



Encapsulated hydrogen-bonded dimers of amide and carboxylic acid

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ABSTRACT

A theoretical DFT study on benzamide and benzoic acid dimers in the gas phase and encapsulated in two cages of different size has been carried out in order to explain experimental observations regarding the % distributions of the different dimers formed in these cages. The results show that the % distribution of encapsulated dimers in the larger cage is similar to the gas-phase distribution. In the smaller cage interaction of amide with the cage leads to lower dimerization energy and a reduced % fraction of the corresponding encapsulated dimers, compared to the large cage % distribution, in agreement with experiment.

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1. Introduction

The importance of hydrogen bond interactions in many chemical, biochemical, and biological processes leads to a constant interest in the description of the nature and strength of the hydrogen bond [1–3]. Whereas observation of the individual donor and acceptor hydrogen bond pairs in solution is difficult because their weak interactions result in nanosecond lifetimes and rapid exchange of partners, reversible encapsulation provides temporary isolation of the dimers by mechanical barriers in very small spaces for milliseconds to hours and allows their characterization by NMR methods [4]. In fact, the capsule is considered to act as the solvent, fixed in place around the solute during the synthesis and assembly of the complex [4,5]. Recently, the relative stability of encapsulated homodimeric and heterodimeric hydrogen bonding in *p*-ethylenebenzoic acid, *p*-ethylene benzamide and *p*-ethylenephénylboronic acid in the **1.2₄.1** capsule has been examined both experimentally by NMR [4], and theoretically via DFT methodology [6,7]. The theoretical % distribution of the encapsulated dimers, taking into account statistical factors as well as the calculated dimerization energies are in good agreement with the experimental % distribution [4,6,7]. Furthermore, the calculated % distribution of the encapsulated dimers is similar to those calculated for free dimers in a solvent as well as in the gas phase, indicating negligible effect of encapsulation on the % distribution of the dimers formed. However, this does not seem to be the case when a smaller capsule is employed, according to recent experimental work on benzoic acid and benzamide dimers and the **1.1** cage where different % distribution of the dimers from that of the larger cage is obtained [8]: Whereas, in the larger cage the carboxylic acid–amide heterodimer

has the largest % fraction, in the smaller cage the carboxylic acid dimer predominates. Given that the different dimers are of similar size, hydrogen bonding interactions with the walls of the small cage need to be considered.

In the present study, the relative stability of encapsulated homodimers and the heterodimer of benzoic acid and benzamide in the **1.1** and **1.2₄.1** [4] cages has been examined theoretically via DFT methodology, in order to determine the origin of the observed differences in the % distributions of the encapsulated dimers in the two cages.

2. Calculations

The two capsules employed are **1.1** which consists of two cavities **1**, and **1.2₄.1** [4], which consists of two cavities **1** with four glycoluril spacer molecules **2** (see Figure 1). Both capsules are large enough to accommodate the possible dimers formed by benzoic acid (**C**) and benzamide (**A**) molecules. It should be noted that the **A** and **C** monomers are of similar size.

The geometry of the encapsulation complexes, which include 230–296 atoms, were optimized by DFT calculations employing the M06-2X [9] functional in conjunction with the 6-31G(d,p) basis set [10]. The M06-2X functional is a hybrid meta exchange correlation functional, it is highly-nonlocal with double the amount of nonlocal exchange [9] and has been shown previously to lead to good predictions of the dimerization energies of dimers of carboxylic acids and amides compared to corresponding quantities at the MP2/aug-cc-pVQZ and CCSD(T)/aug-cc-pVTZ levels of theory [7]. For all structures determined, basis set superposition error (BSSE) corrections to the dimerization energy have been taken into account using the counterpoise procedure [11]. All calculations were performed using the GAUSSIAN 09 program package [12].

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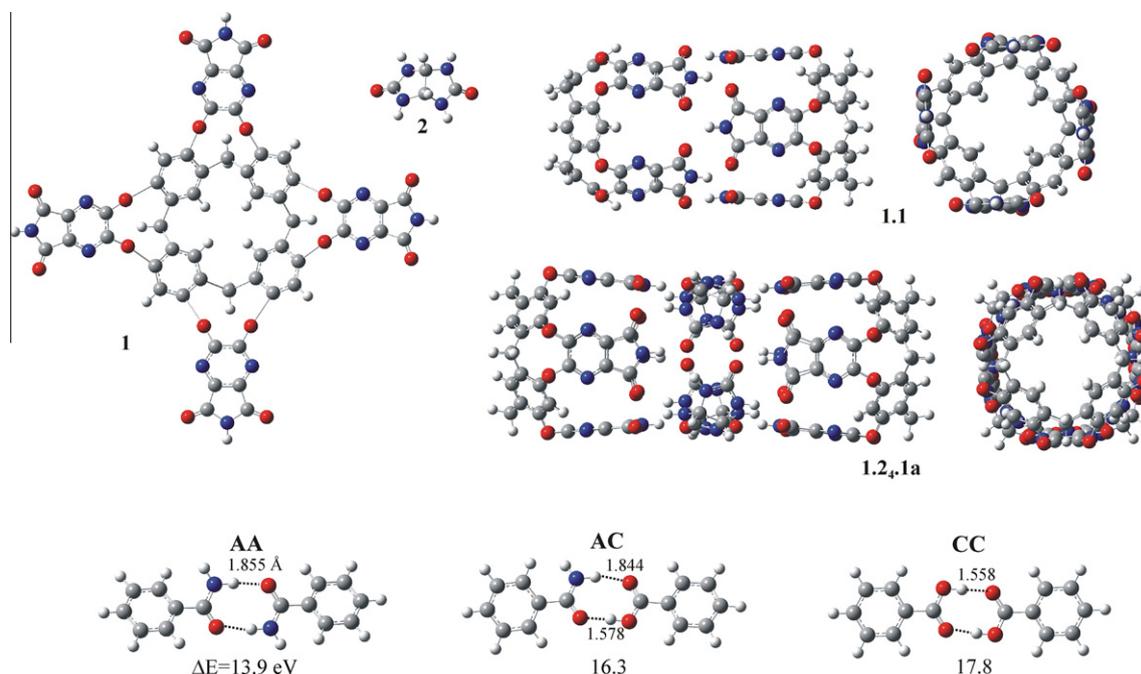


Fig. 1. Structures of the cavitand **1**, the calculated minimum structure of the capsules **1.1** and **1.2.1a** viewed from two different angles, i.e., along the central axis of the capsule and end-on view, and the calculated minimum energy structures of the free dimers of benzamide and benzoic acid, their dimerization energy, ΔE , and their hydrogen bond distances. (H atoms = white spheres, C = grey spheres, O = red spheres and N = blue spheres). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results and discussion

The free heterodimer (**AC**) and the homodimers of benzamide (**AA**) and benzoic acid (**CC**) are shown in Figure 1 along with the **1.1** and **1.2.1a** capsules employed in the present calculations. It may be noted that in Figure 1 the calculated minimum energy structures of the dimers are given, with the hydrogen bond-lengths and dimerization energies (ΔE values), where the smaller H-bond length and largest dimerization energy correspond to the **CC** dimer.

The minimum energy structures calculated to lie within about 3.0 kcal/mol of the lowest energy structures are depicted in Figs. 2a–4a, for the **AA**, **AC** and **CC** dimers, respectively, encapsulated in **1.1**. In Figures 2b–4b the lowest minima calculated for the encapsulated dimers in **1.2.1a**, while in Table 1, the calculated geometries, dimerization energies and interaction energies of all these encapsulated dimers (Figs. 2–4) are given. More complete data are provided in the Supporting Information.

The main result of the present calculations is that while the carboxylic acid dimer (**CC**) has the same type of lowest minimum structure in the small cage as in the large, cf. **1.1-CC_1** (Figure 4a) and **1.2.1-CC** (Figure 4b), in the cases of the amide dimer (**AA**) and carboxylic acid–amide heterodimer (**AC**), encapsulated in the smaller cage, the lowest energy minima involve interaction of the guest **A** molecules with the cage, as will be described below in detail.

The two lowest minima of encapsulated benzamide dimer in the **1.1** cage, **1.1-AA_1** and **1.1-AA_2** (Figure 2a) differ energetically by less than 1 kcal/mol, and they contain **A** monomers which, in addition to the interaction with the other guest molecule, form hydrogen bonds with the cavitands **1** causing a slight distortion of the cage. The interaction between the two **A** monomers is very weak in both the **1.1-AA_1** and **1.1-AA_2** structures, with $\text{NH}\cdots\text{O}$ bond lengths of 2.491 and 2.281 Å respectively and dimerization energy ranging from 0 to 2.1 kcal/mol (Table 1 under ΔE), whereas the calculated dimerization energy for free **AA** dimer is 13.9 kcal/mol at the M06-2X/6-31G(d,p) level of theory, and the $\text{NH}\cdots\text{O}$

bond length is 1.855 Å, cf. Figure 1. The above two encapsulated structures differ in the relative position of the dimer with respect to the cage, see Figure 2a. Structures **1.1-AA_3** and **1.1-AA_4** which have an encapsulated **AA** dimer with structure resembling that of free **AA**, lie energetically only at 1.2 and 2.0 kcal/mol, respectively, above the **1.1-AA_1** minimum, have calculated $\text{NH}\cdots\text{O}$ bond lengths 1.831 and 1.850 Å and dimerization energy 10.1 and 9.2 kcal/mol, respectively (cf. Table 1).

In the case of the benzamide–benzoic acid heterodimer, the two lowest minima, i.e., **1.1-AC_1** and **1.1-AC_2**, differ energetically by only 0.7 kcal/mol, cf. Figure 3a. In **1.1-AC_1**, a typical hydrogen bond $\text{OH}\cdots\text{O}$ (of length 1.634 Å) between the two monomers is formed while the second hydrogen bond, $\text{NH}\cdots\text{O}$, is weak (length 2.303 Å). In **1.1-AC_2** both hydrogen bonding interactions between the monomers are weak, cf. bond lengths of 2.822 and 2.063 Å, respectively, in Table 1. The calculated dimerization energies (under ΔE in Table 1) are 9.5 and 1.3 kcal/mol for the two minima, respectively, significantly lower than the 16.3 kcal/mol value calculated for free **AC**. Finally, the lowest energy structure in which the **AC** dimer has structure resembling that of free **AC**, **1.1-AC_3**, lies energetically about 2.3 kcal/mol above the **1.1-AC_1** minimum (see Figure 3a).

Contrary to the above results on encapsulated **AA** and **AC** dimers, the lowest minimum of encapsulated benzoic acid dimer, **1.1-CC_1**, (cf. Figure 4a) contains the **CC** dimer of similar structure as that of free **CC** and that of the larger cage complex, (cf. Figure 4b), without any distortion of the cage. Accordingly, the calculated dimerization energy of **CC** in **1.1** (15.9 kcal/mol) is close to that of free **CC** (17.8 kcal/mol). In the larger, **1.2.1a**, capsule the lowest minima for all three encapsulated dimers, namely **1.2.1-AA**, **1.2.1-AC**, and **1.2.1-CC**, (cf. Figures 2b–4b) have dimers with geometries similar to those of the free dimers, with only elongation of up to 0.17 Å calculated for the hydrogen bond distances, cf. Figure 1 and Table 1. Accordingly dimerization energies of 12.6, 15.0 and 16.8 kcal/mol (cf. Table 1) are calculated for the above three encapsulated dimers, respectively. Similar results have been

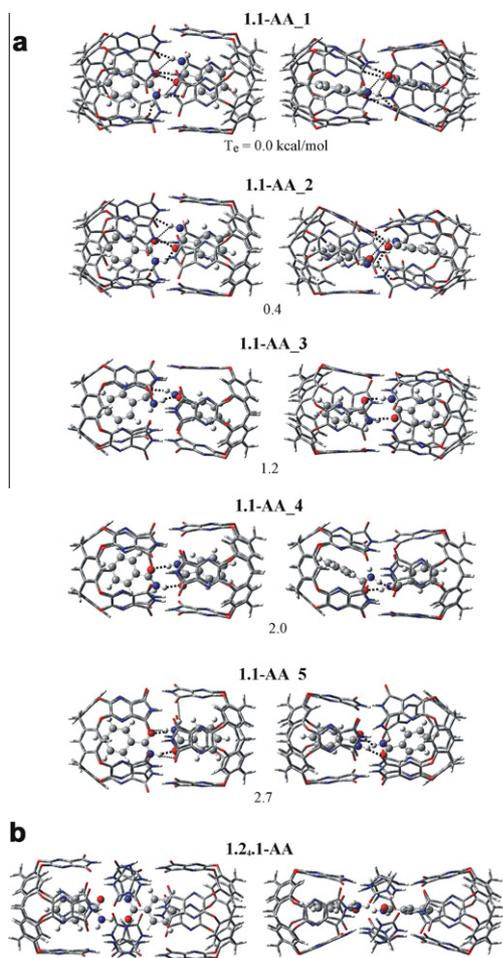


Fig. 2. Calculated structures of the (a) lowest minima of the **1.1-AA** species, along with the corresponding T_e values, (b) lowest minimum of the **1.24.1-AA** species, viewed from two different angles. (H atoms = white spheres, C = grey spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with stick bonds for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Calculated hydrogen bond distances in Å, dimerization energies^a of the dimers inside the cage (ΔE) in kcal/mol, and interaction energies^a in kcal/mol of the encapsulated complexes **1.1-AA**, **1.1-AC**, **1.1-CC**, **1.24.1-AA**, **1.24.1-AC**, and **1.24.1-CC** with respect to the free cage and the dimers (ΔE_1), with respect to the free cage and the monomers (ΔE_2), and with respect to the four (1.1 cage) or eight (1.24.1 cage) components of fully disassembled complexes (ΔE_3).

	$R_{\text{NH}\cdots\text{O}}^b$	$R_{\text{O}\cdots\text{Hc}}^c$	$R_{\text{NH}\cdots\text{Oc}}^d$	$R_{\text{NH}\cdots\text{Oc}}^e$	$R_{\text{NH}\cdots\text{O}}^b$	$R_{\text{O}\cdots\text{Hc}}^c$	$R_{\text{NH}\cdots\text{Oc}}^d$	$R_{\text{NH}\cdots\text{Oc}}^e$	ΔE	ΔE_1	ΔE_2	ΔE_3
1.1-AA_1	2.491	1.683	2.200	2.059	2.834	1.765	2.066	2.290	0.5	29.5	44.4	117.1
1.1-AA_2	2.281	1.696	2.283	2.051	2.677	1.787	2.050	2.543	2.1	29.8	44.5	116.7
1.1-AA_3	1.831	3.014	3.140	2.076	1.968	3.084	3.558	2.062	10.1	31.7	45.5	115.9
1.1-AA_4	1.850	3.038	3.154	2.068	1.977	2.998	3.209	2.070	9.2	31.0	44.8	115.1
1.1-AA_5	2.140	1.824	2.351	2.230	2.242	1.824	2.270	2.123	5.3	28.3	42.8	114.4
1.24.1-AA	1.933				2.008				12.6	34.0	47.9	215.3
	$R_{\text{OH}\cdots\text{O}}^b$	$R_{\text{O}\cdots\text{Hc}}^c$	$R_{\text{OH}\cdots\text{Oc}}^d$	$R_{\text{NH}\cdots\text{O}}^b$	$R_{\text{O}\cdots\text{Hc}}^c$	$R_{\text{NH}\cdots\text{Oc}}^d$	$R_{\text{NH}\cdots\text{Oc}}^e$					
1.1-AC_1	1.634			2.303	1.980	2.176	2.120		9.5	28.2	44.6	116.0
1.1-AC_2	2.822	1.779	2.063	2.329	1.694	2.206	2.061		1.3	26.0	43.4	115.3
1.1-AC_3	1.552	3.363	3.040	1.849	2.830	3.315	2.568		15.3	27.6	43.6	113.7
1.1-AC_4	1.543	3.123	3.352	1.952	3.084	3.328	1.980		12.8	27.3	43.3	113.4
1.1-AC_5	1.771	1.888	3.204	2.612	2.429	2.074	2.068		6.0	24.9	41.5	112.9
1.24.1-AC	1.653			1.940					15.0	31.3	47.5	215.0
	$R_{\text{OH}\cdots\text{O}}^b$	$R_{\text{OH}\cdots\text{O}}^b$										
1.1-CC_1	1.578	1.600							15.9	24.9	42.3	112.4
1.1-CC_2	1.523	1.574							16.1	23.7	41.0	112.1
1.1-CC_3	1.726	2.200							9.4	23.0	40.9	111.8
1.1-CC_4	1.516	1.534							17.0	22.2	39.5	111.5
1.24.1-CC	1.636	1.732							16.8	28.3	45.9	213.6

^a BSSE corrected values.

^b Hydrogen bond distance between the two monomers A or C.

^c Hydrogen bond distance between oxygen atom of the monomers A or C and hydrogen atom of the cage.

^d Hydrogen bond distance between hydrogen atom of the monomers A or C and oxygen atom of the cage.

^e Hydrogen bond distance between hydrogen atom of A which does not interact with the other monomer A or C and oxygen atom of the cage.

reported for the *p*-ethylenebenzoic acid and *p*-ethylene benzamide dimers in the **1.24.1**, capsule [6].

As shown in Table 1, the minimum energy structures of encapsulated benzoic acid dimer, benzamide–benzoic acid heterodimer and benzamide dimer in the **1.1** cage involve two, one and zero typical hydrogen bonds found in the corresponding free dimers whereas in the larger cage, **1.24.1**, all encapsulated dimers involve two typical hydrogen bonds in their lowest minima, similar to the gas-phase structures.

A theoretical % distribution of the different dimers was introduced previously, [6,7], based on the BSSE-corrected dimerization energy and statistical factors, as for example the formation of the heterodimer is twice as probable as of each the monomer. In Table 2, the calculated % distributions of the free and encapsulated dimers of the present study and for comparison of the previous study [6] are collected. In the present situation where near degeneracy is found between **1.1-AA_1** and **1.1-AA_2** and between **1.1-AC_1**, and **1.1-AC_2**, the average value of dimerization energy is employed in the calculation of the % distribution. The theoretical distributions resulting from the calculated ΔE dimerization values of the **1.1-AA_1**, **1.1-AA_2**, **1.1-AC_1**, **1.1-AC_2**, and **1.1-CC_1** dimers are 5, 38 and 57%, respectively. Compared to the experimental % distributions of 19, 22 and 59%, respectively [8], the trend is reproduced. If additional minimum energy structures (cf. Figures 2a–4a), lying within 2 kcal/mol from the lowest minima are taken into account, the corresponding % distribution becomes 18%, 35%, and 47%, respectively, which is in better agreement with the experimental, cf. Table 2. This might be an indication that in addition to the lowest energy structures, the other low-lying minima are also formed in the experiment. As shown in Table 2, encapsulation of the dimers in the smaller cage **1.1** leads to totally different % distribution from that of the dimers in the **1.24.1** capsule whereas the % distributions of the **AA**, **AC** and **CC** dimers, free and encapsulated in the **1.24.1** capsule are almost the same, i.e., 21%, 51% and 28 %, respectively. Similar distributions have been calculated previously for free and encapsulated *p*-ethyl substituted dimers, i.e., *p*-ethylbenzoic acid and *p*-ethylbenzamide dimers, in the **1.24.1** cage [6], in good agreement with the experimental values [4]. These values are also included in Table 2, for comparison.

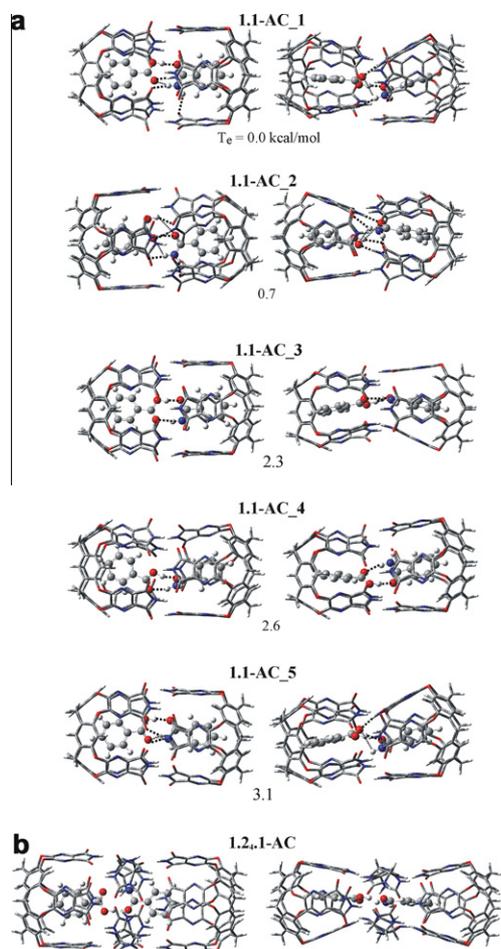


Fig. 3. Calculated structures of the (a) lowest minima of the **1.1-AC** species, along with the corresponding T_e values, (b) lowest minimum of the **1.24-1-AC** species, viewed from two different angles. (H atoms = white spheres, C = grey spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with stick bonds for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Summarizing, the theoretical % distributions (see Table 2) are in general agreement with the experimental % distributions in both the large and in the small cage and reflect the difference between the two cages. The % fraction of the encapsulated **CC** dimer in the small cage is larger by about a factor of two than that of the **CC** free dimer or encapsulated in the larger cage, both theoretically and experimentally.

4. Conclusions

Density functional theory calculations have been carried out on encapsulated homodimers and the heterodimer of benzoic acid and benzamide in two cages of different size, **1.1** and **1.24.1**, in order to rationalize the observed differences in the % distributions of the dimers formed. The results of the calculations show that in the case of the smaller cage, **1.1**, the lowest energy minimum structures of encapsulated benzamide–benzoic acid heterodimer and benzamide dimer involve hydrogen bonding interactions of the amide segments with the cage, thus weakening the hydrogen bonds in the corresponding dimers and resulting in lower dimerization energy. As a result, the % distribution is different in the smaller cage from those in the larger cage and the free dimers. In this manner, the present calculations explain the observed % distributions of the dimers in the small and large cages.

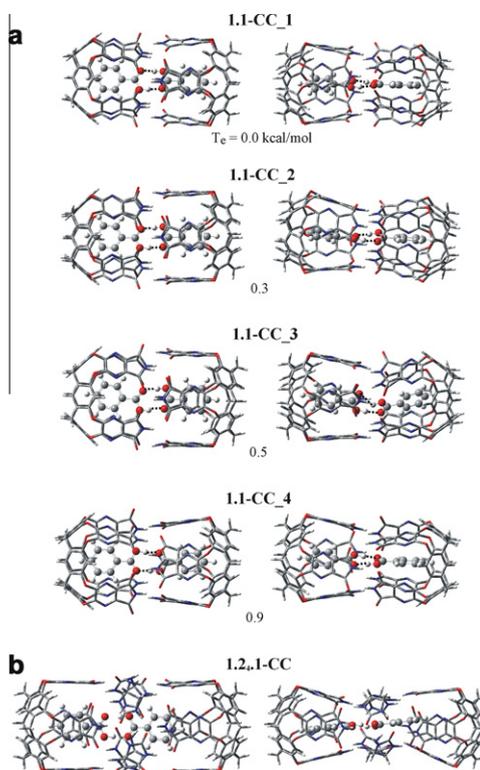


Fig. 4. Calculated structures of the (a) lowest minima of the **1.1-CC** species, along with the corresponding T_e values, (b) lowest minimum of the **1.24-1-CC** species, viewed from two different angles. (H atoms = white spheres, C = grey spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with stick bonds for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2

Dimer BSSE corrected % distribution of the AA, AC, and CC species free and encapsulated.

Dimers	AA	AC	CC
Free	21.6	50.7	27.7
In 1.1	5, 18 ^a	38, 35 ^a	57, 47 ^a
	19 ^b	22 ^b	59 ^b
In 1.24.1	21.3	50.5	28.2
Free ^c	21.6	50.7	27.7
In 1.24.1 ^c	21.3	50.3	28.4
	11 ^d	53 ^d	36 ^d

^a Additional minimum energy structures lying within 2 kcal/mol are taken into account.

^b Experimental data, Ref. [8].

^c Ref. [6], *p*-ethylbenzamide and *p*-ethylbenzoic acid dimers.

^d Experimental data, *p*-ethylbenzamide and *p*-ethylbenzoic acid dimers, Ref. [4].

Supporting Information is provided including the absolute energies, the BSSE corrections, the geometries and the dimerization energies of the calculated structures.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cplett.2012.08.024>.

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