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Theoretical Study of Hydrogen Bonding in Homodimers and Heterodimers of Amide, Boronic Acid, and Carboxylic Acid, Free and in Encapsulation Complexes

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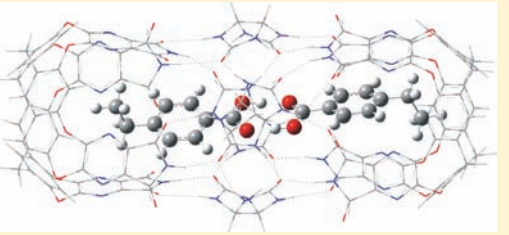
Supporting Information

ABSTRACT: The homodimers and the heterodimers of two amides, two boronic acids, and two carboxylic acids have been calculated in the gas phase and in *N*,*N*-dimethylformamide (DMF) and CCl_4 solvents using the DFT (M06-2X and M06-L) and the MP2 methods in conjunction with the 6-31G(d,p) and 6-311+G(d,p) basis sets. Furthermore, their pairwise coencapsulation was studied to examine its effect on the calculated properties of the hydrogen bonds at the ONIOM[M06-2X/6-31G(d,p);PM6], ONIOM-[MP2/6-31G(d,p); PM6], and M06-2X/6-31G(d,p) levels of theory. The present work is directed toward the theoretical rationalization and interpretation of recent experimental results on hydrogen bonding in encaptulation complexes [D. Ajami et al. *J. Am. Chem. Soc.* **2011**, *133*, 9689−9691]. The calculated dimerization energy (ΔE) values range from 0.74 to 0.35 eV for the different dimers in the gas phase, with the ordering carboxylic homodimers > amide-carboxylic dimers > amide homodimers > boronic-carboxylic dimers > amide-boronic dimers > boronic homodimers. In solvents, generally smaller ΔE values are calculated with only small variations in the ordering. In the capsule, the ΔE values range between 0.67 and 0.33 eV with practically the same ordering as in the gas phase. The calculated % distributions of the encapsulated dimers, taking into account statistical factors, are in agreement with the experimental distribution, where the occurrence of boronic homodimer dominates, even though it is calculated to have the smallest ΔE.



1. INTRODUCTION

Hydrogen bonds play an essential role in numerous chemical, biochemical, and biological processes and provide stability in many systems.[1,2] As a result, many experimental and theoretical publications are devoted to the description of the nature and strength of the hydrogen bond.[3,4] Many types of molecules can form hydrogen bonds, for example carboxylic acids, amides, and boronic acids. These molecules can form homodimers and heterodimers.

Dimers of carboxylic acids exist both in solution[5] and in solid state.[6] The hydrogen bonds in these dimers have considerable strength and are highly directive, and as a result carboxylic acids have been extensively used as buildings blocks for the construction of hydrogen-bonded supramolecular species.[7−9] The hydrogen bonds N−H···O═C, in the amide homodimers, are very important bonds because of their outstanding role in protein folding and, in heterocyclic contexts, in DNA base pairing. Boronic acids also form dimeric units, and even though they are not as common as carboxylic acids,[7] boronic acids are objects of increasing interest because of their applications in organic synthesis,[10] catalysis,[10] supramolecular chemistry,[11] materials science,[12] biology,[13] pharmacology,[14] and medicine.[10] Moreover, they also serve as chemical sensors.[15]

The relative stability of homodimeric and heterodimeric hydrogen bonding in carboxylic acids, primary amides, and boronic acids has been examined recently by means of reversible encapsulation, whereby the dimers are isolated for sufficiently long times to observe them directly by NMR.[16] Within a capsule, the interacting guests are separated from solvent molecules by mechanical barriers, and they do not exchange partners rapidly as they do in solution. In fact, the capsule *is* the solvent, fixed in place around the solute during the synthesis and assembly of the complex.[16,17] The efficiency of the different systems to act as hydrogen-bonding partners within the capsule has been determined, and boronic acids were found to be most efficient owing to their adaptable stuctures.[16] Theoretical calculation leads to direct dimerization energies which can aid in the interpretation of the experimental results and this is the main purpose of the work presented here.

More specifically, in the present study, the homodimers and the heterodimers of two amides (**A** and **A′**), two boronic acids (**B** and **B′**), and two carboxylic acids (**C** and **C′**) have been calculated (see Figure 1 for the unit systems and Figure 2 for the dimers) in the gas phase and in DMF and CCl_4 solvents. The primed and unprimed labels refer to methyl-substituted and *p*-ethyl-phenylene substituted compounds, respectively. The effect

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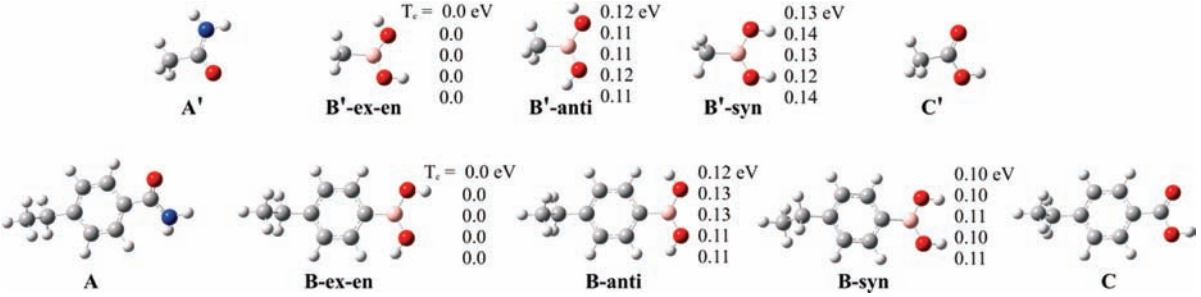


Figure 1. Calculated amides (**A** and **A**′), boronic acids (**B** and **B**′), and carboxylic acids (**C** and **C**′). The three lowest isomers exo-endo, anti, and syn of the boronic acids are given. The relative energies T_e are calculated at the M06-2X/6-31G(d,p) (first entry), M06-2X/6-311+G(d,p) (second entry), M06-L/6-311+G(d,p) (third entry), MP2/6-31G(d,p) (fourth entry), and MP2/6-311+G(d,p) (fifth entry) (H = white spheres, C = gray spheres, O = red spheres, B = pink spheres, and N = blue spheres).

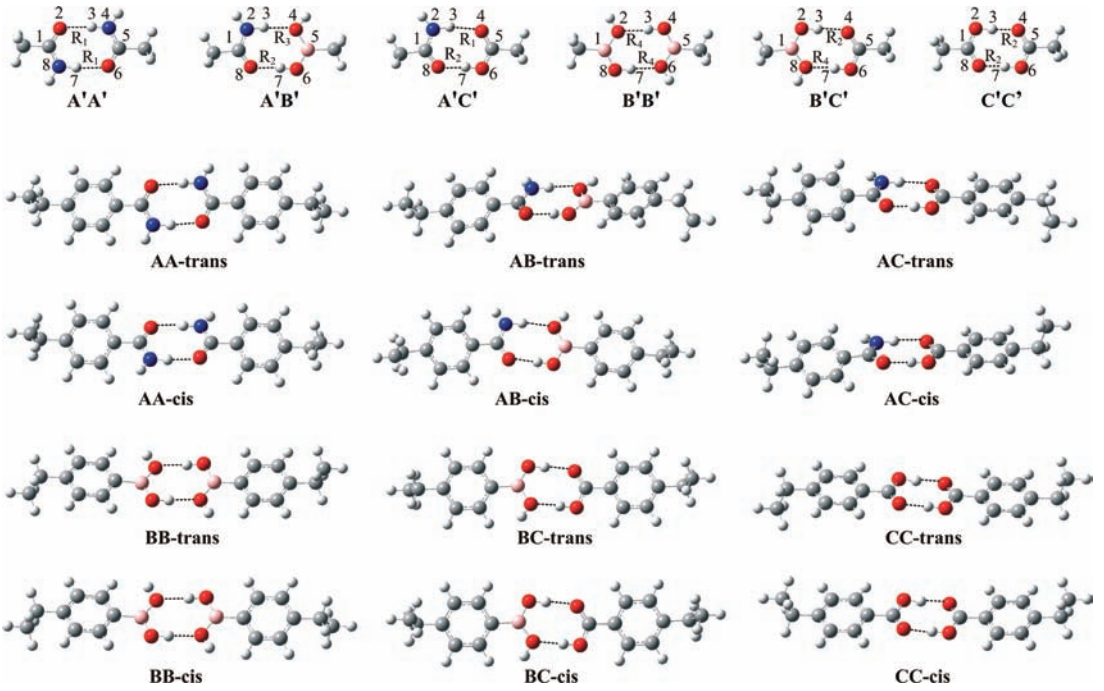


Figure 2. Calculated dimers of amides (**A** and **A**′), boronic acids (**B** and **B**′), and carboxylic acids (**C** and **C**′) (H = white spheres, C = gray spheres, O = red spheres, B = pink spheres, and N = blue spheres).

of encapsulation on the calculated properties of the hydrogen bonds has been investigated by calculations on the pairwise encapsulation complexes of **A**, **B**, and **C** molecules. For the latter calculations, the capsule employed is **1.2$_4$.1**[16] which consists of two cavitands **1** and four glycoluril molecules **2** and for which we calculated two isomers, **a** and **b**; see Figure 3.

For some of the dimers studied here there have been previous studies, namely for the **C**′**C**′, **B**′**C**′, **B**′**B**′, and **A**′**C**′ dimers either in the gas phase and/or in solvent,[7,18,19] and comparison with those studies will be given in later sections. Similarly, several reports of work on other related dimers exist.[20−25]

2. COMPUTATIONAL DETAILS

As mentioned above, six types of dimers, shown in Figure 2, with methyl (primed labels) and *p*-ethylphenylene substituents have been calculated in the gas phase and in solvents and, for the p-ethylphenylenes, encapsulated. To enable comparison with previous work, calculations were also performed on the homodimers of unsubstituted boronic and formic acids (see following section).

In the gas phase, all calculated dimers were fully optimized by both DFT calculations using the M06-2X[26,27] and M06-L[27,28] functionals and MP2 calculations in conjunction with the 6-31G(d,p) and 6-311+G(d,p)[29] basis sets. M06-2X[26,27] is a hybrid meta exchange correlation functional, it is a highly nonlocal functional with double the amount of nonlocal exchange, and it is recommended for applications involving main-group elements, kinetics, noncovalent interactions, and electronic excitation energies to valence and Rydberg states. The M06-L[27,28] is a meta GGA functional, in which the functional also depends on the up and down spin kinetic energy densities. M06-L is also designed for main-group thermochemistry and noncovalent interactions.[27,28]

Geometry optimizations calculations for the dimers in DMF (ϵ = 37.219) and CCl_4 (ϵ = 2.2280) solvents were carried out at the DFT and MP2 levels employing the polarizable continuum model (PCM).[30] This model is divided into a solute part lying inside a cavity, surrounded by the solvent part represented as a structureless material characterized by its macroscopic properties, i.e., dielectric constants and solvent radius.

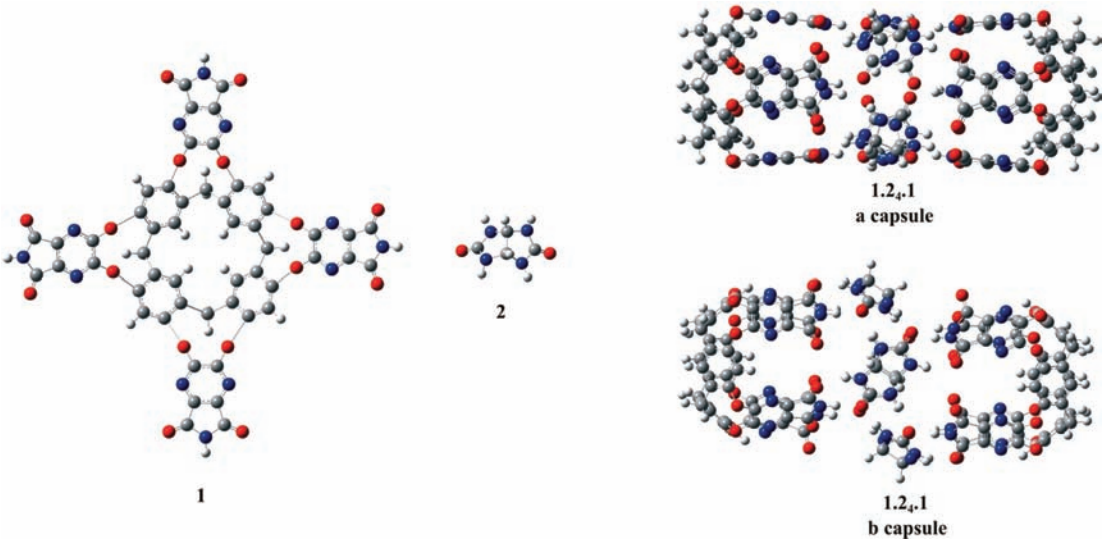


Figure 3. Structures of the cavitand **1** and glycoluril **2** components and the calculated structures of two capsules **1.2$_4$.1** (H = white spheres, C = gray spheres, O = red spheres, and N = blue spheres).

This method reproduces solvent effects well.[31] Moreover, for comparison, single point calculations in the geometry obtained with the PCM were carried out using the self-consistent isodensity PCM (SCI-PCM) in DMF solvent.[32] This model uses a static isodensity surface for the cavity.

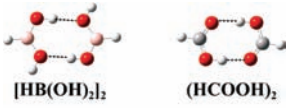
Preliminary geometry optimization calculations were performed on the encapsulation complexes using the ONIOM[33] method, where the systems were defined as two regions (layers) with the high layer that is the dimers calculated at the M06-2X/6-31G(d,p) and MP2/6-31G(d,p) levels of theory and the low layer that is the capsule calculated at the PM6 level of theory. Finally, geometry optimization calculations for the encapsulation complexes were carried out at the M06-2X/6-31G(d,p) level of theory.

For all structures determined, basis set superposition error (BSSE) corrections to the dimerization energy have been taken into account using the counterpoise procedure[34] since such corrections are important for the weak and medium size interactions[35] that are involved in the structures calculated here. All calculations were performed using the Gaussian 09 program package.[36] The coordinates of all the optimum structures are included in the accompanying Supporting Information.

3. RESULTS AND DISCUSSION

The calculated minimum energy structures of the monomers of the amides (**A** and **A′**), boronic acids (**B** and **B′**), and carboxylic acids (**C** and **C′**) are given in Figure 1. In the case of the boronic acids, where different forms are possible, the three lowest isomers exo-endo, anti, and syn have been calculated. The lowest minimum is the exo-endo isomer, and according to the present calculations (see below) this isomer forms the lowest energy homodimers and heterodimers involving boronic acid. The anti and syn isomers are practically degenerate, and they lie about 0.1 eV above the exo-endo isomer (cf. Figure 1). The homodimer and the heterodimer of the **A′**, **B′**, and **C′** molecules and of the **A**, **B**, and **C** molecules are depicted in Figure 2. For each dimer formed by **A**, **B**, and **C**, there are two isomers, cis and trans, depending on the relative position of the terminal methyl of the *p*-ethyl-phenylene group; see Figure 2. While it is expected that the cis and trans isomers will have the same interaction energy, it is of interest to examine whether this also holds in the capsule.

As mentioned above, only 4 of the 12 dimers studied here have been previously calculated, i.e., **C′C′**, **B′C′**, **B′B′**, and **A′C′** dimers .[7,18,19] For these systems, a comparison is given of the present results with those of previous studies in Table 1, where, in addition, data on the homodimers of boronic and formic acid (see **I** below) are included, as test systems for calibration of the different methods of calculation employed in the present work. As shown in Table 1, the dimerization energies of the present work employing M06-2X/6-311+G(d,p) (first row of Table 1) are within 0.04 eV of the values obtained by the best methods employed in the literature, e.g. at the MP2/aug-cc-pVTZ and MP2/aug-cc-pVTZ//MP2/aug-cc-pVDZ levels of theory.[18,24] Because the interest of the present work includes encapsulated complexes, it is not feasible to carry out the calculations at the MP2/aug-cc-pVTZ//MP2/aug-cc-pVDZ level and the M06-2X/6-311+G(d,p) method is considered to be a good compromise.



I

Table 2 shows the ΔE values of the six types of dimers (Figure 2) with methyl (first group, primed labels), i.e., **C′C′**, **A′C′**, **A′A′**, **B′C′**, **A′B′**, **B′B′**, and with *p*-ethyl-phenylene substituents (second group) i.e., **CC**, **AC**, **AA**, **BC**, **AB**, and **BB**, in DMF and CCl_4 solvents and for *p*-ethyl-phenylene encapsulated in **1.2$_4$.1a** and **1.2$_4$.1b** capsules, calculated at various levels of theory. This information is also presented pictorially in the Supporting Information, Figures 1S and 2S. We observe in Table 2 that the corresponding primed and unprimed dimers have similar ΔE values with differences up to 0.04 eV, within a particular method of calculation (i.e., across a row of Table 2). Moreover, it might be noted that the ΔE values are the same whether the BSSE correction has been taken into account subsequent to the geometry optimization or when the geometry optimization is carried out with respect to the BSSE (see results for M06-2X/6-311+G(d,p) and MP2/6-31G(d,p) in Table 2).

The hydrogen bond distances of the dimers in the gas phase and in solvent are given in Table 3. Other geometrical data are given in Table 1S of the Supporting Information. In what follows

Table 1. BSSE Corrected Dimerization Energy, ΔE in eV, and Hydrogen Bond Distances in Å of the $(HBOHOH)_2$, $(HCOOH)_2$, A′C′, B′B′, B′C′, and C′C′ Dimers (Previous Experimental and Theoretical Data Are Also Given)

	$(HBOHOH)_2$		$(HCOOH)_2$		A′C′			B′B′		B′C′			C′C′	
Method	ΔE	$R_{H\cdots O}$	ΔE	$R_{H\cdots O}$	ΔE	$R_{NH\cdots O}$	$R_{OH\cdots O}$	ΔE	$R_{H\cdots O}$	ΔE	$R_{BH\cdots O}$	$R_{CH\cdots O}$	ΔE	$R_{H\cdots O}$
M06-2X/6-311+G(d,p)	0.45	1.855	0.69	1.708	0.69	1.887	1.648	0.46	1.848	0.55	1.825	1.756	0.71	1.686
MP2/6-31G(d,p)	0.38	1.863	0.56	1.716	0.57	1.889	1.678	0.40[h]	1.859[h]	0.46[i]	1.837[i]	1.761[i]	0.58	1.699
MP2/6-311+G(d,p)	0.34	1.865	0.51	1.725	0.51	1.907	1.681	0.35[j]	1.848	0.42	1.837	1.766	0.53	1.704
MP2/6-31+G(d,p)[a]				1.721										
B3LYP/6-31G(d,p)[b]				1.642										
Expt[c]				1.667										
CCSD(T)/cc-pCVDZ[d]		1.858												
MP2/aug-cc-pVTZ[d]	0.41	1.833												
MP2/6-311++G(d,p)[e]			0.57	1.726									0.53	1.705
MP2/ATZ//MP2/ADZ[e]			0.66										0.69	
B3LYP/TZVPP[f]					0.62	1.877	1.654						0.66	1.664
MP2/6-31G(d,p)[g]								0.55[h]	1.859	0.65[h]	1.837	1.760	0.81[h]	1.698

[a] Reference 23a. [b] Reference 23b. [c] Reference 23c. [d] Reference 24. [e] Reference 18, MP2/aug-cc-pVTZ//MP2/aug-cc-pVDZ. [f] Reference 19. [g] Reference 7. BSSE uncorrected dimerization energies. [h] BSSE optimized geometry results in ΔE = 0.40 eV and $R_{H\cdots O}$ = 1.936 Å. [i] BSSE optimized geometry results in ΔE = 0.47 eV, $R_{BH\cdots O}$ = 1.918 Å, and $R_{CH\cdots O}$ = 1.838 Å. [j] Geometry optimization at the MP2/aug-cc-pVDZ (DF-LMP2/aug-cc-pVDZ) [DF-LMP2/cc-pVDZ-F12] {DF-LCCSD(T0)/aug-cc-pVDZ} levels of theory results in dimerization energy of 0.39(0.34)[0.36]{0.33} eV for the **B′B′** dimer.

the results on the free dimers will be discussed first, followed by those on the encapsulated dimers.

3.1. Free Dimers. In the gas phase and in all three methods, M06-2X, M06-L, and MP2, in conjunction with two basis sets 6-31G(d,p) and 6-311+G(d,p), the homodimers of the carboxylic acid (**C′C′** and **CC**) present the largest while the boronic homodimers the smallest dimerization energy (ΔE). The ΔE ordering is **C′C′** > **A′C′** > **A′A′** > **B′C′** > **A′B′** > **B′B′** and similarly **CC** > **AC** > **AA** > **BC** > **AB** > **BB** with values ranging from 0.71 to 0.46 eV at the M06-2X/6-311+G(d,p) level of theory and from 0.53 to 0.35 eV at the MP2/6-311+G(d,p) level of theory for the first (primed) group and from 0.74 to 0.43 eV at the M06-2X/6-311+G(d,p) level of theory for the second group. The present results are in agreement with previous results on the relative strength of hydrogen bonding in unsubstituted boronic and formic acids.[24]

In CCl_4 solvent using the PCM model, the above order is retained with the exception that the **A′A′** and **B′C′** dimers are found to have the same interaction energy, and similarly for the **AA** and **BC** dimers. The corresponding ΔE values are smaller than in the gas phase, and they range from 0.64 to 0.41 eV at the M06-2X/6-311+G(d,p) level of theory and from 0.52 to 0.36 eV at the MP2/6-31G(d,p) level of theory for the second group; see Table 2.

In DMF solvent, using both the PCM and SCI-PCM models, the order of the gas phase is retained with the exception that the **A′A′** and **AA** dimers have the smallest dimerization energies. Thus, the order becomes **C′C′** ≥ **A′C′** > **B′C′** > **A′B′** ≥ **B′B′** > **A′A′** and **CC** > **AC** > **BC** > **AB** > **BB** > **AA**. The ΔE values range from 0.53 to 0.34 eV at the M06-2X/6-311+G(d,p) level of theory and from 0.43 to 0.30 eV at the MP2/6-31G(d,p) level of theory for the second group; see Table 2. The SCI-PCM model predicts a slightly smaller interaction energy than the PCM model. It might be noted that in both PCM and SCI-PCM models and in both DMF and CCl_4 solvents the range of the dimerization energy becomes shorter than in the gas phase, while in DMF the interaction energy is smaller by 0.1 eV than in CCl_4 solvent.

In the systems of interest here there are four types of hydrogen bonds. The first one is the C═O···H−O bond in the homodimers of carboxylic acids, in amide−carboxylic acid dimers, in boronic-carboxylic acid dimers, and in amide-boronic acid dimers (R_2 distance in Figure 2 and Table 3). The boronic-carboxylic dimers present the longest hydrogen bond, followed by amide-boronic dimers, then by carboxylic acid dimers, while the amide-carboxylic acid dimers have the shortest hydrogen bond lengths. The length of the C═O···H−O bond in the four different dimers varies by up to 0.2 Å. The second hydrogen bond type is the C═O···H−N bond in the amide homodimers and in amide-carboxylic acid dimers (R_1), with the homodimers having the longest distances by up to 0.05 Å. The third type of hydrogen bond is the −O···H−O bond in the boronic acid homodimers and in boronic-carboxylic acid dimers (R_4), with the homodimers having the longest hydrogen bond distances by up to 0.12 Å. The last type of hydrogen bond is the −O···H−N bond, and it is observed only in the amide-boronic acid dimers (R_3). The two groups of dimers (primed and unprimed) have similar corresponding hydrogen bond distances. In general, the methyl substituted (primed) group presents longer hydrogen bonds, by up to 0.06 Å, than the (unprimed) ethylphenylene substituted group. In the two solvents, the hydrogen bond distances are similar and they differ by up to ±0.03 Å with respect to the corresponding values in the gas phase.

Comparison with experiment is only possible for the phenylboronic acid homodimer, for which crystallographic data indicate hydrogen bond distances at 1.81(2) and 1.89(3) Å, i.e., the asymmetric unit of the crystal cell contains two nonequivalent phenylboronic acids.[20] These values are very close to ours of 1.866 Å, at the M06-2X/6-311+G(d,p) level of theory for the case of *p*-ethyl-phenylboronic acid homodimers.

The dihedral angles between the planes of the two phenylene groups in the case of the **AA** and **CC** dimers are almost zero. In the case of the **BC** dimer, the dihedral angle is about ∼10°, while in the case of **BB**, **AB**, and **AC** dimers the angle is about 20° on average; see Table 1S of the Supporting Information.

Geometry optimization of the dimers with respect to the BSSE correction does not change the dimerization energy, cf. Table 2, as noted above, but it leads to an increase of the hydrogen bond

Table 2. Dimerization Energies in eV of the C′C′, A′C′, A′A′, B′C′, A′B′, B′B′, CC, AC, AA, BC, AB, and BB Dimers in the Gas Phase in *n*,*n*-Dimethylformamide and CCl_4 Solvents and in $1.2_4.1$ Capsules, at Various Levels of Theory

Method	C′C′	A′C′	A′A′	B′C′	A′B′	B′B′
M06-2X/6-31G(d,p)	0.74	0.71	0.63	0.56	0.51	0.46
M06-2X/6-311+G(d,p)	0.71(0.71)[g]	0.69(0.69)[g]	0.62(0.62)[g]	0.55(0.55)[g]	0.50(0.50)[g]	0.46(0.46)[g]
M06-L/6-311+G(d,p)	0.71	0.69	0.63	0.54	0.49	0.44
MP2/6-31G(d,p)	0.58(0.59)[g]	0.57(0.58)[g]	0.52(0.53)[g]	0.46(0.47)[g]	0.43(0.43)[g]	0.40(0.40)[g]
MP2/6-311+G(d,p)	0.53	0.51	0.48	0.42	0.39	0.35
M06-2X/6-31G(d,p)[a,b]	0.55	0.51	0.38	0.46	0.41	0.40
M06-2X/6-31G(d,p)[a,c]	0.47	0.46	0.34	0.40	0.37	0.36
M06-2X/6-311+G(d,p)[a,b]	0.50	0.47	0.34	0.43	0.38	0.37
M06-2X/6-311+G(d,p)[a,c]	0.46	0.45	0.33	0.41	0.36	0.36
MP2/6-31G(d,p)[a,b]	0.40	0.39	0.30	0.36	0.33	0.32
MP2/6-31G(d,p)[a,c]	0.34	0.34	0.26	0.31	0.29	0.29
M06-2X/6-311+G(d,p)[d,b]	0.61	0.59	0.49	0.49	0.44	0.42
MP2/6-31G(d,p)[d,b]	0.49	0.49	0.42	0.41	0.37	0.36
Oniom-M06-2X/6-31G(d,p)[e]	–	–	–	–	–	–
Oniom-M06-2X/6-31G(d,p)[f]	–	–	–	–	–	–
Oniom-MP2/6-31G(d,p)[e]	–	–	–	–	–	–
M06-2X/6-31G(d,p)[e]	–	–	–	–	–	–

Method	CC	AC	AA	BC	AB	BB
M06-2X/6-31G(d,p)	0.77	0.71	0.60	0.58	0.51	0.47
M06-2X/6-311+G(d,p)	0.74(0.74)[g]	0.69(0.69)[g]	0.59(0.59)[g]	0.56(0.56)[g]	0.50(0.50)[g]	0.45(0.45)[g]
M06-L/6-311+G(d,p)	0.74	0.69	0.60	0.55	0.49	0.43
MP2/6-31G(d,p)	0.61(0.62)[g]	0.58(0.58)[g]	0.51(0.51)[g]	0.48(0.49)[g]	0.43(0.44)[g]	0.40(0.41)[g]
MP2/6-311+G(d,p)	–	–	–	–	–	–
M06-2X/6-31G(d,p)[a,b]	0.57	0.52	0.37	0.45	0.40	0.38
M06-2X/6-31G(d,p)[a,c]	0.50	0.45	0.32	0.38	0.34	0.32
M06-2X/6-311+G(d,p)[a,b]	0.53	0.48	0.34	0.43	0.38	0.36
M06-2X/6-311+G(d,p)[a,c]	0.47	0.44	[h]	0.39	0.35	*h*
MP2/6-31G(d,p)[a,b]	0.43	0.40	0.30	0.36	0.33	0.32
MP2/6-31G(d,p)[a,c]	0.36	0.35	0.26	0.31	0.28	0.27
M06-2X/6-311+G(d,p)[d,b]	0.64	0.59	0.48	0.50	0.44	0.41
MP2/6-31G(d,p)[d,b]	0.52	0.49	0.41	0.42	0.37	0.36
Oniom-M06-2X/6-31G(d,p)[e]	0.74	0.63/0.65[i]	0.58/0.57[i]	0.55/0.54[i]	0.46	0.43/0.44[i]
Oniom-M06-2X/6-31G(d,p)[f]	–	–	0.56/–[i]	0.53/–[i]	0.47/–[i]	–/0.41[i]
Oniom-MP2/6-31G(d,p)[e]	0.57/0.56[i]	0.51/0.50[i]	0.48/0.46[i]	0.44	0.38/0.37[i]	0.36/0.37[i]
M06-2X/6-31G(d,p)[e]	0.67	0.60	0.50	0.38	0.41	0.33

[a] In *n*,*n*-dimethylformamide solvent ($\varepsilon = 37.219$). [b] PCM model. [c] SCI-PCM model, single point calculation at the geometry of PCM model. [d] In CCl_4 solvent ($\varepsilon = 2.2280$). [e] In capsule **a**. [f] In capsule **b**. [g] BSSE optimized geometry. [h] No convergence. [i] Trans/cis; in all other cases the trans and cis structures have the same dimerization energies.

distance by up to 0.02 Å at the M06-2X/6-311+G(d,p) level of theory and up to 0.08 Å at the MP2/6-31G(d,p) level of theory, cf. Table 3.

3.2. Encapsulated Dimers. As mentioned above, for the **A**, **B**, and **C** molecules we calculate their pairwise coencapsulation to examine the effect of encapsulation on the calculated properties of the hydrogen bonds. The calculated capsule $\mathbf{1.2_4.1}$ consists of two cavitands **1** which are stitched together through the four glycoluril molecules by 32 and 24 hydrogen bonds in the $\mathbf{1.2_4.1a}$ and $\mathbf{1.2_4.1b}$ structures; see Figure 3. In the **a** structure each glycoluril molecule forms hydrogen bonds with both cavitands and with its adjacent glycoluril molecules. In contrast, in the **b** isomer, two glycoluril molecules form hydrogen bonds with both cavitands and with their adjacent glycoluril molecules; the other two glycoluril molecules form hydrogen bonds with only one cavitand and with their two adjacent glycoluril molecules. The **b** structure is more stable than the **a** isomer by 0.09 eV at the M06-2X/6-31G(d,p) level of theory. The **a** isomer has been reported for the first time in 2009, and it has been deduced from NMR evidence.[37] The encapsulated cis and trans dimers are depicted in Figure 4 and in Figure 3S of the Supporting Information. Most of the calculated data presented here involve capsule **a**, which is the one involved in the experimental work.[16] It might be noted that both the **a** and **b** isomers of the $\mathbf{1.2_4.1}$ capsule predict nearly the same dimerization energies (see Table 2), while use of the **b** isomers leads to convergence problems for the optimization of the encapsulated structures.

Initially, geometry calculations on capsule **a** of Figure 3 were performed using the ONIOM method. As mentioned in the computational details, the high layer is the dimers and the calculations on this layer were carried out at the M06-2X/6-31G(d,p) and

Table 3. Hydrogen Bond Distances, R (Å) of the Dimers C′C′, A′C′, A′A′, B′C′, A′B′, and B′B′ and the Trans Dimers of the CC, AC, AA, BC, AB, and BB Species in the Gas Phase, in *n,n*-Dimethylformamide and CCl_4 Solvents and in $1.2_4.1$ Capsules, at Various Levels of Theory

	C′C′	A′C′		A′A′	B′C′		A′B′		B′B′
Method	R_2	R_1	R_2	R_1	R_2	R_4	R_3	R_2	R_4
M06-2X/6-31G(d,p)	1.586	1.843	1.593	1.846	1.811	1.729	1.921	1.765	1.842
M06-2X/6-311+G(d,p)	1.685	1.887	1.648	1.866	1.825	1.756	1.951	1.775	1.848
M06-2X/6-311+G(d,p)[a]	1.701	1.902	1.662	1.879	1.843	1.775	1.973	1.791	1.870
M06-L/6-311+G(d,p)	1.697	1.865	1.677	1.839	1.816	1.765	1.928	1.781	1.844
MP2/6-31G(d,p)	1.699	1.889	1.678	1.878	1.837	1.761	1.949	1.793	1.859
MP2/6-31G(d,p)[a]	1.781	1.967	1.750	1.949	1.918	1.838	2.028	1.865	1.936
MP2/6-311+G(d,p)	1.704	1.907	1.681	1.880	1.837	1.766	1.970	1.785	1.856
M06-2X/6-31G(d,p)[b]	1.584	1.890	1.547	1.881	1.794	1.703	1.933	1.729	1.825
M06-2X/6-311+G(d,p)[b]	1.685	1.950	1.606	1.900	1.810	1.733	1.964	1.744	1.829
MP2/6-31G(d,p)[b]	1.702	1.939	1.648	1.907	1.826	1.741	1.961	1.767	1.841
M06-2X/6-311+G(d,p)[c]	1.683	1.908	1.626	1.882	1.820	1.742	1.959	1.763	1.840
MP2/6-31G(d,p)[c]	1.699	1.911	1.663	1.890	1.835	1.750	1.955	1.780	1.851
Oniom-M06-2X/6-31G(d,p)[d]	–	–	–	–	–	–	–	–	–
Oniom-M06-2X/6-31G(d,p)[e]	–	–	–	–	–	–	–	–	–
Oniom-MP2/6-31G(d,p)[d]	–	–	–	–	–	–	–	–	–
M06-2X/6-31G(d,p)[d]	–	–	–	–	–	–	–	–	–
	CC	**AC**		**AA**	**BC**		**AB**		**BB**
Method	R_2	R_1	R_2	R_1	R_2	R_4	R_3	R_2	R_4[f]
M06-2X/6-31G(d,p)	1.557	1.841	1.582	1.858	1.795	1.729	1.926	1.759	1.832
M06-2X/6-311+G(d,p)	1.657	1.881	1.632	1.867	1.802	1.760	1.956	1.768	1.850
M06-2X/6-311+G(d,p)[a]	1.674	1.895	1.647	1.882	1.818	1.780	1.976	1.782	1.866
M06-L/6-311+G(d,p)	1.683	1.858	1.667	1.839	1.796	1.773	1.931	1.771	1.841
MP2/6-31G(d,p)	1.676	1.884	1.666	1.879	1.819	1.755	1.952	1.781	1.850
MP2/6-31G(d,p)[a]	1.757	1.962	1.739	1.951	1.897	1.831	2.030	1.854	1.926
MP2/6-311+G(d,p)	–	–	–	–	–	–	–	–	–
M06-2X/6-31G(d,p)[b]	1.557	1.888	1.541	1.881	1.779	1.706	1.941	1.726	1.833
M06-2X/6-311+G(d,p)[b]	1.659	1.930	1.594	1.897	1.786	1.746	1.968	1.740	1.838
MP2/6-31G(d,p)[b]	1.681	1.928	1.595	1.903	1.809	1.737	1.961	1.756	1.835
M06-2X/6-311+G(d,p)[c]	1.657	1.900	1.614	1.879	1.797	1.754	1.962	1.756	1.838
MP2/6-31G(d,p)[c]	1.677	1.902	1.654	1.887	1.815	1.748	1.957	1.771	1.844
Oniom-M06-2X/6-31G(d,p)[d]	1.536	1.782	1.584	1.877	1.781	1.673	1.904	1.739	1.868
Oniom-M06-2X/6-31G(d,p)[e]	1.650	–	–	1.872	1.808	1.680	1.879	1.785	1.867
Oniom-MP2/6-31G(d,p)[d]	1.669	1.818	1.686	1.903	1.813	1.710	1.930	1.761	1.877
M06-2X/6-31G(d,p)[d]	1.602	1.856	1.561	1.902	1.796	1.682	1.906	1.782	1.781

[a] BSSE optimized geometry. [b] In *n,n*-dimethylformamide solvent (ϵ = 37.219), PCM model. [c] In CCl_4 solvent (ϵ = 2.2280), PCM model. [d] In capsule **a**. [e] In capsule **b**. [f] Reference 20; crystallographic data for phenylboronic acid dimer of 1.81(2), 1.89(3) Å.

MP2/6-31G(d,p) levels of theory and the low layer is the capsule and the calculations were carried out at the PM6 level of theory. Subsequently, geometry optimizations at the M06-2X/6-31G(d,p) level of theory were carried out for the full systems, capsule + dimer. Comparing the hydrogen bond distances of the free dimers with the values of the encapsulated dimers at the M06-2X/6-31G(d,p) level of theory (see Table 3), there are differences of up to ±0.05 Å. The hydrogen bonds are increased in the encapsulation for the **CC** and **AA** dimers and are decreased for the **BB**, the R_1 value of the **AB** dimer, and the R_2 value of the **BC** dimer. For the **AC** dimer the hydrogen bond distances are similar in the free complexes and in the encapsulated. In general, the ONIOM[M06-2X/6-31G(d,p);PM6] method predicts shorter hydrogen bond distances than the M06-2X/6-31G(d,p) method by up to 0.07 Å. The ONIOM[MP2/6-31G(d,p);PM6] method predicts longer distances than the M06-2X/6-31G(d,p) method for most hydrogen bond distances. In general, in the encapsulated dimers, the dihedral angle of the planes of the two phenylene groups are increased; see Table 1S of the Supporting Information.

The calculated ΔE values for the encapsulated complexes, given in Table 2, show that using the ONIOM method in both levels leads to the ordering of ΔE as **CC** > **AC** > **AA** > **BC** > **AB** > **BB**, i.e., identical to the order in the gas phase. At the M06-2X/6-31G(d,p) level of theory, the ordering is slightly different **CC** > **AC** > **AA** > **AB** > **BC** > **BB**, with **BC** predicted to be less stable than the **AB** dimer only by 0.03 eV. The calculated ΔE values for

the encapsulated complexes at the M06-2X/6-31G(d,p) level of theory range between 0.67 and 0.33 eV (see Table 2). The ONIOM[M06-2X/6-31G(d,p);PM6] method predicts larger values and ONIOM[MP2/6-31G(d,p);PM6] smaller values than the above M06-2X/6-31G(d,p) values by up to 0.1 eV. It might be noted that, in terms of computational effort, the ONIOM calculations were faster by a factor of about 30 and it is thus a very good method to obtain an initial guess for our systems, which in different even larger systems might be the best calculation that can be performed. For the systems treated here, the use of PM6 at the ONIOM lower level proved to be sufficient (cf. results in Table 2).

Finally, as shown in Table 2, the cis and trans isomers of the dimers (with R = ethylphenylene) have a slightly different interaction energy in the capsule by up to 0.02 eV.

It is instructive to calculate the interaction energy (ΔE_1) between the capsule and the dimers and between the capsule and monomers guest molecules (ΔE_2), and such quantities calculated at the M06-2X/6-31G(d,p) level of theory are given in Table 4. As shown in Table 4, the ΔE_1 values have reverse ordering with respect to the ΔE dimerization energies; the **BB** dimer has the largest interaction energy of 2.07 eV; see Table 4. Finally, the interaction energy values, ΔE_2, are practically the same in all cases, ranging from 2.40 to 2.52 eV.

The encapsulation of homodimers and heterodimers of amide, boronic, and carboxylic acid gives the opportunity to determine experimentally the relative efficiency of dimer formation. Ajami et al.[16] measured the experimental concentration of **CC**, **AC**, **AA**, **BC**, **AB**, and **BB** in the capsule, where, statistically, the occurrence of the heterodimers is twice as probable as the homodimers **CC** and **AA** and the occurrence of **BB** is 4 times as probable.[16] The exo-endo boronic acid dimer has twice as many ways to be formed as the **CC** and **AA** dimers. Furthermore, the dimer formed by the anti boronic with the syn boronic acid, calculated at a slightly higher energy than the exo-endo, has the same ΔE value with respect to its monomers as the exo-endo, resulting in an overall factor of 4 in the probability of the occurrence of **BB.** Taking into account the above considerations it is possible to calculate % distributions, analogous to the experimental, employing the calculated ΔE, and the results are given in Table 5, along with the experimental distributions. Taking into account the statistical factors, as shown in Table 5, all three methods predict similar distributions for the four cases of coencapsulation, i.e, **A** + **C**, **B** + **C**, **A** + **B**, and **A** + **B** + **C**, considered in the experimental work.[16] The ordering is retained in all three methods, and it is in good qualitative agreement with the experimental distributions, in that the occurrence of **BB** dominates. Thus, as noted in Ajami et al.[16] the highest occurrence observed for the **BB** dimer does not imply stronger hydrogen bonding, and in fact we calculate it to have the smallest ΔE value of all dimers considered. It should be noted that similar distributions as given in Table 5 for the encaptulation complexes are obtained if the ΔE values calculated for the free dimers are used in the above analysis (see Tables S2 and S3), showing that indeed the effect of encapsulation on the hydrogen bonds is similar to that of a solvent.

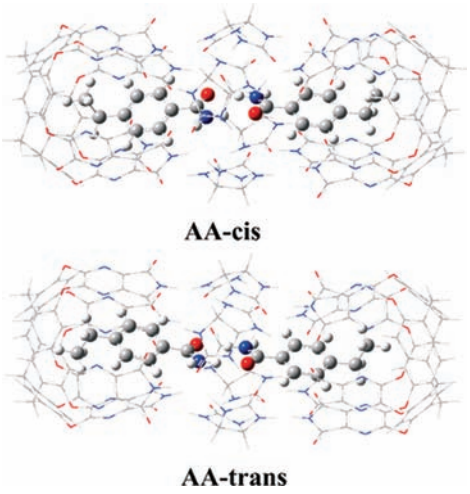


Figure 4. Structures of the encapsulated **AA-cis** and **AA-trans** dimers in the **a** capsule **1.2$_4$.1**. (H = white spheres, C = gray spheres, O = red spheres, and N = blue spheres). The atoms of the capsule are designed with stick bonds for clarity. The structures of the all encapsulated dimers are given in the Supporting Information.

Table 4. Dimerization Energy ΔE (eV) of the AA, AB, AC, BB, BC, and CC Dimers in the a Capsule, Interaction Energy of the Capsule with the Dimers ΔE_1(eV), and the Total Interaction Energy ΔE_2(eV) of the Capsule with the Two Guest Molecules[a]

Dimer	ΔE	ΔE_1	ΔE_2
CC-trans	0.67	1.68	2.44
AC-trans	0.60	1.77	2.46
AA-trans	0.50	1.81	2.40
AB-trans	0.41	1.94	2.44
BC-trans	0.38	1.92	2.48
BB-trans	0.33	2.07	2.52

[a] All interaction energies are BSSE corrected.

Table 5. Encapsulated Dimer % Distribution of the CC, AC, AA, BC, AB, and BB Species at Various Levels of Theory

	A + C			B + C			A + B			A + B + C					
	AC	CC	AA	BB	BC	CC	BB	AB	AA	BB	AC	BC	CC	AB	AA
Oniom-M06-2X/6-31G(d,p)	50	28	22	49	30.6	20.6	54	28	18	28	20	17	12	14	9
Oniom-MP2/6-31G(d,p)	49	28	23	51	30	19	54	28	18	29	20	17	11	15	9
M06-2X/6-31G(d,p)	51	28	21	48	28	24	50	31	19	25	23	14	13	16	9
Expt[a]	53	36	11	61	21	18	75	12.5	12.5	34	23	18	15	6	4

[a] Reference 16.

4. CONCLUSIONS

In the present study, six types of dimers were studied for two groups of molecules. The homodimers and the heterodimers of two amides, two boronic acids, and two carboxylic acids have been calculated, in the gas phase and in *n*,*n*-dimethylformamide and CCl_4 solvents using the DFT (M06-2X and M06-L) and the MP2 methods in conjunction with the 6-31G(d,p) and 6-311+G(d,p) basis sets. Moreover, their coencapsulations were studied to examine the effect of encaptulation on the calculated properties of the hydrogen bonds of the dimers at the M06-2X/6-31G(d,p) method and with the ONIOM[M06-2X/6-31G(d,p);PM6] and ONIOM-[MP2/6-31G(d,p); PM6] methods.

The dimerization energy (ΔE) ordering, in the gas phase, is carboxylic homodimers > amide-carboxylic dimers > amide homodimers > boronic-carboxylic dimers > amide-boronic dimers > boronic homodimers, and it ranges from 0.74 to 0.43 eV and from 0.53 to 0.35 eV at the M06-2X/6-311+G(d,p) and MP2/6-311+G(d,p) levels of theory. Only small differences in the ΔE ordering calculated in solvents from that of the gas phase are found: In CCl_4 solvent, the above order is retained with the exception that the amide homodimers and the boronic-carboxylic dimers have the same interaction energy. In DMF solvent, the order of the gas phase is retained with the exception that the amide homodimers have the smallest ΔE values.

In the capsule, the ΔE ordering is practically the same as that in the gas phase with the exception that the amide-boronic dimer is slightly more stable than the boronic-carboxylic dimer at the M06-2X/6-31G(d,p) level of theory. At the M06-2X/6-31G(d,p) level of theory, the ΔE values range between 0.67 and 0.33 eV.

The dimerization energies of the two groups of dimers (methyl and *p*-ethylphenylene substituted) have similar trends as can be seen in Figures 1S and 2S. Likewise, the two groups of dimers have similar corresponding hydrogen bond lengths. In general, the methyl-substituted group presents the longest hydrogen bond lengths, by up to 0.06 Å. Comparing the hydrogen bond distances of the free dimers with the values of the encapsulated dimers at the M06-2X/6-31G(d,p) level of theory, there are differences up to ±0.05 Å.

Finally, the calculated % distributions of the encapsulated dimers in the case of **A** + **C**, **B** + **C**, **A** + **B**, and **A** + **B** + **C** in solution are in general agreement with the experimental distribution, and it is thus asserted that the highest occurrence of the boronic acid homodimer derives from its adaptable structure.

■ ASSOCIATED CONTENT

Supporting Information. Table 1S: Geometries of the dimers in the gas phase, in solvent and encapsulated. Tables 2S, 3S: Dimer % distribution of the different dimers. Tables 4S−7S: Absolute energies of the calculated structures. Table 8S: Coordinates of the calculated species. Figures 1S, 2S: Dimerization energies of the different dimers. Figure 3S: All calculated dimers in encapsulation complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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