

A DFT Investigation of The Host-Guest Interactions Between Boron-Based Aromatic Systems and β -Cyclodextrin

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A DFT investigation of the host-guest interactions between boron-based aromatic systems and β -cyclodextrin

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Abstract

Density-functional theory calculations including dispersion at BLYP-D3(BJ)/def2-SVP level of theory were performed for a series of systems based on cyclodextrin complexation with boron-based aromatic compounds. Elaborated investigations were carried out using different quantum chemical parameters such as computed complexation energies, theoretical association constants and natural bond orbital (NBO) analysis. Several configurations and inclusion modes were considered in this work. The calculated complexation energies were consistent with the experimental classification of these systems on the basis of occurring interactions. Reduced density gradient (RDG) and independent gradient model (IGM) approaches determined the nature and strength of non-covalent interactions which played a central role in the formation of the complexes. Thus, phenylboronic acid (PBA) and benzoxaborole (Bxb) act mainly as hydrogen-bonded complexes with β -cyclodextrin, while mainly Van der Waals (vdW) interactions stabilize both catechol (PhBcat) and pinacol esters

29 of phenylboronic acid (PhBpin) complexes. The ferroceneboronic acid (FcBA) exhibits a
30 mixture of H-bonds and vdW interactions with β -cyclodextrin.

31 **Keywords:** β -cyclodextrin, boron-based compounds, non-covalent interactions, inclusion
32 complexes, DFT-D3

33 **1. Introduction**

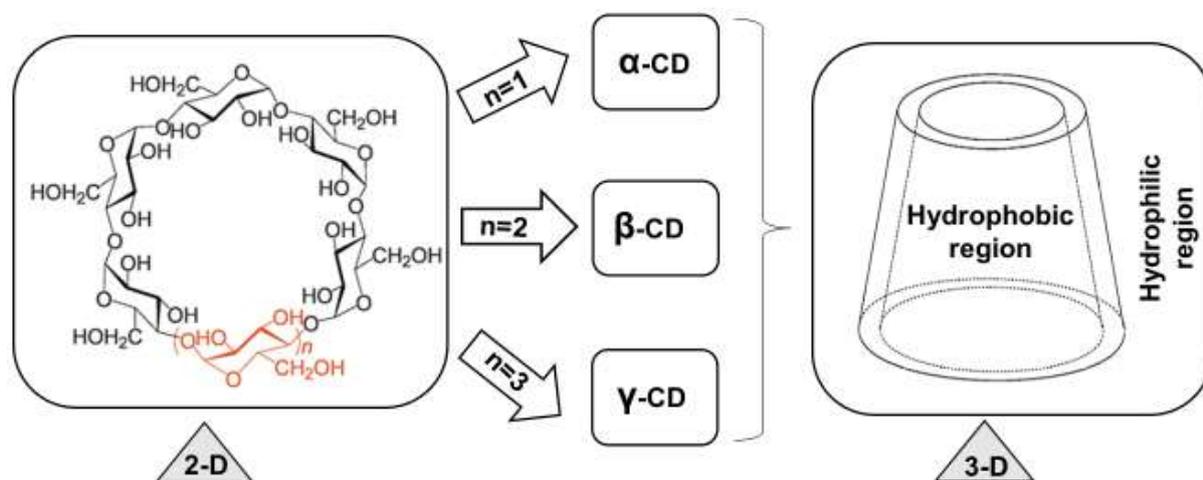
34 In recent years, organoboron compounds have become one of the most versatile classes of
35 heteroatom-substituted organic molecules [1-3]. Organoboron-based compounds and their
36 derivatives are a class of organic molecules with several applications in various fields of
37 chemistry such as analytical and supramolecular chemistry, catalysis, energy storage and
38 carbon capture (H₂, CH₄, CO₂...) [4-8]. Indeed, boronic acids have been successfully used as
39 catalysts, e.g, for the formation of amide bonds and enantioselective reactions [9-12]. Since
40 2005, boronic acids have been used by Omar Yaghi and his collaborators as secondary
41 building blocks to synthesize nanoporous materials, in particular covalent organic-framework
42 like COF-1 [6].

43 The complexes which are based on the interaction of boric acid and its derivatives [13] with
44 macromolecular systems such as carbohydrates have several important applications, notably
45 in the area of drug delivery. For instance, it is reported that ferroceneboronic acid (FcBA) and
46 its derivatives could act as electrochemical biosensors for detecting sugars [14].

47 Boron atom is more electropositive than carbon, and this fundamental property is exploited to
48 the fullest in organic synthesis, becoming one of the most prominent areas of application of
49 organoboron compounds. The mildly Lewis acidic character of the boron atom is suitable in
50 the context of carbohydrate and fluoride sensing that is enabled by the formation of
51 tetracoordinate borates with fluoride anions and polyols [3, 15-19].

52 In addition to the application areas mentioned before, boronic acids are used as therapeutic
53 agents and biological probes. The first-in-class anticancer drug bortezomib has been joined by

54 the recently approved antifungal tavaborole, and anti-eczema drug crisaborole, while many
55 other boronic acid derivatives have shown promising activities in a large number of clinical
56 and preclinical studies [20, 21]. In this arena, boronic acids are complexed with
57 supramolecular structures involving inclusion complexes with cyclodextrins. These studies
58 have resulted in new commercially available drugs which have been of great benefit [22].



59

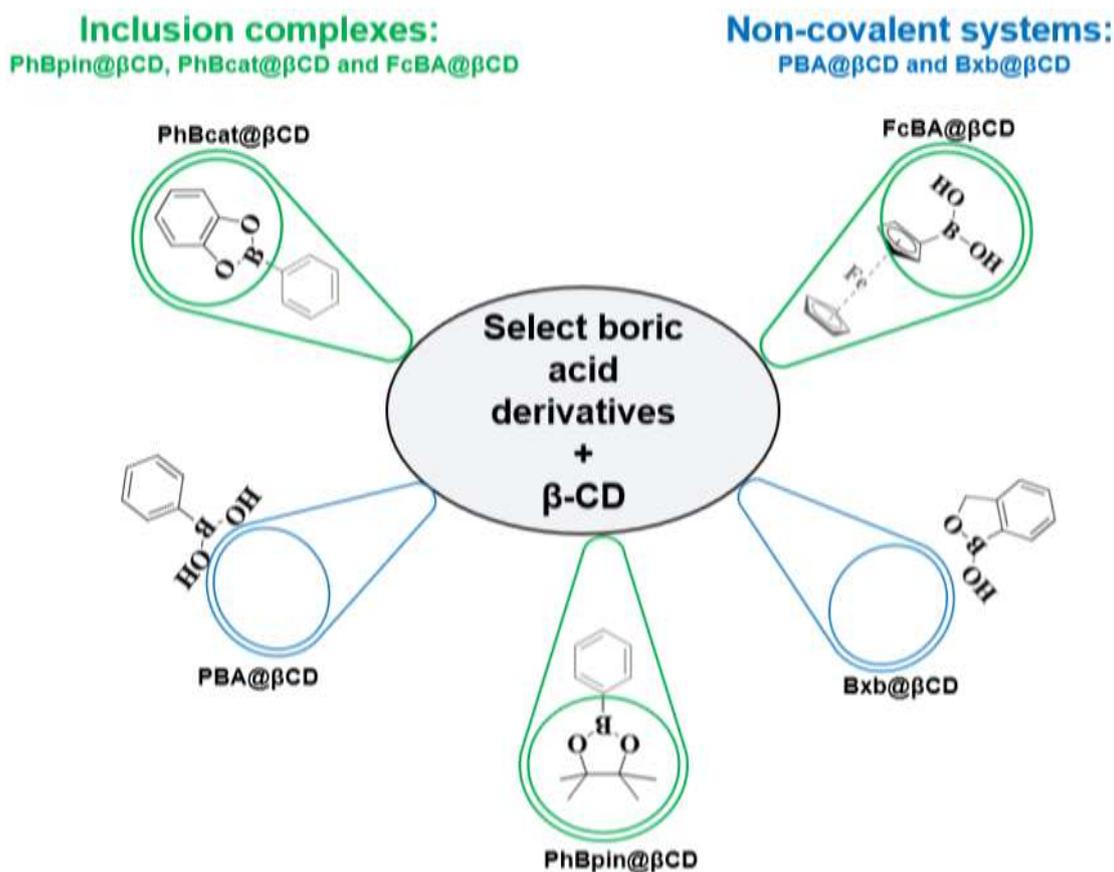
60

Fig. 1 Chemical structure and 3D-model of cyclodextrins.

61 Cyclodextrins (CDs) have been used extensively due to their advantages of non-toxicity,
62 facile modification, good water-solubility and high biological availability. CDs have been
63 approved as pharmaceutical excipients for the manufacture of pharmaceutical preparations.
64 CDs are cyclic oligosaccharides formed by 6, 7 or 8 glucoses units, which are called α , β , γ -
65 cyclodextrin respectively (See Fig. 1) [23-25].

66 The 3D structure of CDs shows hollow truncated cone-shaped macrocycles in space, their
67 inside cavity is hydrophobic while the outside is hydrophilic. CDs form inclusion complexes
68 with a wide variety of boronic acids [26-29]. In this context, Kasprzak et al. studied the
69 interactions of some boric acid derivatives with β -cyclodextrin using spectroscopic methods:
70 Proton nuclear magnetic resonance (^1H NMR), ^1H Diffusion-Ordered Spectroscopy nuclear
71 magnetic resonance (^1H DOSY NMR) and Fourier-transform infrared spectroscopy

72 (FTIR)[30]. They found that phenylboronic acid (PBA) and benzoxaborole (Bxb) form non-
 73 covalent hydrogen bonding-based systems with β -cyclodextrin, whereas catechol (PhBcat)
 74 and pinacol esters of phenylboronic acid (PhBpin) as well as ferroceneboronic acid (FcBA)
 75 form host-guest inclusion complexes. The proposed structural models for the studied
 76 complexes are represented in Fig 2.



77

78 **Fig. 2** Interactions of boron-based aromatic systems with β -cyclodextrin [30].

79 To quantify the interaction between the studied boron-based aromatic systems and β -
 80 cyclodextrin, Kasprzak et al. determined the association constant (K_a) of formed complexes.
 81 In their study, the experimental association constant follows the trend: FcBa@ β -CD ($\approx 85 \text{ M}^{-1}$)
 82 $>$ PhBcat@ β -CD (≈ 46.4) $>$ PBA@ β -CD (≈ 42.1) $>$ PhBpin@ β -CD (≈ 31.1) $>$ Bxb@ β -CD
 83 (≈ 14.8). According to the authors, the strength of the K_a is proportional to the number of
 84 established hydrogen bonds.

85 Furthermore, despite the diversity of characterization techniques used, the authors did not
86 explain the mechanism of inclusion. That is why the current study is aimed at a more
87 profound understanding of the inclusion complex formation between select aromatic boron-
88 based compounds (PBA, PhBcat, PhBpin, Bxb and FcBA) and β -CD using density functional
89 theory. To the best of our knowledge, this is the first theoretical study aiming to quantify the
90 interactions between a class of aromatic boron compounds and β -cyclodextrin using
91 exclusively DFT-based calculations.

92 **2. Computational details**

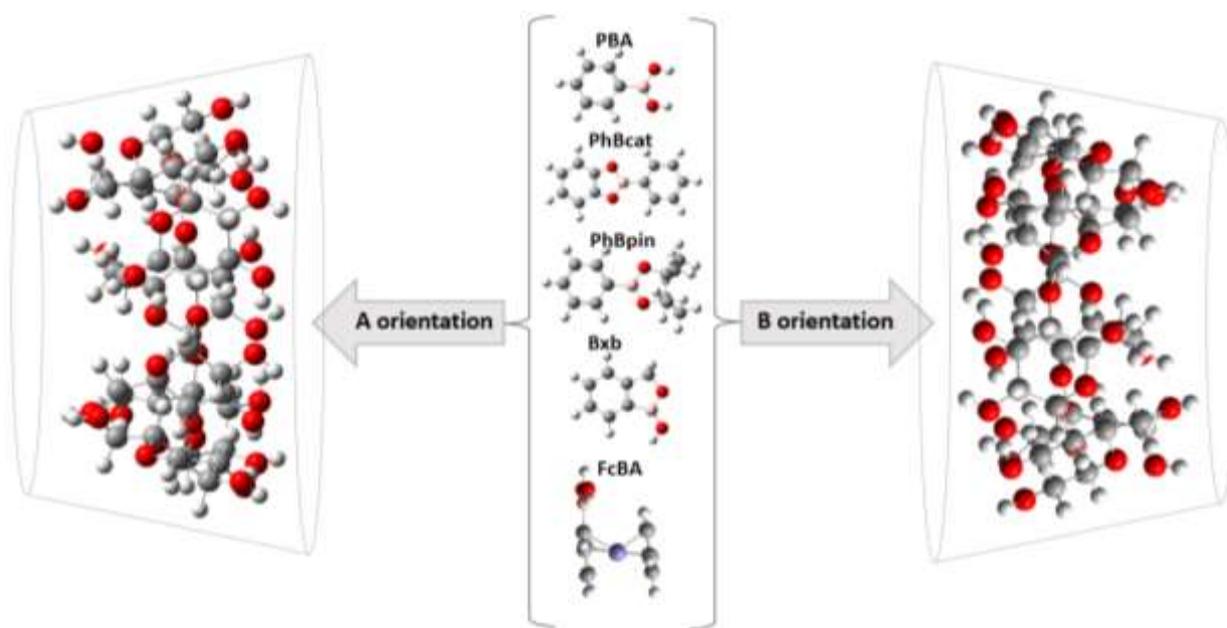
93 DFT-based computations were carried out with ORCA program (version 4.2.0) [31] and
94 Gaussian 09 quantum computational package [32]. The optimization of the whole inclusion
95 process between select boron compounds and β -CD was performed in vacuum and in water
96 with a conductor-like polarizable continuum model (CPCM) [33] at DFT level of theory using
97 BLYP functional in conjunction with Becke-Johnson (BJ) damping function dispersion
98 correction D3(BJ) [34-38] and def2-SVP basis set [39-41]. For improving the computational
99 efficiency of our large scale calculations, we employed the resolution of the identity (RI)
100 approximation [42, 43].

101 A geometrical counterpoise correction scheme (gCP) to the def2-SVP for the intra- and inter-
102 molecular basis set superposition error was applied [44]. Default values convergence criteria
103 were used for all optimizations. Several studies have shown the reliability of BLYP-D3(BJ) in
104 describing satisfactory non-covalent interactions [45-48].

105 The natural bond orbital (NBO) calculations were carried out with the Gaussian 09 code in the
106 same manner as the precedent protocol (BLYP-D3(BJ)) but with the larger basis set def2-
107 TZVPP to elucidate the nature of hydrogen bonding in the studied complexes.

108 The initial structure of β -CD was taken from Chem-Office 3D ultra (Version 10, Cambridge
109 Software) [49]. The starting geometries of studied boron compounds were constructed using
110 Hyperchem 7.5 molecular modeling package [50].

111 The coordinate system defining the process of complexation is represented in Fig. 3.



112

113 **Fig. 3** Coordinate system used to define the inclusion process between studied boron
114 compounds and β -CD. Atom's color code: pink for B, purple for Fe, grey for C, red for O and
115 white for H.

116 Following the method proposed by Liu and Guo [51], the glycosidic oxygen atoms of β -CD
117 were positioned onto the XY plane; their center was set as the origin of the coordinate system.

118 The secondary hydroxyl groups of the β -CD were placed pointing toward the positive Z-axis.

119 The guest molecules (Aromatic boron compounds) were initially placed at the center of the
120 coordinate system (0 Å), then translated from -5 to +5 Å along the Z-axis in both directions
121 with steps of 1 Å, thus resulting in two possible modes of inclusion A and B (Fig. 3). The

122 structures of guest molecules were initially pre-optimized. All the generated configurations
123 were fully optimized in both gas phase and aqueous solution (CPCM solvent model) at

124 BLYP-D3/def2-SVP level of theory. The complexation energies for each structure were
125 determined using the following equation:

$$126 \quad \Delta E_{\text{complexation}} = E_{\text{guest@}\beta\text{-CD}} - (E_{\text{guest}} + E_{\beta\text{-CD}}) \quad (1)$$

127 where $\Delta E_{\text{complexation}}$ represent the energy gain due to complexation, $E_{\text{guest@}\beta\text{-CD}}$, E_{guest} and
128 $E_{\beta\text{-CD}}$ are the energies of optimized geometries of the complex, the free guest and the free β -
129 CD, respectively.

130 For an exploration of the nature and the strength of the interactions [52-56] existing between
131 the aromatic boron compounds and β -CD, we performed a reduced density gradient (RDG)
132 [57] and independent gradient model (IGM) analysis [58]. The non-covalent interactions
133 (NCI) [59] maps were characterized with Multiwfn software [60] and visualized with VMD
134 program [61], they are represented by generating colored graphs of RDG isosurfaces, where
135 the blue, green and red regions are associated, respectively, to H-bonds, Van der Waals
136 interactions and steric effect.

137 **3. Results and discussion**

138 **3.1 Inclusion complexation energy evaluation**

139 The values of the computed complexation energy in gas and aqueous phases as a function of
140 the Z coordinate during the inclusion process for A and B models are reported in Table 1 and
141 2, where both models exhibit negative energies indicating that the occurring process is
142 thermodynamically favored.

143 When the guest molecules approach β -CD in gas phase calculations, several local minima
144 were observed, but the most stable geometries based on the lowest complexation energies for
145 PBA@ β -CD, PhBcat@ β -CD, PhBpin@ β -CD, Bxb@ β -CD and FcBA@ β -CD were located
146 respectively at $Z_B = 3.0 \text{ \AA}$, $Z_A = 1.0 \text{ \AA}$, $Z_B = -4.0 \text{ \AA}$, $Z_A = -5.0 \text{ \AA}$ and $Z_A = 0.0 \text{ \AA}$ and

147 correspond to the following energies -153.8, -155.5, -172.2, -147.4 and -167.1 kJ/mol (Table
 148 1).

149

150

151 **Table 1.** Complexation energies (in kJ/mol) of β -CD with aromatic boron compounds
 152 calculated in vacuum at BLYP-D3(BJ)/def2-SVP level.

Inclusion mode and related configurations	PBA@ β -CD	PhBcat@ β -CD	PhBpin@ β -CD	Bxb@ β -CD	FcBA@ β -CD
-5.0A	-143.9	-136.3	-116.1	<u>-147.4</u>	-132.0
-4.0A	-127.1	-122.8	-142.3	-141.6	-131.8
-3.0A	-126.8	-144.9	-141.6	-141.4	-153.5
-2.0A	-130.7	-140.3	-148.5	-141.4	-167.1
-1.0A	-130.6	-148.6	-147.6	-135.7	-154.5
0.0A	-120.7	-148.7	-155.0	-129.2	<u>-167.1</u>
1.0A	-130.3	<u>-155.6</u>	-156.3	-129.2	-141.7
2.0A	-128.1	-133.2	-163.8	-129.2	-127.5
3.0A	-128.2	-145.7	-157.5	-129.2	-131.4
4.0A	-125.6	-134.8	-125.5	-129.4	-155.5
5.0A	-116.6	-121.8	-162.0	-105.4	-150.0
-5.0B	-130.6	-138.4	-140.1	-140.7	-132.5
-4.0B	-125.8	-145.1	<u>-172.2</u>	-136.2	-137.9
-3.0B	-145.1	-153.3	-149.4	-135.8	-117.8
-2.0B	-116.6	-147.8	-140.5	-128.2	-132.5
-1.0B	-130.6	-147.5	-140.6	-127.8	-143.0
0.0B	-153.8	-153.3	-142.1	-123.8	-161.0
1.0B	-153.8	-148.5	-142.0	-144.6	-141.9
2.0B	-153.8	-148.5	-136.7	-118.2	-157.0
3.0B	<u>-153.8</u>	-128.0	-136.6	-114.2	-153.0
4.0B	-131.3	-143.9	-142.4	-129.8	-164.3
5.0B	-139.1	-129.9	-118.1	-132.4	-164.6

153

154 In aqueous phase calculations, the most stable geometries based on the lowest complexation
 155 energies for PBA@ β -CD, PhBcat@ β -CD, PhBpin@ β -CD, Bxb@ β -CD and FcBA@ β -CD
 156 were located respectively at $Z_B = -2.0 \text{ \AA}$, $Z_A = 1.0 \text{ \AA}$, $Z_A = 3.0 \text{ \AA}$, $Z_A = -1.0 \text{ \AA}$ and $Z_A = -5.0$

157 Å and correspond to the following energies -87.0, -96.6, -101.0, -83.8 and -105.3 kJ/mol
 158 (Table 2).

159 **Table 2.** Complexation energies (in kJ/mol) of β -CD with aromatic boron compounds
 160 calculated in water solvent (cpcm solvation model) at BLYP-D3(BJ)/def2-SVP level.

Inclusion mode and related configurations	PBA@ β -CD	PhBcat@ β -CD	PhBpin@ β -CD	Bxb@ β -CD	FcBA@ β -CD
-5.0A	-61.5	-77.5	-55.9	-82.9	<u>-105.3</u>
-4.0A	-61.0	-76.0	-69.9	-73.6	-103.5
-3.0A	-57.6	-90.0	-75.0	-72.2	-102.4
-2.0A	-51.9	-81.7	-74.1	-82.6	-99.2
-1.0A	-63.2	-79.2	-74.6	<u>-83.8</u>	-104.0
0.0A	-72.1	-82.5	-85.8	-53.3	-104.4
1.0A	-61.8	<u>-96.6</u>	-88.8	-77.1	-97.2
2.0A	-78.5	-96.5	-71.9	-72.9	-73.5
3.0A	-76.7	-74.6	<u>-101.0</u>	-81.0	-95.4
4.0A	-62.8	-62.4	-75.9	-65.9	-95.3
5.0A	-81.1	-75.7	-77.0	-74.2	-66.0
-5.0B	-76.5	-83.7	-94.7	-78.7	-72.1
-4.0B	-77.2	-36.9	-84.8	-69.1	-97.2
-3.0B	-76.7	-81.9	-83.2	-79.2	-71.4
-2.0B	<u>-87.0</u>	-87.4	-84.9	-79.1	-58.2
-1.0B	-76.8	-88.3	-83.6	-78.6	-72.2
0.0B	-69.3	-87.1	-83.5	-69.4	-93.7
1.0B	-65.0	-88.7	-83.5	-55.5	-93.9
2.0B	-64.6	-89.2	-74.6	-70.5	-87.9
3.0B	-64.2	-80.3	-81.0	-70.5	-29.2
4.0B	-72.4	-82.9	-73.2	-77.5	-90.5
5.0B	-24.1	-69.7	-54.1	-68.9	-100.8

161
 162 The complexation energies are more negative in vacuum than in aqueous solution, they range
 163 between -147.4 and -172.2 kJ/mol in gas phase and between -83.8 and -105.2 kJ/mol in water
 164 solution. Due to the water solvent effects, the interaction between aromatic boron compounds
 165 and β -CD is weakened; showing, therefore, that inclusion process is more exothermic in gas
 166 phase than in water.

167 The calculations carried out in aqueous phase show the same trend towards the complexation
168 energy except that FcBA@ β -CD is more stable than PhBpin@ β -CD.

169 It is also observed that complexation energies calculated both in vacuum and in aqueous
170 solution are correlated with the experimental nature of the assembly between the aromatic
171 boron compounds and β -CD. Indeed, the PhBcat@ β -CD, PhBpin@ β -CD and FcBA@ β -CD
172 form inclusion complexes, whereas PBA@ β -CD and Bxb@ β -CD favor the formation of
173 hydrogen-bonded systems.

174 The resulting gas phase optimized geometries at BLYP-D3(BJ)/def2-SVP level will be used
175 in the subsequent calculations of NBO and RDG function.

176 **3.2. Theoretical determination of association constant**

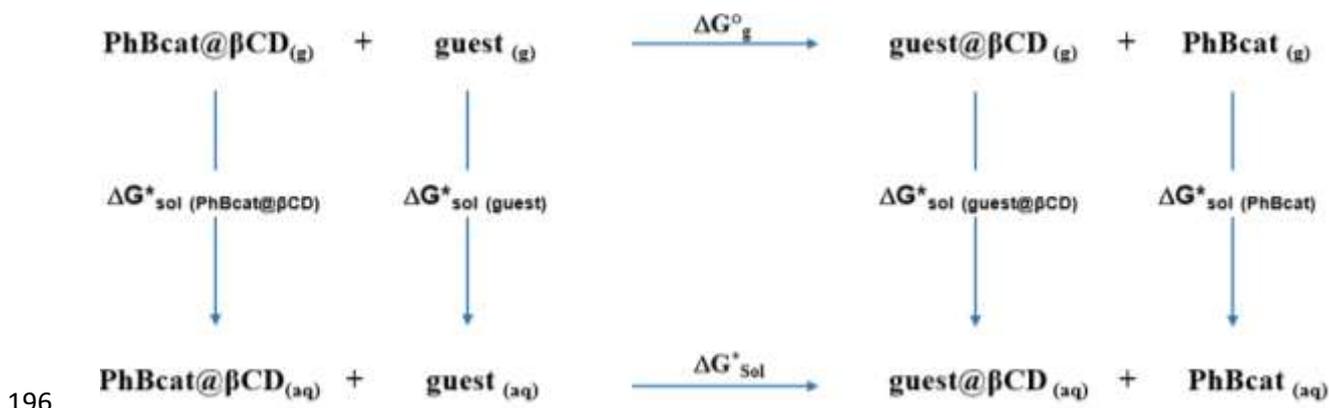
177 From a computational viewpoint, the association constant K_a could be calculated according to
178 the following reaction:



180 However, the association constants are determined experimentally in the aqueous phase. To
181 be able to compare the experiment K_a with the results of quantum chemistry calculations, it is,
182 therefore, necessary to take into account the effects of solvation on the calculation of the free
183 reaction enthalpies using CPCM solvent model. It is known that in these types of systems, a
184 continuous model for the solvent can strongly fail since it does not allow evaluating the role
185 of specific interactions between the water molecules and the guest/host molecules.
186 Nevertheless, Champion et al. have proposed a strategy and applied it successfully in
187 predicting reaction equilibrium constants, for instance, for reactions similar to the ones
188 studied in our work [62, 63]. They have shown that more accurate results can be obtained
189 when the thermodynamic cycle involves not direct complexation reactions, but rather ligand-
190 exchange reactions by determining the exchange constant K_{exc} . The basic reasoning justifying

191 the use of this strategy is based on error cancellation mechanisms between the species at the
 192 left and the right-hand side.

193 We hence proceeded accordingly, and, in our calculations, we employed boron compounds
 194 exchange reactions involving the $\text{guest@}\beta\text{CD}$ species as shown in Fig. 4. We chose the
 195 phenylboronic acid catechol (PhBCat) as a reference.



197 **Fig. 4** Thermodynamic cycle used to compute free energy changes in aqueous solution.
 198 The boron compounds exchange equilibrium constant, K_{exc} , is then calculated from the free
 199 energy change in aqueous solution, ΔG_{sol}^* , which can be expressed as:

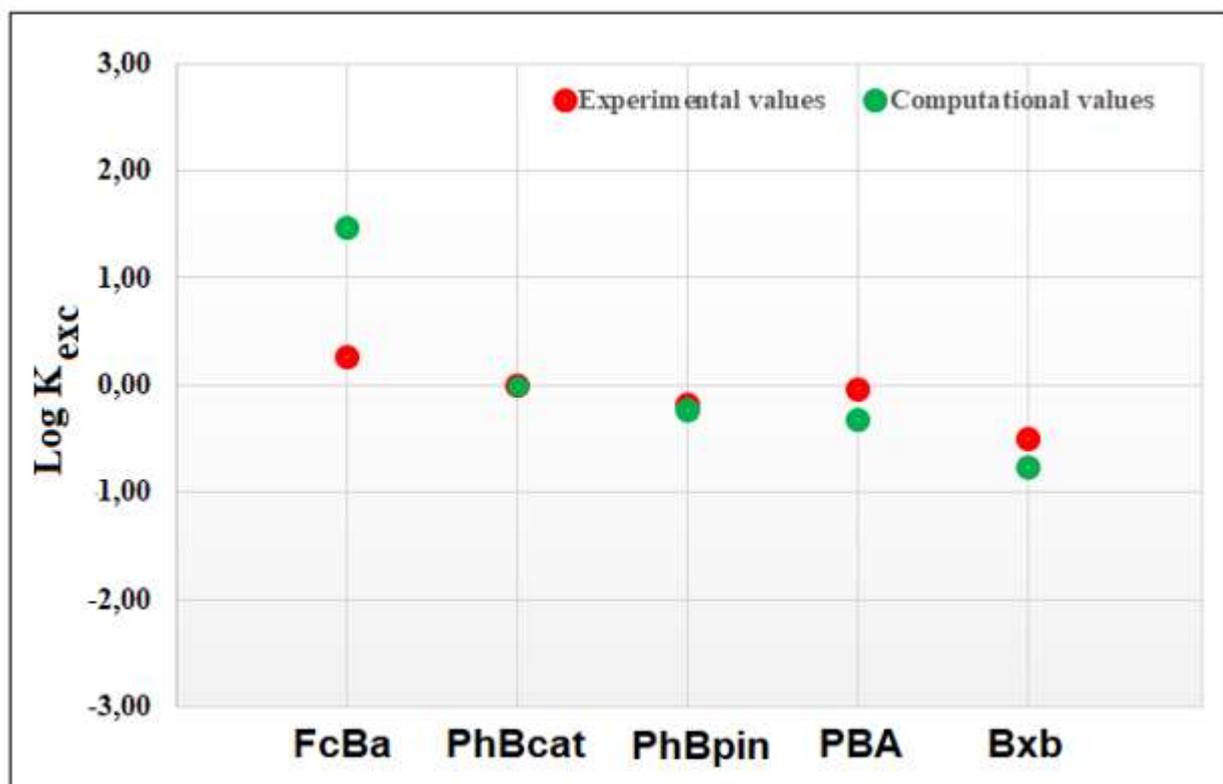
200
$$\Delta G_{\text{sol}}^* = \Delta G_g^0 + \Delta G_{\text{sol}}^*(\text{guest@}\beta\text{-CD}) + \Delta G_{\text{sol}}^*(\text{PhBcat}) - \Delta G_{\text{sol}}^*(\text{guest}) - \Delta G_{\text{sol}}^*(\text{PhBcat@}\beta\text{-CD}) \quad (2)$$

201 Where ΔG_g^0 is the free energy change in the gas-phase and $\Delta G_{\text{sol}}^*(\text{guest@}\beta\text{CD})$, $\Delta G_{\text{sol}}^*(\text{PhBcat@}\beta\text{CD})$,
 202 $\Delta G_{\text{sol}}^*(\text{guest})$ and $\Delta G_{\text{sol}}^*(\text{PhBcat})$ are the free energies of solvation of the respective species in
 203 water. For each species, its Gibbs free energy at 25°C is obtained using the computed energy
 204 with the BLYP-D3(BJ)/def2-SVP level, and the thermodynamic corrections from the
 205 frequency calculation performed with the same functional and basis set in gas-phase. The
 206 computed Gibbs free energies at 25°C are regrouped in Table S1. Note that some guests and
 207 $\text{guest@}\beta\text{CD}$ complexes exhibit several competitive configurations (see, for instance, the case
 208 of $\text{Bxb@}\beta\text{CD}$, Fig. S1), their Gibbs free energies have then been evaluated using a Boltzmann
 209 distribution:

210
$$G_{[A]}^0 = -RT \ln \sum_{i \in [A]} e^{-G_i^0 / RT} \quad (3)$$

211 where the summation runs over all the most stable configurations of the A species. The
 212 cartesian coordinates of the different configurations used in the determination of the exchange
 213 constant are presented in Table S2.

214 The exchange equilibrium constants (**Log K_{exc}**) computed at the BLYP-D3/def2-SVP level of
 215 theory, and the experimental values, are presented in Fig. 5.



216
 217 **Fig. 5** Correlation of experimental and computational Log K_{exc} values for the studied
 218 complexes

219 From the computed Log K_{exc} (the dots in green color, Fig. 5), it is clear that the complexes
 220 PhBcat@ β -CD, PhBpin@ β -CD and FcBA@ β -CD (inclusion complexes) have the three
 221 strongest association constants, while the complexes forming hydrogen-bonded systems have
 222 the lowest ones. This finding confirms the previous results concerning the complexation
 223 energies.

224 On the other hand, we notice that for the FcBA, PhBcat, PhBpin, PBA and Bxb, the
225 computational values agree well with the experimental results. The mean absolute deviation
226 (MAD) between the experimental and computed $\text{Log}K_{\text{exc}}$ values is rather small (0.37).

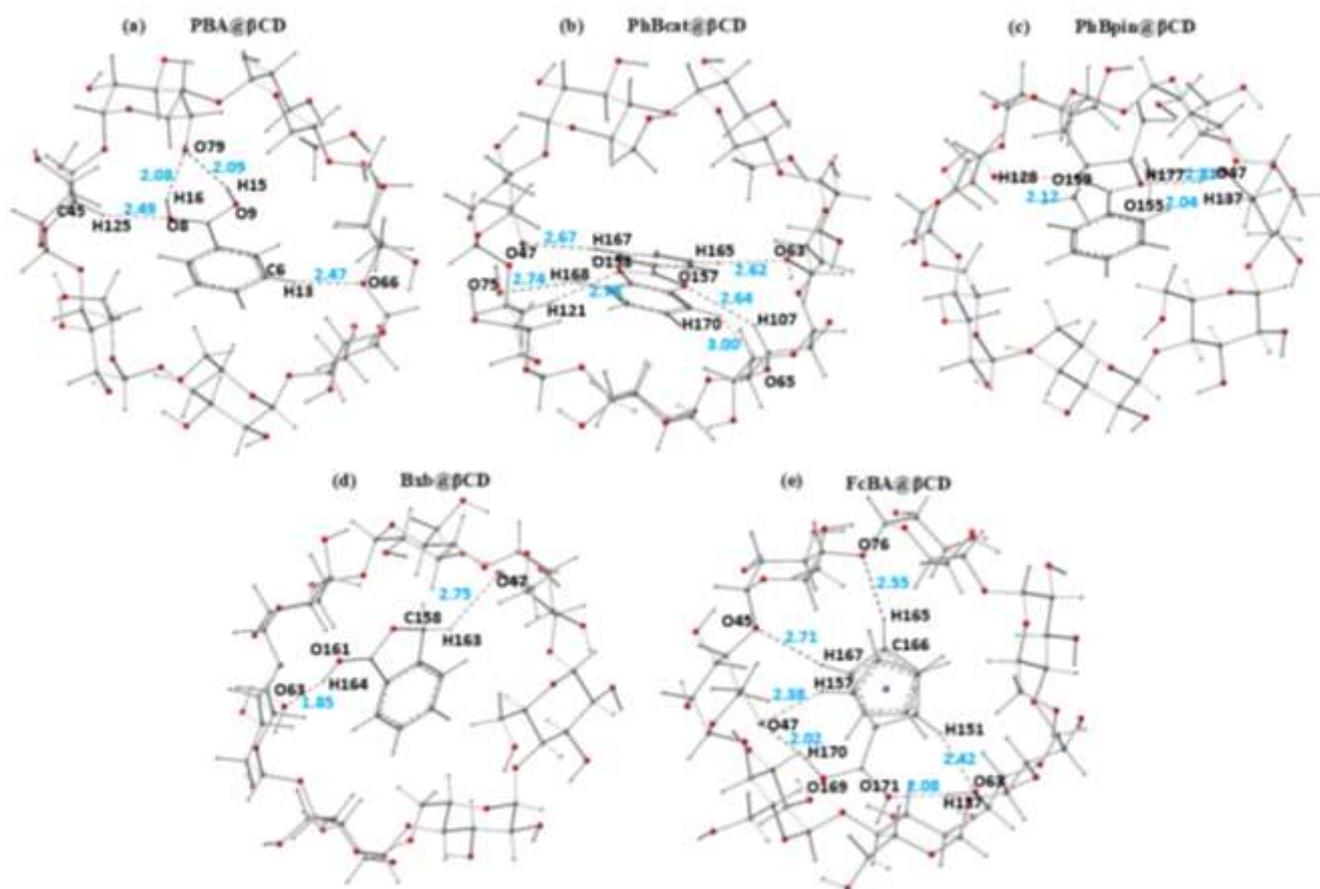
227 **3.3. Intermolecular hydrogen-bonding effects**

228 This section is intended to shed light on the ability of the aromatic boron compounds to
229 interact through hydrogen bonds (HBs) with β -CD.

230 NBO method consists in interpreting the electronic wave function in terms of Lewis structures
231 by considering all possible interactions between filled donor (i) and empty acceptor (j) NBOs
232 and evaluating their stabilizing energy through the second-order perturbation theory. The
233 results of NBO analysis associated with the bond length and the stabilization energy of
234 intermolecular hydrogen bonding in the studied complexes are reported in Table 3.

235 A comparison of significant hydrogen bond lengths shows that the values fluctuate between
236 1.85 and 2.76 Å (Fig. 6), the shortest lengths (1.85-2.10 Å) corresponding to strong donor–
237 acceptor interactions [64, 65] with higher stabilization energies are associated to the
238 complexes PBA@ β -CD, Bxb@ β -CD and FcBA@ β -CD.

239



240

241 **Fig. 6** Intermolecular hydrogen bonds illustrated by dashed lines and the corresponding H...O
 242 distances (Å). Atom's color code: pink for B, purple for Fe, grey for C, red for O and white
 243 for H.

244 The strength of intermolecular hydrogen bonds varies from weak for PhBcat@β-CD and
 245 PhBpin@β-CD to moderate for the complexes PBA@β-CD, Bxb@β-CD and FcBA@β-CD.

246 Indeed, as reported in Table 3, the intermolecular hydrogen-bond lengths of PhBcat@β-CD
 247 and PhBpin@β-CD complexes are averagely longer than those of PBA@β-CD, Bxb@β-CD
 248 and FcBA@β-CD and their corresponding energies are consequently lower.

249

250

251

252

253 **Table 3.** NBO analysis of the second-order perturbation energies $E^{(2)}$ (kJ/mol) of the
 254 hydrogen bonds in studied complexes calculated at BLYP-D3(BJ)-def2-TZVPP level
 255

Complex	Donor	acceptor	H-bond (Å)	$E^{(2)}$ (kJ/mol)
PBA@ β -CD	β -CD (donor)	PBA (acceptor)		
	LP(2) O79	BD*(1) O9-H16	2.08	13.68
	LP(1) O79	BD*(1) O8-H15	2.09	11.97
	LP(1) O79	BD*(1) O9-H16	2.08	4.56
	LP(1) O66	BD*(1) C6-H13	2.47	2.85
	PBA (donor)	β -CD (acceptor)		
PhBcat@ β -CD	LP(1) O8	BD*(1) C45-H125	2.49	3.31
	β -CD (donor)	PhBcat (acceptor)		
	LP(2) O47	BD*(1) C155-H167	2.61	2.76
	LP(2) O63	BD*(1) C153-H165	2.62	2.72
	LP(2) O65	BD*(1) C161-H170	3.00	0.92
	LP(2) O75	BD*(1) C159-H168	2.74	1.84
PhBpin@ β -CD	PhBcat (donor)	β -CD (acceptor)		
	LP(1) O157	BD*(1) C27-H107	2.64	0.92
	PhBpin (donor)	β -CD (acceptor)		
	LP(1) O155	BD*(1) O63-H137	2.04	14.35
	LP(1) O159	BD*(1) O47-H128	2.12	9.33
	LP(3) O155	BD*(1) O63-H137	2.04	0.92
Bxb@ β -CD	β -CD (donor)	PhBpin (acceptor)		
	LP(2) O47	BD*(1) C162-H177	2.81	1.00
	β -CD (donor)	Bxb (acceptor)		
	LP(2) O47	BD*(1) C158-H163	2.75	1.30
	LP(1) O63	BD*(1) O161-H164	1.85	28.74
	LP(2) O63	BD*(1) O161-H164	1.85	6.95
FcBA@ β -CD	β -CD (donor)	FcBA (acceptor)		
	LP(1) O47	BD*(1) O169-H170	2.02	11.76
	LP(2) O47	BD*(1) C156-H157	2.38	5.31
	LP(2) O47	BD*(1) O169-H170	2.02	8.45
	LP(2) O63	BD*(1) C150-H151	2.42	5.27
	LP(1) O76	BD*(1) C164-H165	2.55	2.18
	LP(1) O45	BD*(1) C166-H167	2.71	1.21
	FcBA (donor)	β -CD (acceptor)		
LP(1) O171	BD*(1) O63-H137	2.08	15.77	

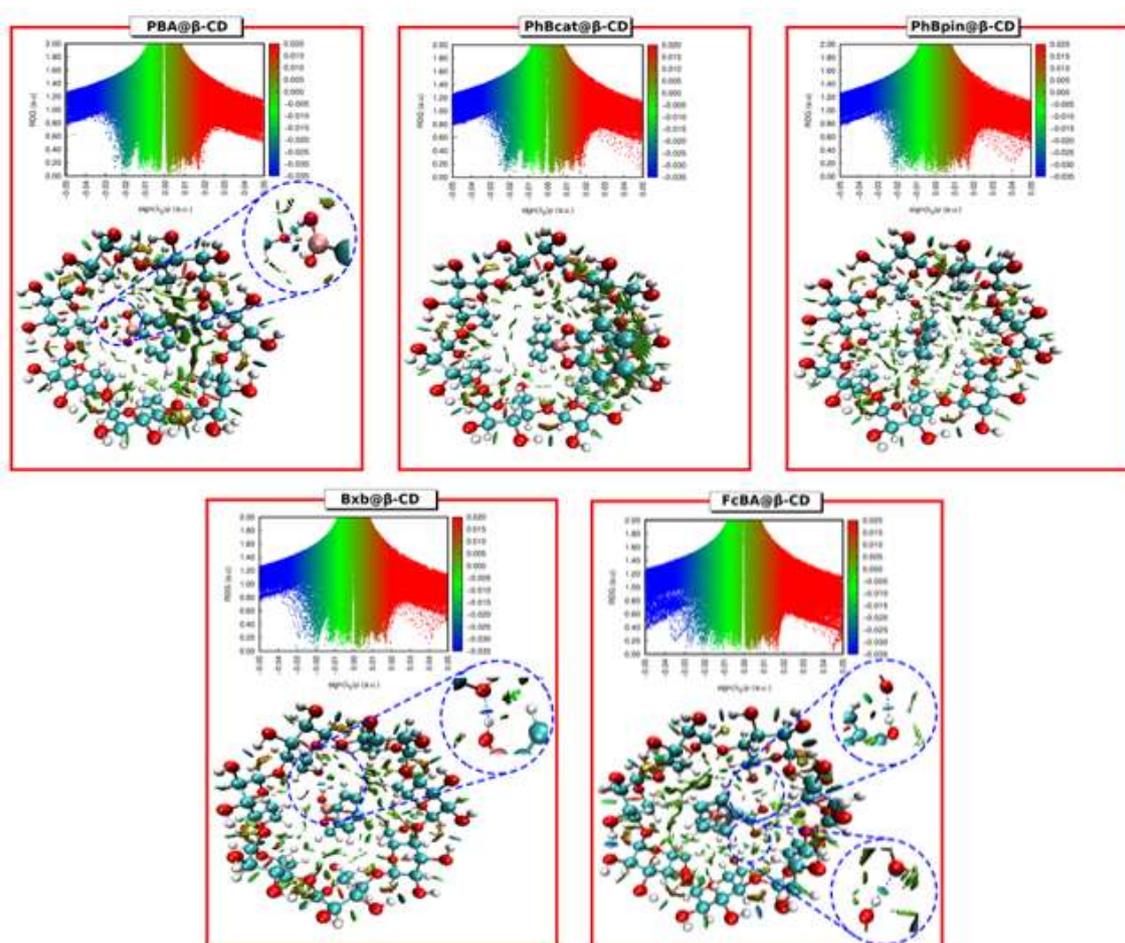
256
 257 BD denotes σ bonding orbital; BD* denotes σ^* antibonding orbital, LP denotes lone pair.

258 3.4. Nature of noncovalent interactions

259 RDG and IGM plots were carried out by an isosurface value of 0.50 and illustrated in Fig. S2
 260 (supplementary data). Red, green and blue colors represent respectively steric repulsion, weak
 261 Van der Waals interactions and strong attractive interactions like H-bonds.

262 The RDG results illustrated in Fig. S2 show clearly that the inclusion of PBA, PhBcat,
 263 PhBpin, Bxb and FcBA molecules in β -cyclodextrin exhibited different behavior. The two

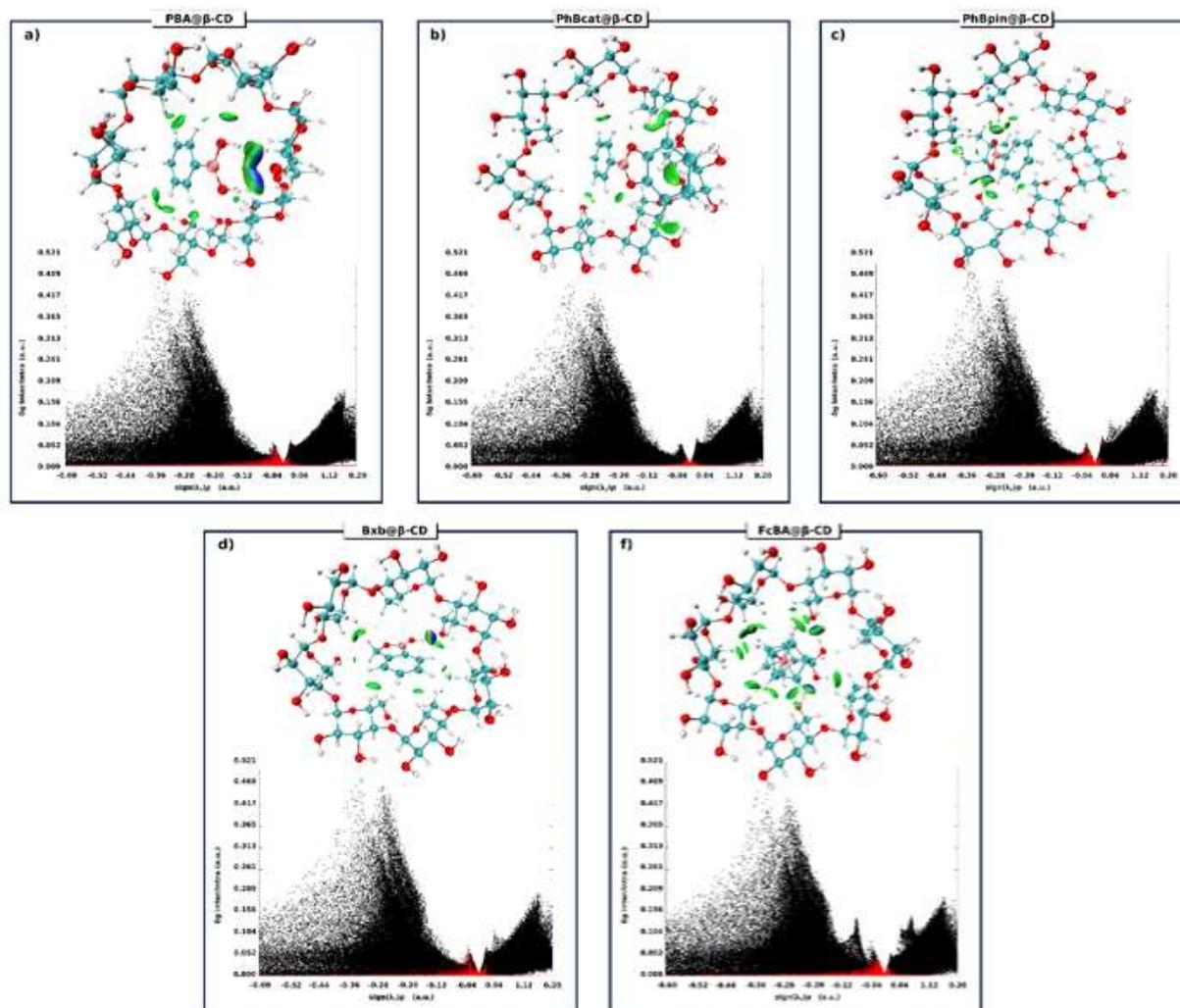
264 guest molecules PhBcat and PhBpin are wrapped by green isosurfaces, indicating weak Van
 265 der Waals interactions occurring between the PhBcat and PhBpin molecules and β -CD,
 266 whereas for the complexes PBA@ β -CD, Bxb@ β -CD and FcBA@ β -CD, RDG results reveal
 267 the presence of weak vdW interactions, as well as the existence of H-bonding interactions
 268 involving oxygen atoms of hydroxyl groups (-OH) of PBA, Bxb and FcBA and the hydrogen
 269 atoms of OH groups belonging to β -CD, as shown in the circled regions of Fig. S2.



270
 271 **Fig. 7** RDG-isosurfaces of the studied complexes computed at BLYP-D3(BJ) level. Atom's
 272 color code: pink for B, purple for Fe, blue for C, red for O and white for H.

273
 274 Visual inspection of the RDG scatter plots shows the new spikes compared with isolated β -
 275 CD (Fig. 7), in the ranges [0.000 to -0.015] and [-0.020 to -0.025] a.u. which correspond
 276 respectively, to the vdW and hydrogen bond intermolecular interactions. Additionally, the

277 intermolecular interactions between β -CD and guest molecules are quantified through the
 278 independent gradient model (IGM) to identify the nature of the intermolecular interactions,
 279 which can be provided by the δg_{inter} and δg_{intra} .



280
 281 **Fig. 8** IGM isosurfaces and scatter plots of the studied complexes. Atom's color code: pink for
 282 B, purple for Fe, blue for C, red for O and white for H.
 283 The Fig. 8 represents the IGM isosurfaces of δg_{inter} for the five complexes, where the green-
 284 colored isosurfaces denote weak van der Waals interactions, whereas blue regions indicate
 285 stronger attractive interactions associated with hydrogen bonds.
 286 The scatter plots between δg_{inter} and δg_{intra} versus $sign(\lambda^2)\rho$ was shown in lower figures of
 287 Fig. 8, in which the red and black points, correspond respectively, to δg^{inter} and δg^{intra} .

288 The plotted IGM isosurfaces confirmed the nature of occurring interactions. Indeed, the
289 complexes PBA@ β -CD and Bxb@ β -CD can be considered as hydrogen-bonded complexes,
290 while mainly vdW interactions stabilize PhBcat@ β -CD and PhBpin@ β -CD. The formation of
291 the complex FcBA@ β -CD is a combination of H-bonds and vdW interactions.
292 Overall, van der Waals (vdW) dispersion interactions strongly affect the stability.

293 **4. Conclusions**

294 In conclusion, we proposed the first DFT study of five systems based on cyclodextrin
295 complexation with a series of aromatic boron compounds. The DFT-D3 investigation results
296 confirmed their experimental ranking based on the formation of inclusion complexes or
297 hydrogen-bonded systems and showed that dispersion interactions are the major contributors
298 to the formation of complexes.

299 The inclusion process performed in vacuum and in water showed that PhBpin@ β -CD and
300 FcBA@ β -CD have respectively the highest complexation energies.

301 The natural bond orbital (NBO), reduced density gradient (RDG) and the independent
302 gradient model (IGM) calculations in gas phase showed that PBA@ β -CD and Bxb@ β -CD
303 form hydrogen-bonded systems, while mainly vdW interactions stabilize PhBcat@ β -CD and
304 PhBpin@ β -CD. FcBA@ β -CD complex is stabilized by a combination of H-bonds and vdW
305 interactions.

306 One significant result of this study is the higher stability of ferroceneboronic acid upon its
307 inclusion in the β -cyclodextrin cavity; since ferroceneboronic acid and its derivatives are used
308 as biosensors, this study could serve as a starting point in experiments for overcoming
309 problems of solubility and bioavailability by considering their inclusion in β -cyclodextrin.

310

311

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317 Not applicable

318 ***Code availability**

319 Not applicable

320 ***Authors' contributions**

321 **Seyfeddine Rahali:** Conceptualization; Formal analysis ; Writing – original draft;
322 Investigation. **Youghourta Belhocine:** Formal analysis ; Software ; review &
323 editing ; Supervision ; Validation. **Hamza Allal:** Methodology ; Software ;
324 Visualization. **Abdelaziz Bouhadiba:** Data curation_ Formal analysis. **Ibtissem**
325 **Meriem Assabac:** Writing – original draft. **Mahamadou Seydou:** review &
326 editing .

327 All authors provided critical feedback and helped shape the research, analysis and
328 manuscript.

329

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Figures

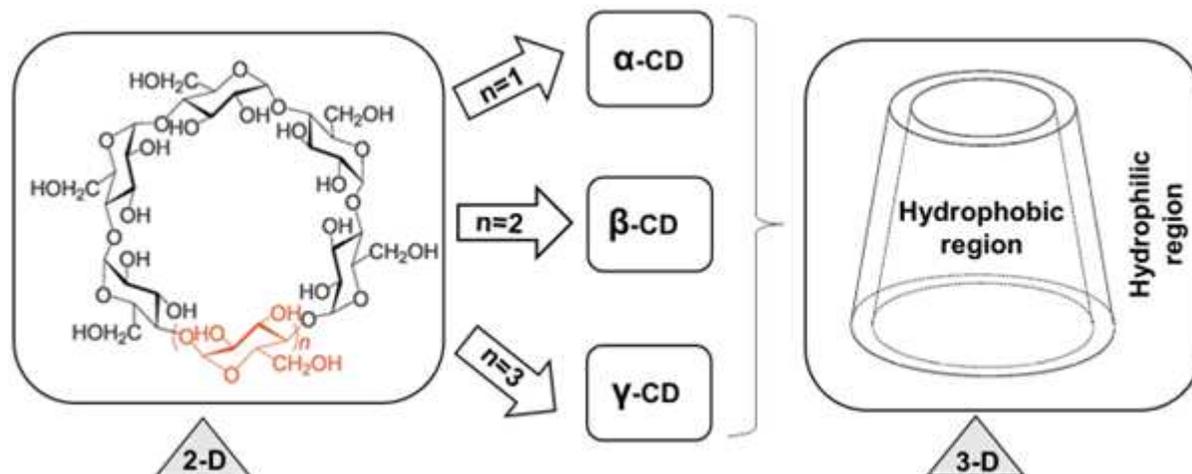


Figure 1

Chemical structure and 3D-model of cyclodextrins.

Inclusion complexes:
PhBpin@ β CD, **PhBcat@ β CD** and **FcBA@ β CD**

Non-covalent systems:
PBA@ β CD and **Bxb@ β CD**

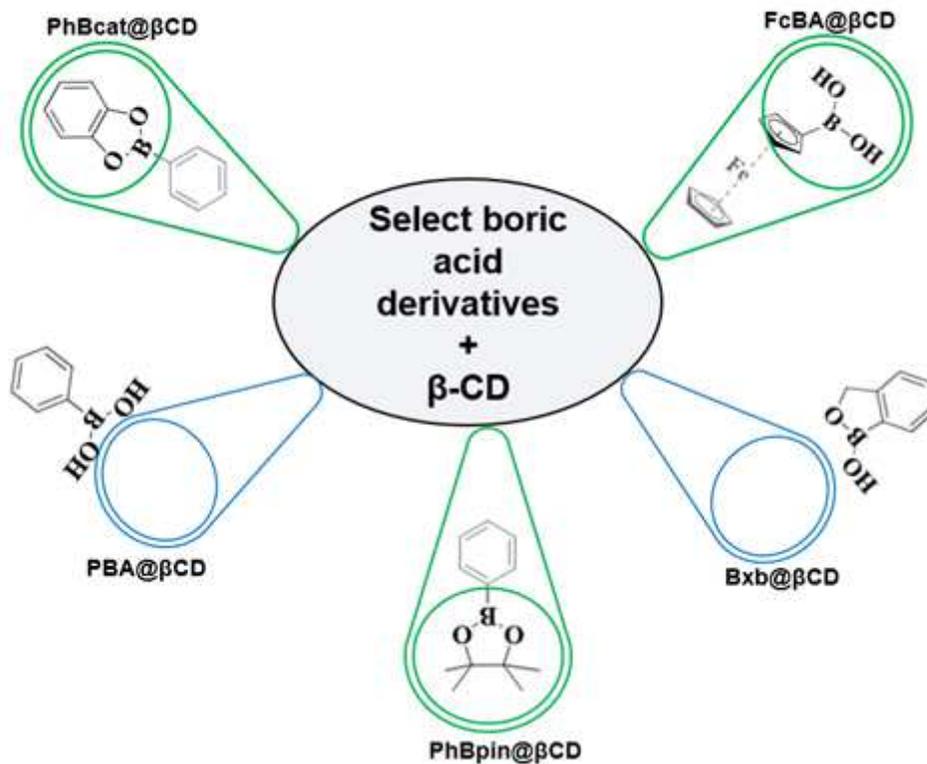


Figure 2

Interactions of boron-based aromatic systems with β -cyclodextrin [30].

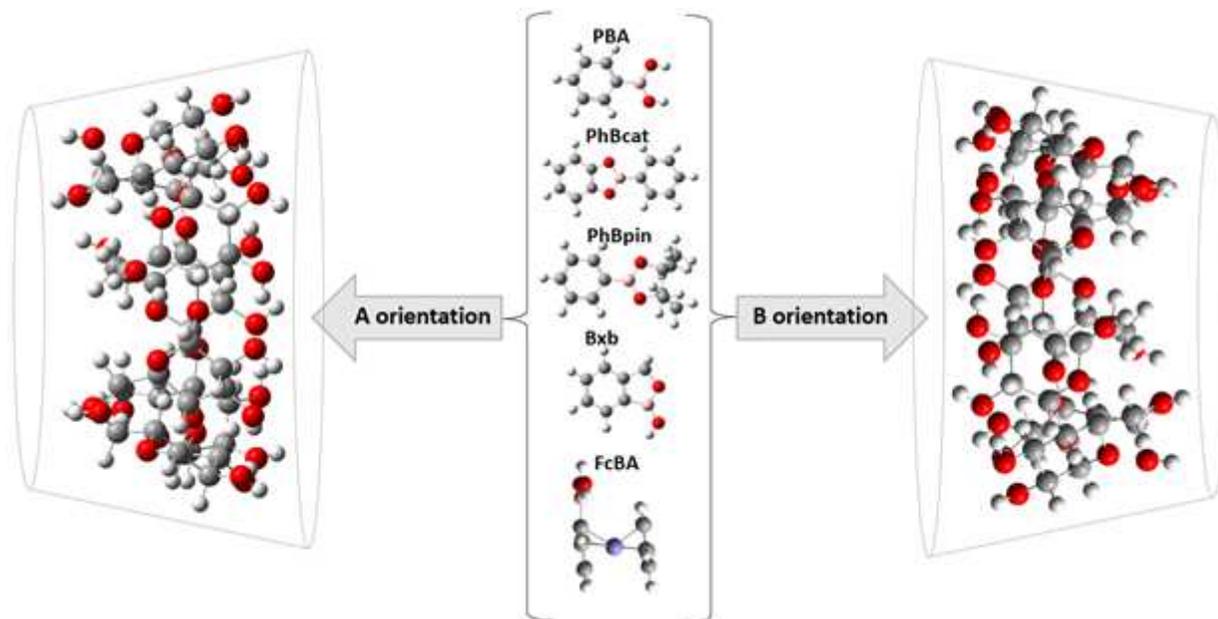


Figure 3

Coordinate system used to define the inclusion process between studied boron compounds and β -CD. Atom's color code: pink for B, purple for Fe, grey for C, red for O and white for H.

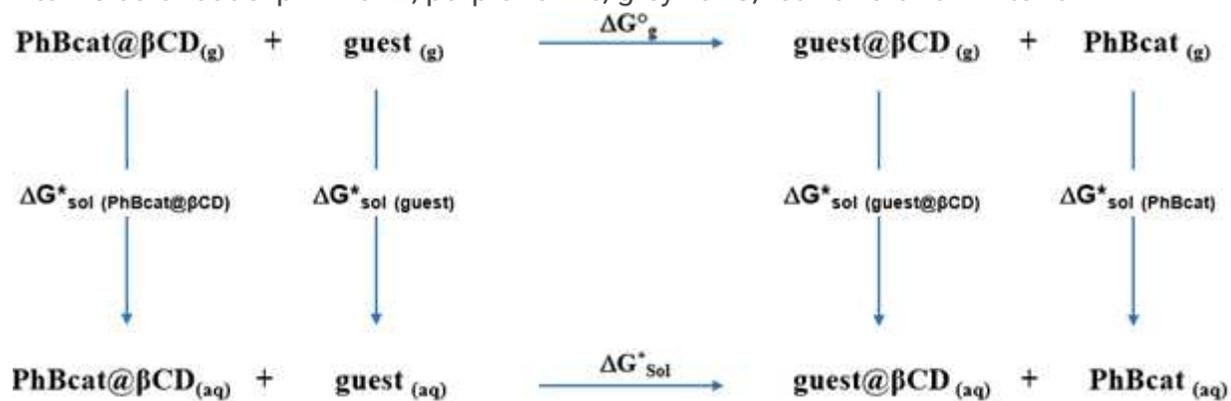


Figure 4

Thermodynamic cycle used to compute free energy changes in aqueous solution.

Figure 6

Intermolecular hydrogen bonds illustrated by dashed lines and the corresponding H...O distances (Å). Atom's color code: pink for B, purple for Fe, grey for C, red for O and white for H.

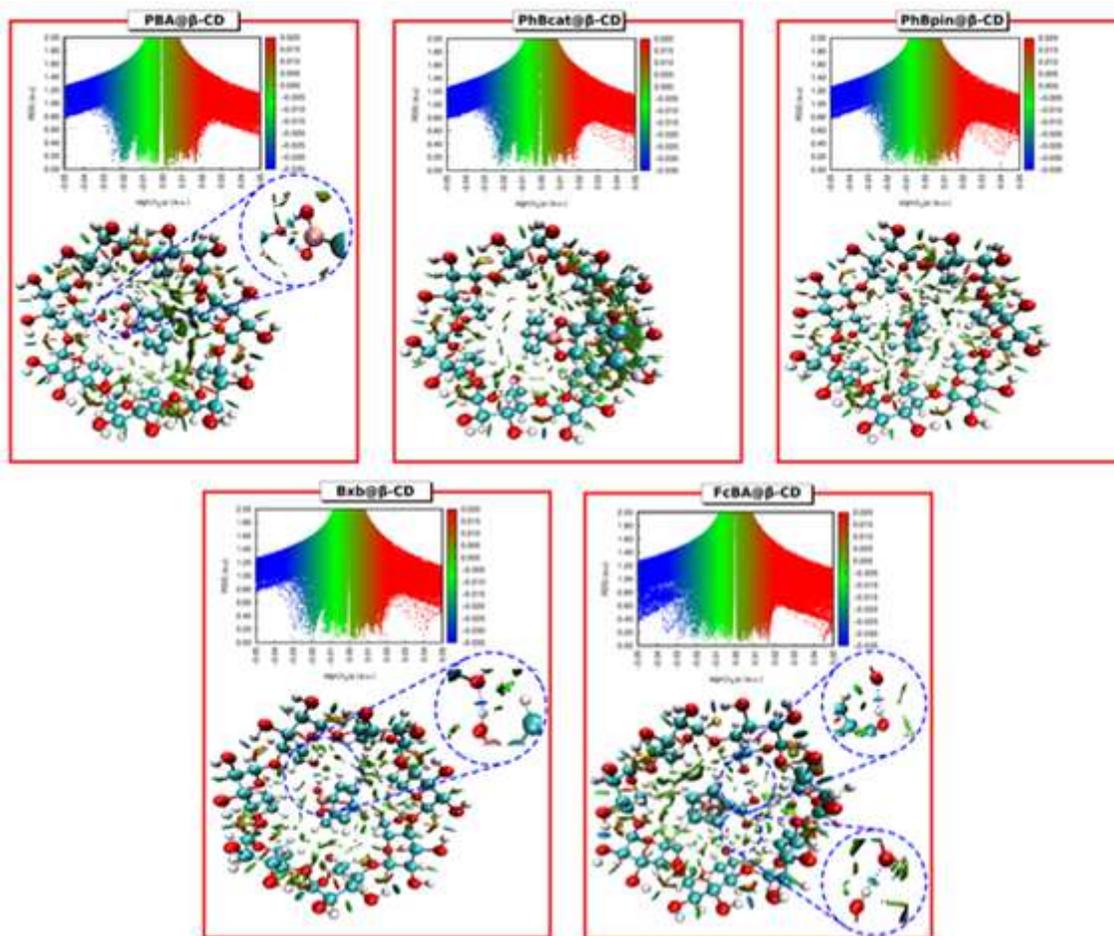


Figure 7

RDG-isosurfaces of the studied complexes computed at BLYP-D3(BJ) level. Atom's color code: pink for B, purple for Fe, blue for C, red for O and white for H.

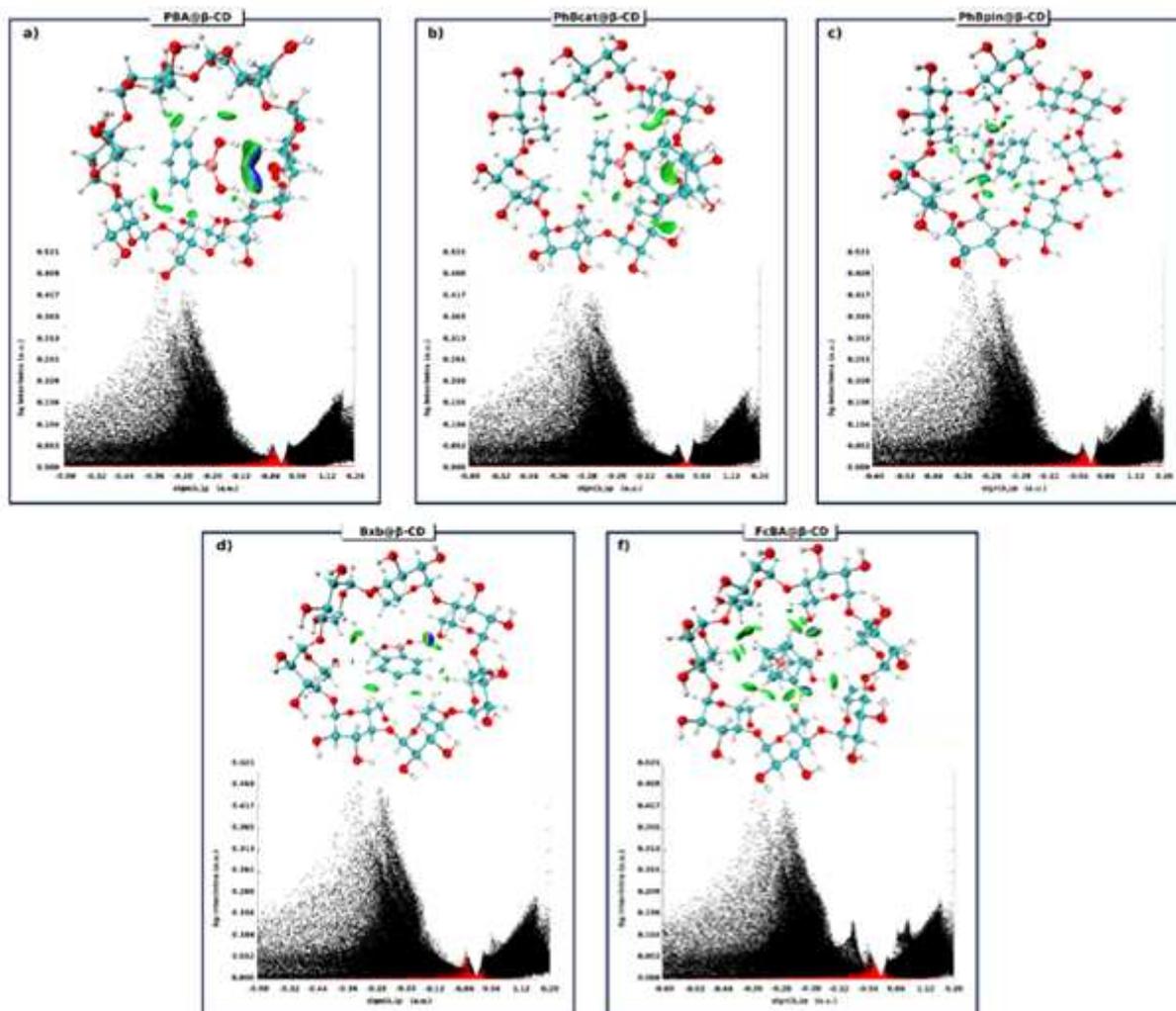


Figure 8

IGM isosurfaces and scatter plots of the studied complexes. Atom's color code: pink for B, purple for Fe, blue for C, red for O and white for H.

Supplementary Files

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- [Supplementarydata.docx](#)