from DFT full-geometry optimization. [a]

| | β-CD–PRT | β-CD–MPL | β-CD–NRT [f] | β-CD–DPM [g] | β-CD–AMT [f] | β-CD–IPM [g] | β-CD–CPM [h] | β-CD–$E$-DXP [h] | β-CD–$Z$-DXP [h] |
|---|---|---|---|---|---|---|---|---|---|
| $E_{cpx}$ [b] | −5063.43953 | −5102.71021 | −5063.43343 | −5080.72090 | −5102.68430 | −5119.98451 | −5579.58468 | −5138.63232 | −5138.63454 |
| $E_{β\text{-}CD\_opt}$ [c] | −4272.96510 | −4272.96490 | −4272.96876 | −4272.96328 | −4272.96532 | −4272.96689 | −4272.98021 | −4272.96876 | −4272.97420 |
| $E_{D\_opt}$ | −790.46387 | −829.73394 | −790.45569 | −807.75084 | −829.71091 | −847.00646 | −1306.59775 | −865.65107 | −865.64700 |
| $E_{β\text{-}CD\_sp}$ | −4272.96318 | −4272.96412 | −4272.96673 | −4272.96081 | −4272.96295 | −4272.96524 | −4272.97744 | −4272.96787 | −4272.97340 |
| $E_{D\_sp}$ | −790.46371 | −829.73380 | −790.45534 | −807.74992 | −829.71070 | −847.00618 | −1306.59752 | −865.64185 | −865.63828 |
| $ΔE_{stb}$ [Hartree] [d] | −0.01055 | −0.01137 | −0.00898 | −0.00678 | −0.00807 | −0.01115 | −0.00673 | −0.01249 | −0.01334 |
| $ΔE_{stb}$ [kcal mol$^{-1}$] | −6.62 | −7.13 | −5.64 | −4.25 | −5.06 | −7.00 | −4.22 | −7.84 | −8.37 |
| $ΔE_{int}$ [Hartree] [e] | −0.01264 | −0.01228 | −0.01136 | −0.01017 | −0.01065 | −0.01309 | −0.00972 | −0.02261 | −0.02287 |
| $ΔE_{int}$ [kcal mol$^{-1}$] | −7.93 | −7.71 | −7.13 | −6.38 | −6.68 | −8.21 | −6.10 | −14.19 | −14.35 |
| Host-guest interactions | C–H···π | C–H···π | C–H···π | C–H···π | C–H···π | C–H···π | C–H···π | C–H···π | C–H···π |

[a] DFT/B3LYP calculations in the gas phase with mixed basis sets 4−31G for C atoms
and 6−31+G* for H, N, O, F, Cl atoms were carried out using program GAUSSIAN09 [23].
X-ray-derived structures were used as starting models, see also Figure 8 and Table S6.

[b] Original unit of $E$ is Hartree [1 H = 627.5 kcal mol$^{-1}$].

[c] $E_{β\text{-}CD\_opt}$ in vacuum of the uncomplexed β-CD·12H$_2$O [21] is −4272.96662 H.

[d,e] Stabilization energy, $ΔE_{stb} = E_{cpx} − (E_{β\text{-}CD\_opt} + E_{D\_opt})$
Interaction energy, $ΔE_{int} = E_{cpx} − (E_{β\text{-}CD\_sp} + E_{D\_sp})$,
where $E_{cpx}$, $E_{β\text{-}CD\_opt}$ and $E_{D\_opt}$ are the molecular energies from full optimization of complex,
host β-CD and drug TCA in freebase form, respectively;
$E_{β\text{-}CD\_sp}$ and $E_{D\_sp}$ are the corresponding single-point energies in the complexed states.

[f] β-CD inclusion complexes with NRT and AMT [8].

[g] β-CD inclusion complexes with DPM and IPM [12].

[h] β-CD inclusion complexes with CPM and $E$/$Z$-DXP [14].

**Table S8.** Dispersion-corrected interaction energies of eight β-CD–TCA inclusion complexes from DFT/B97D calculations. [a]

| | β-CD–PRT | β-CD–MPL | β-CD–NRT | β-CD–DPM | β-CD–AMT | β-CD–IPM | β-CD–CPM | β-CD–$E$-DXP | β-CD–$Z$-DXP | β-CD–$E$-DXP [d] | β-CD–$E$-DXP [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $E_{cpx}$ [b] | −5060.33917 | −5099.58250 | −5060.33092 | −5077.61098 | −5099.55712 | −5116.84912 | −5576.47218 | −5135.48644 | −5135.49822 | −5138.76012 | −5140.29332 |
| $E_{\beta\text{-CD\_sp}}$ | −4270.36980 | −4270.37381 | −4270.37339 | −4270.36722 | −4270.36849 | −4270.37598 | −4270.38452 | −4270.37939 | −4270.38342 | −4272.69870 | −4274.02846 |
| $E_{D\_sp}$ | −789.90609 | −829.15065 | −789.89585 | −807.18526 | −829.12724 | −846.41818 | −1306.02383 | −865.05040 | −865.04513 | −866.00522 | −866.21921 |
| $\Delta E_{int}$ [Hartree] [c] | −0.06328 | −0.05804 | −0.06168 | −0.05850 | −0.06139 | −0.05495 | −0.06383 | −0.05665 | −0.06967 | −0.05620 | −0.04565 |
| $\Delta E_{int}$ [kcal mol$^{-1}$] | −39.71 | −36.42 | −38.71 | −36.71 | −38.52 | −34.48 | −40.05 | −35.55 | −43.72 | −35.26 | −28.65 |

[a] DFT/B97D calculations in the gas phase with mixed basis sets 4−31G for C atoms
and 6−31+G* for H, N, O, F, Cl atoms were carried out using program GAUSSIAN09 [23].
DFT/B3LYP-optimized structures were used for single-point energy calculations, see also Table S7.
[b] Original unit of $E$ is Hartree [1 H = 627.5 kcal mol$^{-1}$].
[c] Interaction energy, $\Delta E_{int} = E_{cpx} - (E_{\beta\text{-CD\_sp}} + E_{D\_sp})$,
where $E_{cpx}$, $E_{\beta\text{-CD\_sp}}$ and $E_{D\_sp}$ are the single-point energies of complex,
host β-CD and drug TCA in freebase form, respectively.
[d,e] Different basis sets 6-31G(d,p) and 6-311++G(2d,p) were used for single-point energy calculations of the β-CD–$E$-DXP complex.


**Table S9.** BSSE- and dispersion-corrected interaction energies of eight β-CD–TCA inclusion complexes from DFT/B97D calculations. [a]

| | β-CD–PRT | β-CD–MPL | β-CD–NRT | β-CD–DPM | β-CD–AMT | β-CD–IPM | β-CD–CPM | β-CD–$E$-DXP | β-CD–$Z$-DXP |
|---|---|---|---|---|---|---|---|---|---|
| $E_{cpx\_BSSE}$ [b] | −5060.32159 | −5099.56676 | −5060.31412 | −5077.59455 | −5099.53961 | −5116.83408 | −5576.45497 | −5135.47075 | −5135.47897 |
| $E_{\beta\text{-CD(cpx)\_sp}}$ | −4270.37323 | −4270.37701 | −4270.37705 | −4270.37091 | −4270.37180 | −4270.37919 | −4270.38848 | −4270.38283 | −4270.38765 |
| $E_{D(cpx)\_sp}$ | −789.92015 | −829.16331 | −789.90927 | −807.19824 | −829.14144 | −846.43028 | −1306.03692 | −865.06269 | −865.06016 |
| $\Delta E_{BSSE}$ [Hartree] [c] | 0.01758 | 0.01574 | 0.01681 | 0.01643 | 0.01751 | 0.01504 | 0.01721 | 0.01569 | 0.01926 |
| $\Delta E_{BSSE}$ [kcal mol$^{-1}$] | 11.03 | 9.88 | 10.55 | 10.31 | 10.99 | 9.44 | 10.80 | 9.85 | 12.08 |
| $\Delta E_{int\_BSSE}$ [Hartree] [d] | −0.04579 | −0.04218 | −0.04460 | −0.04184 | −0.04388 | −0.03965 | −0.04678 | −0.04092 | −0.05041 |
| $\Delta E_{int\_BSSE}$ [kcal mol$^{-1}$] | −28.73 | −26.47 | −27.99 | −26.25 | −27.54 | −24.88 | −29.35 | −25.68 | −31.63 |

[a] DFT/B97D calculations in the gas phase with mixed basis sets 4−31G for C atoms
and 6−31+G* for H, N, O, F, Cl atoms were carried out using program GAUSSIAN09 [23].
DFT/B3LYP-optimized structures were used for single-point energy calculations, see also Tables S7 and S8.
[b] Original unit of $E$ is Hartree [1 H = 627.5 kcal mol$^{-1}$].
[c] The basis set superposition error (BSSE) energy by counterpoise correction [24], $\Delta E_{BSSE} = E_{cpx\_BSSE} - E_{cpx} = [E_{\beta\text{-CD\_sp}} - E_{\beta\text{-CD(cpx)\_sp}}] + [E_{D\_sp} - E_{D(cpx)\_sp}]$
where $E_{cpx\_BSSE}$ and $E_{cpx}$ are corrected and uncorrected complex energies, respectively.
[d] BSSE-corrected interaction energy, $\Delta E_{int\_BSSE} = E_{cpx} - (E_{\beta\text{-CD(cpx)\_sp}} + E_{D(cpx)\_sp}) = \Delta E_{int} + \Delta E_{BSSE}$
where $E_{\beta\text{-CD(cpx)\_sp}}$ and $E_{D(cpx)\_sp}$ are energies of two components in the complex.

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