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Supporting Information

Complexation of Clofazimine by Macrocyclic Cucurbit[7]uril Reduced its Cardiotoxicity without Affecting the Antimycobacterial Efficacy

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Content

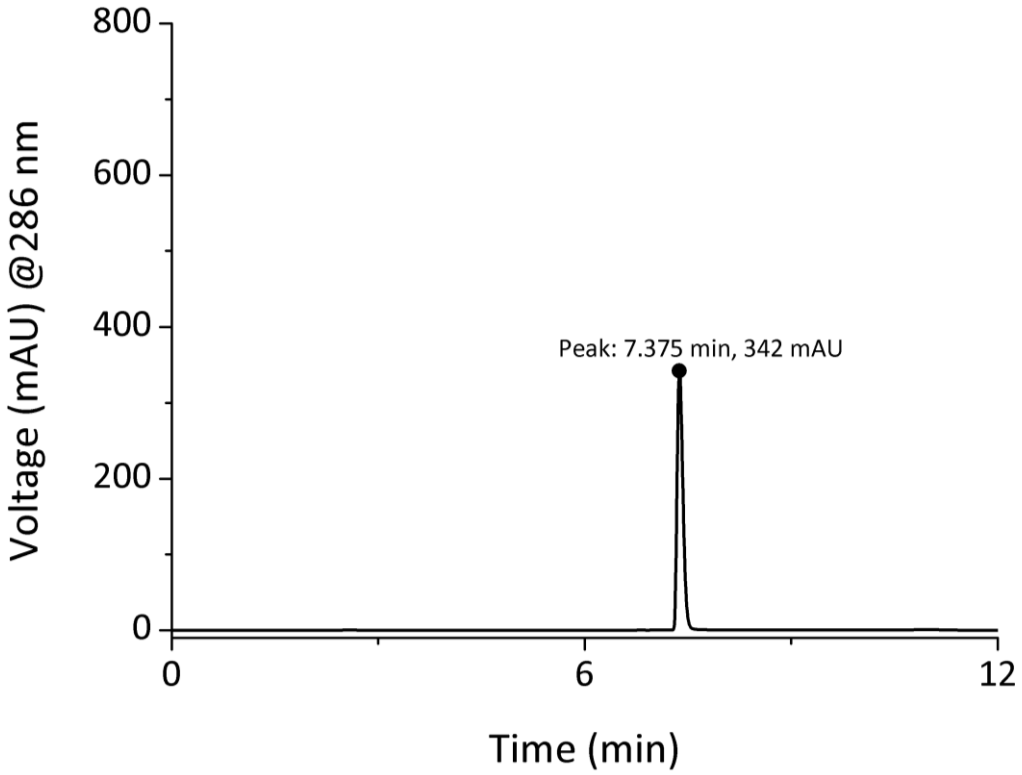


Fig. S1. Representative HPLC results for the phase solubility experiment.

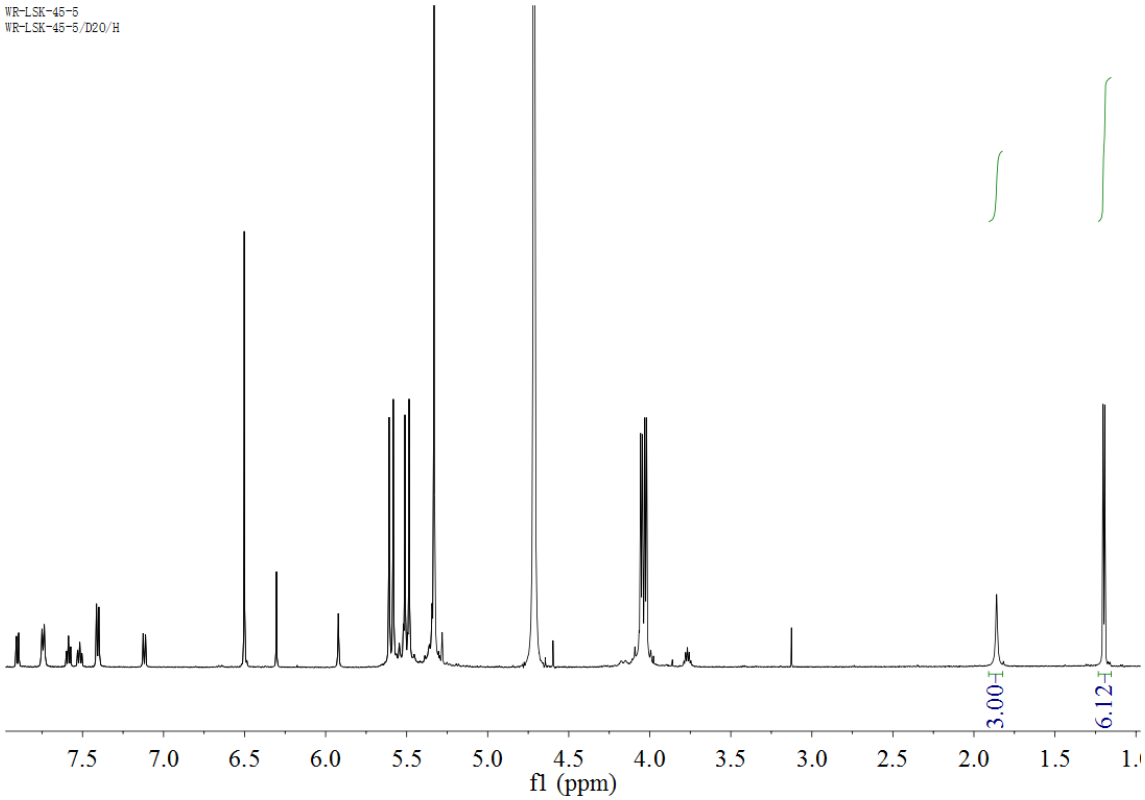


Fig. S2. Representative ^{1}H NMR integration results for the phase solubility experiment.

Binding geometry from DFT calculation

Density Functional Theory (DFT B3LYP/6-31G(d)) was used to further assess the binding geometry. We first calculated the energy of minimized mono-protonated CFZ isomers, since there are four potential sites that could be protonated and the ESI-MS spectrum only showed peaks corresponding to mono-protonated CFZ. The DFT results show that the protonation of CFZ in acidic conditions most likely takes place at the isopropyl amine group, corresponding to a structure at least 9.9 kcal.mol^{-1} more stable than the three other N mono-protonated analogues. This is consistent with previous literature reports in solid state.[1] Once complexed with CB[7], the isopropyl nitrogen atom is still the most favorable protonation site, by at least 19 kcal.mol^{-1} as compared with other mono-protonated complexation species and the proposed structure with an included chlorophenyl ring is shown in Fig. S5. A structure of similar lowest energy was found (or even lower when accounting for BSSE effects) but this complex has its isopropyl group included in CB[7]. Thus, partial inclusion (iPr side) cannot be ruled out. However, these structures are local minima and do not account for the inclusion complexation reaction where high energy water molecules are released from the cavity of CB[7]. The structure showed in Fig. S5 thus appears as the most likely due to the higher number of high-energy water molecules expected to be released by the chlorophenyl ring as compared to the isopropyl group. This phenomenon has recently been described as a very important driving force for the inclusion complexation inside CB[*n*].[2, 3] In the most likely structure (Fig. S5), there are (i) two strong N-H···O=C guest host interactions (1.96 $\alpha_{N\text{-}H\cdots O}$ = 170.5° and 2.05 Å $\alpha_{N\text{-}H\cdots O}$ = 160.4°) at one carbonyl portal of CB[7], (ii) one phenyl group, the one linked to nitrogen β included in the cavity of CB[7] and (iii) the potential for orthogonal halogen bonds. The measured distances between the guest chlorine atom and two host carbonyl atoms Cl···O (3.52 and 3.60 Å) are just above the sum of van der Waals radii (~ 3.3 Å) but the $\alpha_{C=O\cdots Cl}$ angles (93.6 and 95.5°), the $\alpha_{N\text{-}C=O\cdots Cl}$ angles (mean values 91.1 and 91.0°), and the $\alpha_{C\text{-}Cl\cdots O}$ angles (129.2 and 124.6°), could have the attributes of orthogonal halogen bonds.[4]

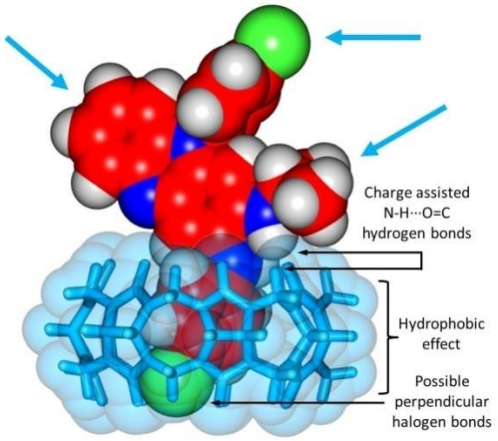
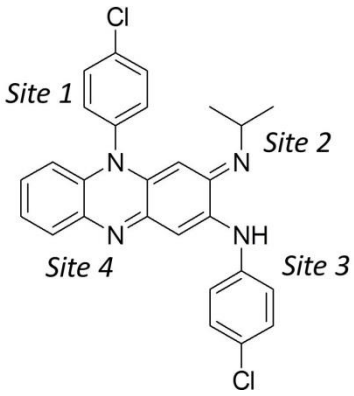


Fig. S3. Proposed DFT minimized structure of the inclusion complex CFZ+1H1+@CB[7] with nitrogen α protonated illustrating the chlorophenyl ring sequestration and the charge assisted N-H···O=C hydrogen bonds. Blue arrows are for alternative binding sites.

DFT calculations: A positively charged guest has been considered due to the pK_a of Clofazimine of ≈ 8.5 and because CB[7] is known to stabilize cationic charges via ion−dipole interactions. As there are four amine sites, four isomers have been calculated where the only variation is the position of the proton on the nitrogen atoms of the +1 charged molecule with Chem3D before further minimization with Gaussian09 Rev.D01 by DFT (B3LYP/6-31G(d)) using the CPCM water continuum model for solvation.

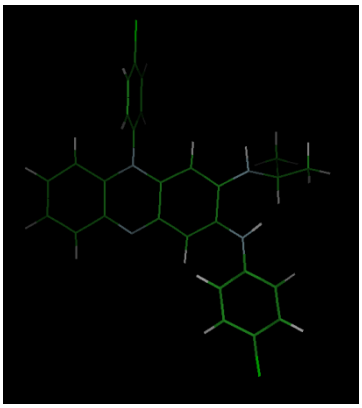


Only one conformer was found with a much lower energy that others and corresponding to the protonated amine site already described in the literature (iPr, structure given below). We then fixed this proton and considered this +1 charged guest for interactions with CB[7]toward the four possible binding sitesand found that sites 2 and 3 are the most likely to be included with protonated N at site 2 (these 2 structures are also given below). In brief, minimized host and guest using Chem3D were manually constructed and docked to allow the considered binding site to be included in CB[7] before DFT minimizations with Gaussian.

On the other hand, it could also happen that CB[7] stabilizes another protonation site due to its tendency to stabilize cationic charges via ion−dipole interactions. We thus did additional calculations as controls in which each of the 4 N sites were protonated and CB[7] placed such as binding the hydrophobic residue near the N-H$^+$ site. We found that considering N-H+ and binding at site 3 afforded less stable structures (variations in the orientation of the iPr group within this series) by at least 21 kcal.mol^{-1}. It is the same conclusion for site 4 where the corresponding amine is protonated and the pendant phenyl ring bound by CB[7] (less stable by ≈ 19 kcal.mol^{-1}). Then site 1 was considered (N-H$^+$ and Cl-Ph ring binding) providing the highest energy structure. All structures have been frequency checked for true minima.

Then, calculations of BSSE (*Basis set superposition errors*) have been performed for the 5 most relevant inclusion complexes with CB[7]. It appeared that the error introduced by the basis set superposition is approximately 10 kcal.mol^{-1} and about the same magnitude for all the cases which does not change the relative stability of the inclusion complexes investigated except for the 2 most stable ones that are discussed in the paper. Briefly, the iPr (site 2) and N-H-Ph-Cl (site 3) positions are discussed in the paper and, before BSSE calculation have the same energy. After BSSE correction, the iPr-*in* complex appears more stable by about 7.4 kcal.mol^{-1}. However, the iPr group doesn't fit well in the CB[7] cavity. DFT calculations accounting for BSSE (i) cannot include solvent effects (Gaussian09) and (ii) do not include the desolvation of the CB[7] internal cavity that is known to be a large contribution of the stabilizing energy of complexation. The presented structure of Figure 5 (N-H-Ph-Cl-*in*) still appears the most likely to us but the iPr-in complex cannot be ruled out. Therefore, the atomic coordinates for these 2 inclusion complexes are disclosed hereafter.

Most stable conformer of the singly charged Clofazimine



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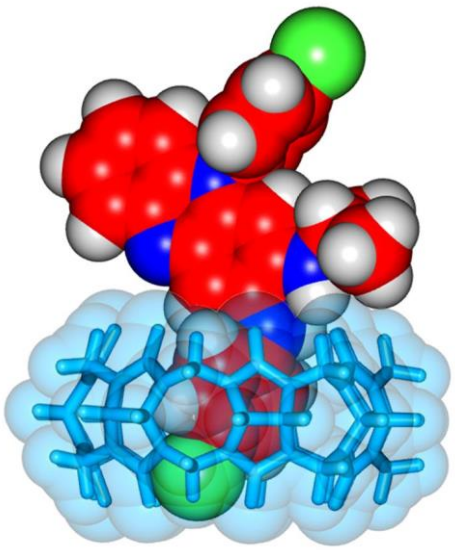
Cl-Ph-in conformer of the singly charged Clofazimine guest inside CB[7]



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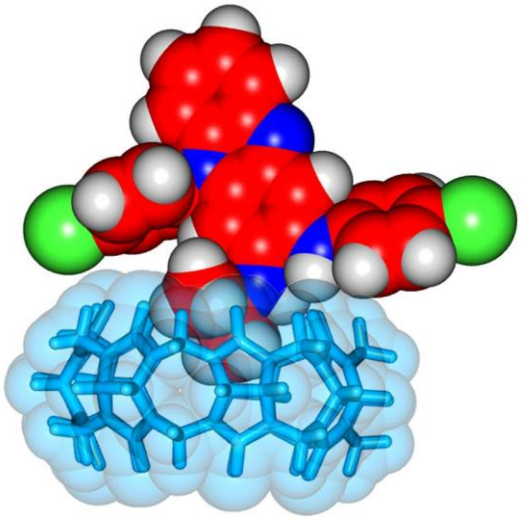
iPr-in conformer of the singly charged Clofazimine guest inside CB[7]



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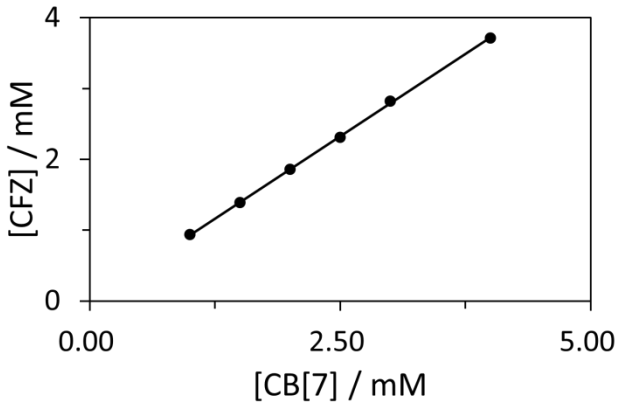

Fig. S4. Phase-solubility diagrams of CFZ and CB[7], determined from proton resonances integrations on 1H NMR spectra (pD = 2, D_2O/DCl, NaOAc as the internal standard, by the linear fit equation: y = 0.9301x + 0.0013, R^2 = 0.9997).

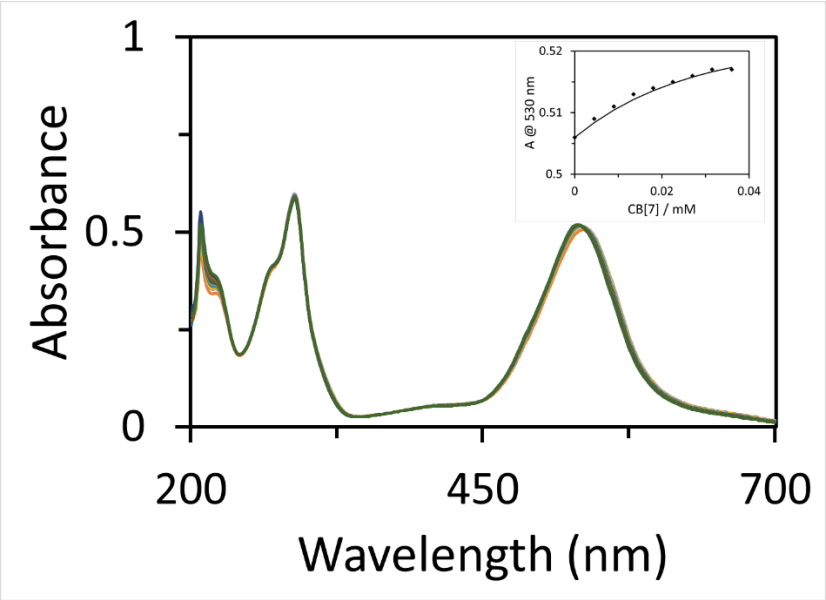

Fig. S5. UV-vis titration of CFZ with increasing amounts of CB[7] in 5 M HCl solution. The inset shows the best fit between experimental points and a 1:1 binding model affording a binding constant Ka = 5.4 (± 0.2) $\times 10^4$ M^{-1}.

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