Supporting Information
for
Inclusion complexes of 2-methoxyestradiol with
dimethylated and permethylated \( \beta \)-cyclodextrins:
models for cyclodextrin–steroid interaction

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Additional data

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1. PXRD traces and single crystal XRD data confirming complex formation between β-CD and 2ME.

**Figure S1:** Experimental PXRD patterns of 2ME, β-CD and various preparations containing the two components.

Interpretation: The traces labelled β-CD–2ME (1:1) neat grinding and β-CD–2ME (2:1) mixture do not indicate complex formation as they contain peaks from both of the starting materials. Instead, a distinctly different, common PXRD trace results from the products of kneading and co-precipitation, indicating probable complex formation.

**Figure S2:** PXRD patterns confirming the isostructurality of the putative complex formed between β-CD and 2ME and the inclusion complex β-cyclodextrin 4-tert-butylbenzyl alcohol decahydrate [KOFJEU, space group $C22_1$, $a = 19.196(7)$, $b = 24.393(6)$, $c = 32.808(9)$ Å at room temp. (283–303 °C)].

Interpretation: Close similarities between the PXRD trace for complex KOFJEU and those for the putative complex between β-CD and 2ME suggested that these phases are isostructural.

Subsequent investigation of the single crystals obtained by co-precipitation of β-CD and 2ME were found to belong to the space group $C22_1$, with $a = 19.376(2)$, $b = 24.053(2)$, $c = 32.412(2)$ Å at −160 °C.
2. Relevant PXRD traces, DSC traces and FTIR spectra confirming complex Formation between the hosts RAMEB and HPBCD and the guest 2ME

Descriptions and interpretations of the figures below appear in the manuscript.

Figure S3: Experimental PXRD patterns of 2ME, RAMEB and various preparations containing the two components.

Figure S4: Experimental PXRD patterns of 2ME, HPBCD and various preparations containing the two components.
Figure S5: FTIR spectra of RAMEB, 2ME and the spectrum of the putative inclusion complex 'RAM2ME'.

Figure S6: FTIR spectra of HPBCD, 2ME and the spectrum of the putative inclusion complex 'HPB2ME'.
**Figure S7:** DSC traces for 2ME, RAMEB, their physical mixture and the putative inclusion complex.

**Figure S8:** DSC traces for 2ME, HPBCD, their physical mixture and the putative inclusion complex.
3. Thermoanalytical characterization of the DIMEB·2ME and TRIMEB·2ME inclusion complexes

Descriptions and interpretations of the figures below appear in the manuscript.

Figure S9: Hot stage micrographs for DIMEB·2ME (left) and TRIMEB·2ME (right).

Figure S10: TGA traces for DIMEB·2ME (left) and TRIMEB·2ME (right).

Figure S11: DSC traces for DIMEB·2ME (left) and TRIMEB·2ME (right).
4. Geometrical data for the host DIMEB in the inclusion complex DIMEB-2ME

TABLE S1: Geometrical data for the host molecule DIMEB in the complex DIMEB-2ME

| Residue | \( r \) (Å) | \( D \) (Å) | \( a \) (°) | \( d \) (°) | \( \phi \) (°) | \( D_3 \) (Å) | \( \alpha \) (Å) | \( \tau_2 \) (°) |
|---------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| G1      | 5.023       | 4.383       | 129.6       | 3.8         | 117.8       | 2.814(5)    | 0.063(3)    | 10.9(2)     |
| G2      | 5.119       | 4.372       | 126.6       | 2.1         | 119.1       | 2.771(5)    | -0.097(2)   | 14.2(2)     |
| G3      | 5.031       | 4.404       | 129.6       | -5.6        | 117.8       | 2.798(6)    | 0.016(2)    | 9.5(4)      |
| G4      | 5.029       | 4.396       | 128.6       | 4.0         | 118.3       | 2.803(4)    | 0.082(3)    | 13.6(3)     |
| G5      | 5.065       | 4.358       | 128.7       | -1.9        | 117.7       | 2.878(5)    | -0.075(2)   | 12.0(1)     |
| G6      | 5.100       | 4.419       | 127.4       | 3.6         | 118.6       | 2.790(6)    | -0.001(2)   | 12.1(2)     |
| G7      | 5.024       | 4.387       | 129.1       | -6.0        | 118.6       | 2.883(6)    | 0.011(2)    | 8.8(4)      |

**These parameters are defined as follows:

- \( r \), the distance of each O4 atom from the centroid of the O4-polygon;
- \( D \), the glycosidic O4(\( n \))--O4(\( n+1 \)) distance;
- \( a \), the O4(\( n-1 \))--O4(\( n \))--O4(\( n+1 \)) angle;
- \( d \), the O4(\( n \))--O4(\( n+1 \))--O4(\( n+2 \))--O4(\( n+3 \)) torsion angle;
- \( \phi \), the intersaccharidic angle C1(\( n-1 \))--O4(\( n \))--C4(\( n \));
- \( D_3 \), the O3(\( n \))--O2(\( n+1 \)) intra-ring distance;
- \( \alpha \), the deviation of each O4 atom from the mean O4-plane;
- \( \tau_2 \), tilt angle: the angle between the plane containing the atoms O4(\( n \)), C4(\( n \)), C1(\( n \)) and O4(\( n+1 \)) of a given glucose ring and the mean O4-plane.

5. Molecular overlay of 2ME molecules (uncomplexed and complexed with DIMEB)

![Overlay of the 2ME molecules in the crystal structure of 2ME (red) and encapsulated in the host molecule in the complex DIMEB-2ME (green). The r.m.s.d of the least-squares fit is 0.084 Å, with a maximum deviation of 0.202 Å.](image)

Figure S12: Overlay of the 2ME molecules in the crystal structure of 2ME (red) and encapsulated in the host molecule in the complex DIMEB-2ME (green). The r.m.s.d of the least-squares fit is 0.084 Å, with a maximum deviation of 0.202 Å.
## 6. Additional hydrogen bond data for TRIMEB-2ME (Table S2)

| Hydrogen bonds based on numbering in Figure 2 | Atom labels | O···O Distance (Å) |
|---------------------------------------------|-------------|-------------------|
| 1--2 O22--O1'                               |             | 2.598(9)          |
| 2--3 O1'--O6G2 i                            |             | 2.736(9)          |
| 1--4 O22--O3''                             |             | 2.674(8)          |
| 2--5 O1'--O2''                             |             | 2.951(11)         |
| 4--5 O3''--O2''                            |             | 2.885(10)         |
| 5--6 O2''--O3G4 ''                          |             | 2.759(7)          |
| 4--7 O3''--O3G7 ''                          |             | 2.780(8)          |
| 5--8 O2''--O8''                            |             | 2.623(17)         |
| 8--9 O8''--O6''                            |             | 2.647*            |
| 8--10 O8''--O7''                           |             | 2.812*            |
| 11--12 O6--O8                              |             | 2.647*            |
| 12--13 O8--O7                              |             | 2.812*            |
| 11--15 O6--O9                              |             | 3.042*            |
| 15--16 O9--O5                              |             | 2.951*            |

Symmetry operators: (i) $2-x, -1/2+y, -z$; (ii) $1+x, y, z$; (iii) $x, y, -1+z$; (iv) $1+x, y, -1+z$.

NOTE: In Figure 2e, water oxygen atoms labelled 8, 9, 10 are the symmetry-related counterparts of 11, 12 and 13 respectively, the former set being located at (iv) $1+x, y, -1+z$ and the latter belonging to the asymmetric unit (symmetry operator $x, y, z$).

*e.s.d.s not calculated by PLATON due to low site-occupancy of atoms involved.
7. Simulated X-ray photographs for the TRIMEB-2ME complex

Figure S13: Comparison of representative reciprocal lattice layers of reflections of type \( hkl \) with \( k = 2n \) and \( k = 2n+1 \) showing typical alternation (strong/weak) in average intensities, indicating the presence of a pseudo-cell with \( b' \approx b/2 \) in the crystal structure of TRIMEB-2ME. (Images created using program LAYER: L. J. Barbour. LAYER – A computer program for the graphic display of intensity data as simulated precession photographs. J. Appl. Cryst., 1999, 32, 351).

8. Overlay of host molecules A and B in the TRIMEB-2ME complex

Figure S14: Overlay of the host TRIMEB molecules in complex units A (green) and B (red) of the TRIMEB-2ME crystal (RMSD = 0.157 Å, max. deviation between two equivalent atoms = 0.649 Å).
9. Overlay of host molecules C and D in the TRIMEB-2ME complex

**Figure S15:** Overlay of the host TRIMEB molecules in complex units C (blue) and D (yellow) of the TRIMEB-2ME crystal (RMSD = 0.819 Å, max. deviation between two equivalent atoms = 3.417 Å).

10. Geometrical parameters for the host molecules A-D in the TRIMEB-2ME complex

**TABLE S3:** Geometrical data for the four independent TRIMEB host molecules in the complex TRIMEB-2ME

| Residue | r (Å) | D (Å) | a (°) | d (°) | ϕ (°) | D3 (Å) | α (Å) | τ2 (°) |
|---------|------|------|------|------|------|-------|------|-------|
| A1      | 5.261| 4.497| 118.4| -13.7| 119.5| 3.908 | -0.333(3)| 10.2(3) |
| A2      | 4.733| 4.427| 138.0| -10.7| 113.7| 3.410 | 0.413(3) | 25.1(3) |
| A3      | 5.248| 4.351| 120.4|  7.8 | 117.4| 3.466 | 0.113(3)| 15.8(3) |
| A4      | 5.042| 4.558| 131.5| 14.2 | 117.0| 3.306 | -0.376(3)| 43.2(2) |
| A5      | 5.147| 4.447| 125.7| -20.3| 116.5| 3.505 | -0.039(3)| 16.2(3) |
| A6      | 5.081| 4.526| 124.9| -1.1 | 117.6| 3.498 | 0.445(3) | 9.1(3)   |
| A7      | 4.904| 4.117| 135.5| 23.8 | 115.9| 3.472 | -0.224(3)| 50.8(2) |

| Residue | r (Å) | D (Å) | a (°) | d (°) | ϕ (°) | D3 (Å) | α (Å) | τ2 (°) |
|---------|------|------|------|------|------|-------|------|-------|
| B7      | 5.091| 4.440| 123.4| -12.8| 118.8| 3.513 | -0.391(3)| 11.0(4) |
| B1      | 4.821| 4.399| 135.1| -10.5| 114.4| 3.447 | 0.406(3) | 23.8(3) |
| B2      | 5.289| 4.378| 120.3|  5.8 | 117.6| 3.490 | 0.142(3) | 15.3(3) |
| B3      | 5.003| 4.570| 132.1| 15.5 | 116.5| 3.327 | -0.359(3)| 43.7(2) |
| B4      | 5.109| 4.487| 126.9| -17.4| 117.2| 3.493 | -0.087(3)| 17.9(3) |
| B5      | 5.183| 4.509| 123.4| -6.2 | 117.6| 3.549 | 0.461(3) | 9.3(3)   |
| B6      | 4.967| 4.168| 133.0| 26.2 | 116.2| 3.411 | -0.173(3)| 45.4(2) |
### TABLE S3: cont’d.

| Residue | \( r \) (Å) | \( D \) (Å) | \( a \) (°) | \( d \) (°) | \( \phi \) (°) | \( D_3 \) (Å) | \( \alpha \) (Å) | \( \tau_2 \) (°) |
|---------|--------------|-------------|--------------|--------------|-------------|--------------|--------------|--------------|
| C1      | 4.959        | 4.483       | 131.8        | 0.2          | 115.3       | 3.219        | -0.309(3)    | 28.8(3)      |
| C2      | 4.773        | 4.497       | 133.2        | 10.6         | 116.1       | 3.258        | 0.201(3)     | 24.0(2)      |
| C3      | 5.235        | 4.309       | 126.8        | 0.9          | 117.2       | 3.237        | 0.225(3)     | 31.2(2)      |
| C4      | 5.449        | 4.452       | 117.8        | -20.5        | 118.9       | 3.662        | -0.272(3)    | -5.8(4)      |
| C5      | 4.612        | 4.508       | 139.8        | 15.2         | 115.4       | 3.236        | -0.151(3)    | 35.2(3)      |
| C6      | 4.983        | 4.353       | 128.7        | 5.1          | 118.4       | 3.191        | 0.407(3)     | 31.4(3)      |
| C7      | 5.506        | 4.392       | 118.1        | -15.3        | 119.4       | 3.476        | -0.100(4)    | 3.6(3)       |

### DATA* FOR HOST MOLECULES C AND D

* These parameters are defined as follows:
- \( r \): the distance of each O4 atom from the centroid of the O4-polygon;
- \( D \): the glycosidic O4(\( n \))···O4(\( n+1 \)) distance;
- \( a \): the O4(\( n-1 \))···O4(\( n \))···O4(\( n+1 \)) angle;
- \( d \): the O4(\( n \))···O4(\( n+1 \))···O4(\( n+2 \))···O4(\( n+3 \)) torsion angle;
- \( \phi \): the intersaccharidic angle C1(\( n-1 \))···O4(\( n \))···C4(\( n \));
- \( D_3 \): the O3(\( n \))···O2(\( n-1 \)) intra-ring distance;
- \( \alpha \): the deviation of each O4 atom from the mean O4-plane;
- \( \tau_2 \): tilt angle: the angle between the plane containing the atoms O4(\( n \)), C4(\( n \)), C1(\( n \)) and O4(\( n+1 \)) of a given glucose ring and the mean O4-plane.

### 11. Overlay of the 2ME molecules in TRIMEB-2ME complex unit C and the DIMEB-2ME complex

[Diagram showing overlay of 2ME molecules in TRIMEB-2ME and DIMEB-2ME complexes]

**Figure S16:** Overlay of the 2ME molecules in the DIMEB-2ME complex (green) and in unit C of the TRIMEB-2ME complex. (R.M.S.D = 0.083 Å with a maximum atomic deviation of 0.161 Å).
12. Dissolution profiles for 2ME and two series of binary products of 2ME and CDs

![Dissolution profiles graph](image)

**Figure S17:** Comparative dissolution profiles for 2ME in physical mixtures (pm) with the native cyclodextrins β- and γ-CD as well as RAMEB and HPBCD.

![Dissolution profile graph](image)

**Figure S18:** Dissolution profile of the inclusion complex (β-CD)$_2$·2ME and those of a series of 2ME/CD samples resulting from kneading (kn) as well as 1:1 inclusion complexes of HPBCD and RAMEB.