

# Theoretical Study of Free and Encapsulated Carboxylic Acid and Amide Dimers

Demeter Tzeli,<sup>\*[a]</sup> Ioannis D. Petsalakis,<sup>[a]</sup> Giannoula Theodorakopoulos,<sup>[a]</sup> Dariush Ajami,<sup>[b]</sup> and Julius Rebek, Jr.<sup>[b]</sup>

The homodimers and heterodimers of four carboxylic acids RCOOH and four amides RCONH<sub>2</sub>, where R = H, methyl, phenyl, *p*-ethylphenylene have been calculated via DFT(M06-2X), MP2, and CCSD(T) methods in conjunction with the 6-31G(d,p), 6-311+G(d,p), aug-cc-pVTZ, and aug-cc-pVQZ basis sets to find out how the substituent R influences their dimerization energy ( $\Delta E$ ) and their hydrogen bond length. The calculated  $\Delta E$  values range from 14 to 17 kcal/mol for the different dimers in the gas phase, with the ordering carboxylic homodimers  $\geq$  amide-carboxylic dimers  $>$  amide homodimers. The M06-2X/6-

311+G(d,p) geometries and  $\Delta E$  values are in very good agreement with the corresponding MP2/aug-cc-pVQZ and CCSD(T)/aug-cc-pVTZ values. Coencapsulation of the dimers was studied to examine its effect on the calculated bond lengths and strength of the hydrogen bonds at the M06-2X/6-31G(d,p) level of theory. The experimental and calculated % distributions of the encapsulated dimers, taking into account statistical factors are in good agreement. © 2012 Wiley Periodicals, Inc.

DOI: 10.1002/qua.24062

## Introduction

Hydrogen bonds are found ubiquitously in nature. They are extremely important in a wide range of fields including clusters, solvation, solution chemistry, biochemistry, and life processes because they provide stability in many systems.<sup>[1–3]</sup> The nature and the strength of the hydrogen bonds have been studied both experimentally and theoretically for many systems; see for instance Refs. [1–7]. However, judging by the number of publications on this topic, in the last few years interest remains unimpaired.

In this study, the relative strength of the hydrogen bonds which are formed in the homodimers and heterodimers of four carboxylic acids and four amides is studied. It is well known that carboxylic acids form dimers both in solution<sup>[8]</sup> and in solid state.<sup>[9]</sup> Hydrogen bonds, that is, C=O...H—O, in these dimers are highly directional and have considerable strength. As a result, carboxylic acids have been used extensively as building blocks for the construction of hydrogen-bonded supramolecular species.<sup>[10]</sup> In addition, the hydrogen bonds C=O...H—N, in the amide homodimers are very important because of their significant role in DNA base-pairing, in protein folding, and in heterocyclic contexts.<sup>[11]</sup>

In the literature, there are a few experimental<sup>[12–14]</sup> and some theoretical studies<sup>[5,14–23]</sup> for the smallest dimers calculated here. The data of previous studies are summarized along with our results in Table 1. Recently, the relative stability of encapsulated homodimeric and heterodimeric hydrogen bonding in carboxylic acids, primary amides, and boronic acids has been examined both experimentally, whereby the dimers are isolated for sufficiently long times to allow direct observation by NMR,<sup>[25]</sup> and theoretically via density functional theory (DFT) methodology.<sup>[24]</sup> Within a capsule, the interacting guests are separated from solvent molecules by mechanical barriers and they do not exchange partners as 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.<sup>[25]</sup> The efficiency of different systems to act as hydrogen-bonding partners within a capsule has been determined and the agreement between experiment and theory is very good.<sup>[24,25]</sup>

In this study, the homodimers and the heterodimers of four amides RCONH<sub>2</sub> and four carboxylic acids RCOOH, where R = H, methyl, phenyl, *p*-ethylphenylene, have been calculated in the gas phase, via MP2, CCSD(T), and DFT methodology, see Figure 1. The aim of this study is to find out how the size of the substituent R influences the dimerization energy of the dimers and the hydrogen bond length. Moreover, the effect of encapsulation on the dimerization energies and hydrogen bond lengths, via DFT calculations, is reported.<sup>[24]</sup>

## Methodology

All calculated dimers were fully optimized by DFT calculations using the M06-2X<sup>[26]</sup> in conjunction with the 6-31G(d,p) and 6-311+G(d,p)<sup>[27]</sup> basis sets. M06-2X<sup>[26]</sup> 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 and noncovalent interactions. In addition, we carried out MP2 and CCSD(T) calculations in conjunction with the 6-311+G(d,p),

[a] D. Tzeli, I. D. Petsalakis, G. Theodorakopoulos  
Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, 48 Vassileos Constantinou, Athens 116 35, Greece  
E-mail: dtzeli@ie.gr

[b] D. Ajami, J. Rebek, Jr  
The Skaggs Institute for Chemical Biology & Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Contract grant sponsor: NATO; contract grant number: CBP.MD.CLG.983711.

© 2012 Wiley Periodicals, Inc.

**Table 1.** Dimerization energies in kcal/mol and hydrogen bond distances in Å of the **C•C**, **A•C**, and **A•A** dimers in the gas phase and in **1.2.4.1** capsule, at various levels of theory.

Methods	$\Delta E_u^a$	$\Delta E^b$	$R_{OH\cdots O}$	$\Delta E_u^a$	$\Delta E^b$	$R_{OH\cdots O}$	$R_{NH\cdots O}$	$\Delta E_u^a$	$\Delta E^b$	$R_{NH\cdots O}$
<b>R = H</b>										
	<b>C<sub>H</sub>•C<sub>H</sub></b>			<b>A<sub>H</sub>•C<sub>H</sub></b>				<b>A<sub>H</sub>•A<sub>H</sub></b>		
M06-2X/6-31G(d,p)	20.0	16.7	1.604	19.5	16.3	1.600	1.858	17.8	14.5	1.854
M06-2X/6-311+G(d,p)	16.7	15.9	1.708	16.5	15.8	1.657	1.914	14.7	14.2	1.883
MP2/6-311+G(d,p)	14.5	11.7	1.723	14.4	12.0	1.689	1.939	13.1	11.1	1.896
MP2/aug-cc-pVTZ	16.8	15.2	1.660	16.6	15.2	1.634	1.859	15.4	14.1	1.833
MP2/aug-cc-pVTZ <sup>c</sup>		15.3	1.693		15.3	1.667	1.890		14.1	1.863
MP2/aug-cc-pVQZ <sup>d</sup>	16.5	15.7		16.3	15.6			15.0	14.4	
RCCSD(T)/aug-cc-pVTZ <sup>d</sup>	16.8	15.3		16.7	15.3			15.5	14.3	
MP2/6-311++G(d,p) <sup>e,f,g,h,i</sup>		13.2 <sup>e</sup>	1.726 <sup>ei</sup>			1.69 <sup>f</sup>	1.93 <sup>f</sup>		11.2 <sup>e</sup>	1.901 <sup>e</sup>
MP2/aug-cc-pVDZ <sup>e</sup>		14.0	1.680						13.4	1.840
MP2/cc-pVTZ <sup>j</sup>								15.6	13.1	1.831
MP2/aug-cc-pVTZ (sp) <sup>k</sup>									15.3 <sup>k</sup>	
MP2/aug-cc-pV5Z (sp) <sup>k</sup>									15.9 <sup>k</sup>	
CCSD(T)/6-311++G(d,p) <sup>g</sup>						1.73	1.98			
CCSD(T)/cc-pVTZ (sp) <sup>l</sup>				16.8	14.5					
CCSD(T)/aug-cc-pVQZ (sp) <sup>k</sup>									16.0 <sup>k</sup>	
Expt			1.667 <sup>m</sup>			1.78 <sup>f</sup>	1.80 <sup>f</sup>			
<b>R = methyl<sup>n</sup></b>										
	<b>C<sub>Me</sub>•C<sub>Me</sub></b>			<b>A<sub>Me</sub>•C<sub>Me</sub></b>				<b>A<sub>Me</sub>•A<sub>Me</sub></b>		
M06-2X/6-31G(d,p)	20.5	17.1	1.586	19.7	16.4	1.593	1.843	17.7	14.6	1.846
M06-2X/6-311+G(d,p)	17.3	16.5	1.685	16.7	16.0	1.648	1.887	14.9	14.3	1.866
M06-2X/6-311+G(d,p) <sup>c</sup>		16.5	1.701		16.0	1.662	1.902		14.3	1.879
MP2/6-311+G(d,p)	15.4	12.3	1.704	15.0	11.8	1.681	1.907	13.6	11.2	1.880
MP2/aug-cc-pVDZ <sup>e</sup>		14.4	1.672							
<b>R = phenyl</b>										
	<b>C<sub>p</sub>•C<sub>p</sub></b>			<b>A<sub>p</sub>•C<sub>p</sub></b>				<b>A<sub>p</sub>•A<sub>p</sub></b>		
M06-2X/6-31G(d,p)	21.0	17.8	1.558	19.4	16.3	1.578	1.844	16.8	13.9	1.855
M06-2X/6-311+G(d,p)	18.0	17.1	1.658	16.8	16.0	1.633	1.882	14.4	13.8	1.868
MP2/6-311+G(d,p)	17.0	12.9	1.671	15.9	12.5	1.661	1.888	14.1	11.2	1.872
<b>R = <i>p</i>-ethylphenylene<sup>n</sup></b>										
	<b>C<sub>Ep</sub>•C<sub>Ep</sub></b>			<b>A<sub>Ep</sub>•C<sub>Ep</sub></b>				<b>A<sub>Ep</sub>•A<sub>Ep</sub></b>		
M06-2X/6-31G(d,p)	21.0	17.8	1.557	19.4	16.3	1.582	1.841	16.8	13.9	1.858
M06-2X/6-311+G(d,p)	18.0	17.2	1.657	16.7	16.0	1.632	1.881	14.2	13.7	1.867
M06-2X/6-311+G(d,p) <sup>c</sup>		17.2	1.674		16.0	1.647	1.895		13.7	1.882
<b>R = <i>p</i>-ethylphenylene<sup>n,o</sup></b>										
	<b>C<sub>Ep</sub>•C<sub>Ep</sub></b>			<b>A<sub>Ep</sub>•C<sub>Ep</sub></b>				<b>A<sub>Ep</sub>•A<sub>Ep</sub></b>		
M06-2X/6-31G(d,p)	18.7	15.5	1.602/1.641	16.8	13.7	1.561	1.856	14.5	11.6	1.902/1.904

[a] Dimerization energies uncorrected for BSSE. [b] BSSE corrected dimerization energies. [c] BSSE optimized geometry. [d] At the optimized MP2/aug-cc-pVTZ geometry. [e] Ref. [5]. [f] Ref. [14]. [g] Ref. [15]. [h] Ref. [16]. [i] Ref. [20]. [j] Ref. [19]. [k] Ref. [18], single point calculations of the monomers and the dimers at the geometry of the MP2/6-31G\*\* level of theory. [l] Ref. [17], single point calculation, CCSD(T)/cc-pVTZ//MP2/aug-cc-pVTZ. [m] Ref. [12]. [n] Ref. [24]. [o] Coencapsulated dimers in the **1.2.4.1** cage.

aug-cc-pVTZ<sup>[28]</sup> and aug-cc-pVQZ<sup>[28]</sup> basis sets for the three smallest dimers, that is, (formamide)<sub>2</sub>, (formic acid)<sub>2</sub>, and formamide-formic acid, in order to test our M06-2X data.

For the encapsulation complexes, which have more than 300 atoms, geometry optimization calculations were carried out at the M06-2X/6-31G(d,p) level of theory.

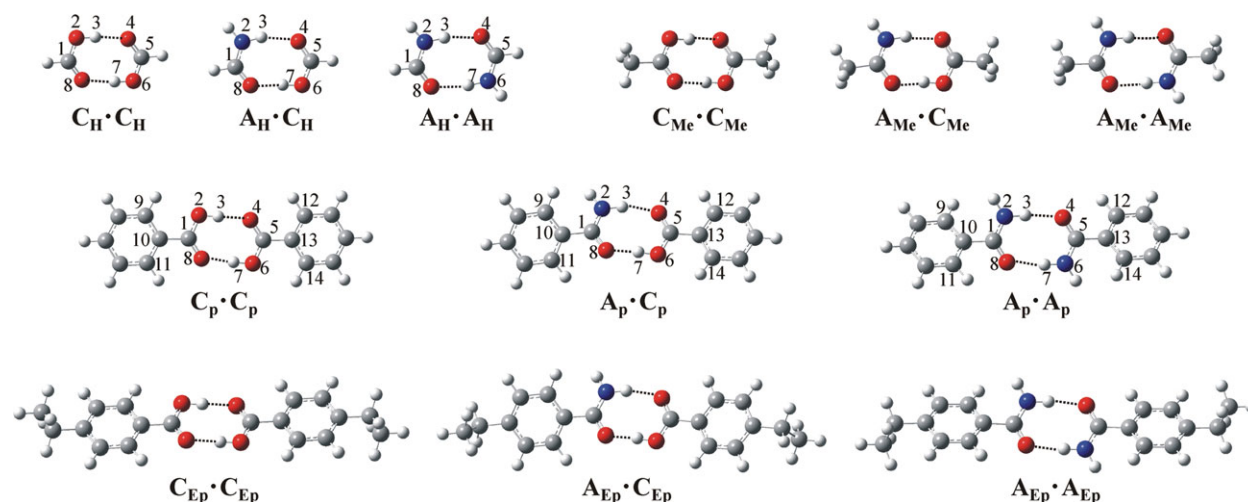
For all structures determined, basis set superposition error (BSSE) corrections to the dimerization energy have been taken into account using the counterpoise procedure.<sup>[29]</sup> A detailed example of the procedure for a BSSE calculation can be found in Ref. [30]. BSSE corrections are important for hydrogen bond interactions.<sup>[31]</sup> In some cases, we carried out geometric optimization with respect to the BSSE corrected energy. All calculations were performed using the Gaussian 09 program package.<sup>[32]</sup>

## Results and Discussion

The calculated minimum energy structures of the homodimers (**C•C** and **A•A**) and the heterodimers (**A•C**) of four carboxylic acids RCOOH and four amides RCONH<sub>2</sub>, where R = H, methyl, phenyl, *p*-ethylphenylene, are depicted in Figure 1. Their dimerization energies and the hydrogen bond lengths are given in Table 1. The geometries of the calculated dimers are given in the Supporting Information.

### R = H: (HCOOH)<sub>2</sub>, (HCONH<sub>2</sub>)<sub>2</sub>, and HCOOH-HCONH<sub>2</sub> dimers

We chose the M06-2X functional because in general it gives good results for hydrogen-bonded systems.<sup>[26,33,34]</sup> However,



**Figure 1.** Optimized structures of homodimers and heterodimers of carboxylic acids and amides. (H atoms = white spheres, C = gray spheres, O = red spheres, and N = blue spheres).

we carried out additional MP2 and CCSD(T) calculations in conjunction with the 6-311+G(d,p), aug-cc-pVTZ and aug-cc-pVQZ basis sets to test our M06-2X calculated data, see Table 1. For these three dimers, there are some previous studies in the literature which are also given in Table 1. However, these previous studies do not treat all three dimers at the same high level of calculation. Thus, it was necessary to carry out high level calculations at the same level on all these dimers.

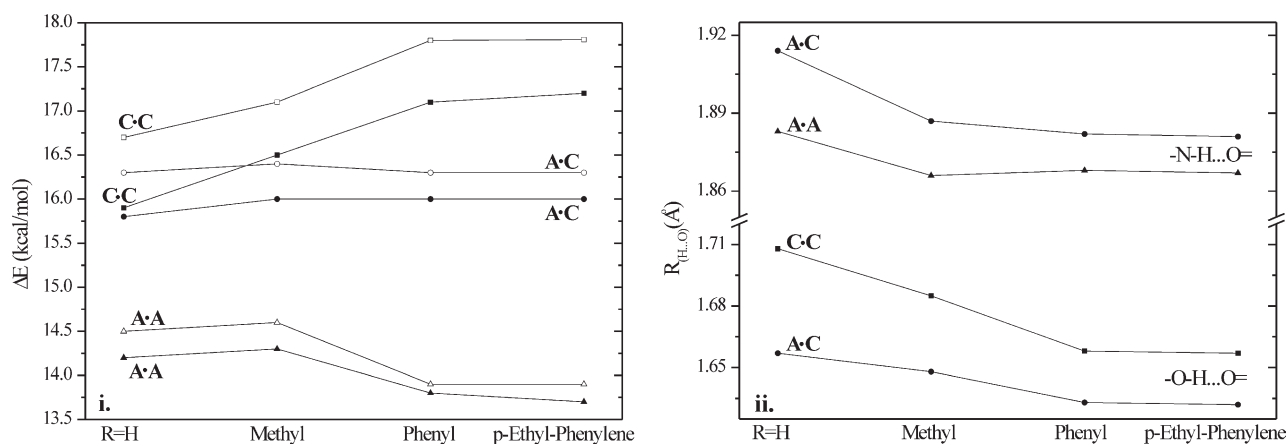
Our best calculations at the MP2/aug-cc-pVTZ, MP2/aug-cc-pVQZ//MP2/aug-cc-pVTZ, and RCCSD(T)/aug-cc-pVTZ//MP2/aug-cc-pVTZ levels of theory, present nearly the same dimerization energies. Our best values, corrected for BSSE, are 15.7, 15.6, and 14.4 kcal/mol for the (HCOOH)<sub>2</sub>, HCOOH–HCONH<sub>2</sub>, and (HCONH<sub>2</sub>)<sub>2</sub> dimers. The corresponding M06-2X/6-311+G(d,p) values are 15.9, 15.8, and 14.2 kcal/mol, in very good agreement with the time consuming MP2/aug-cc-pVQZ and RCCSD(T)/aug-cc-pVTZ methods. The combination of the M06-2X functional with a smaller basis, that is, 6-31G(d,p), predicts the corresponding values of 16.7, 16.3, and 14.5 kcal/mol, which are larger than our best methods by 1–0.1 kcal/mol. The largest discrepancies are observed for the (HCOOH)<sub>2</sub> dimer and the smallest for the (HCONH<sub>2</sub>)<sub>2</sub> dimer. It might be noted that between the M06-2X/6-311+G(d,p) and M06-2X/6-31G(d,p) methods the differences in the corresponding BSSE uncorrected dimerization energies are about 3 kcal/mol, whereas the BSSE correction reduces the differences to a range of 0.3–0.8 kcal/mol. Thus, although the M06-2X/6-311+G(d,p) method is a very good choice for the calculation of the homodimers and the heterodimers of amides carboxylic acids, the M06-2X/6-31G(d,p) method is also a good choice, provided that BSSE is accounted for. Finally, it should be noted that the MP2/6-311+G(d,p) method predicts underestimated dimerization energies; they are smaller by up to 4 kcal/mol than our best MP2/aug-cc-pVQZ and RCCSD(T)/aug-cc-pVTZ methods. The best reported method in the literature is for the formamide dimer at the CCSD(T)/aug-cc-pVQZ//MP2/6-31G\*\* level of theory for both monomers and the dimer and predicts a value of 16.0 kcal/mol by Dedíková et al.<sup>[18]</sup> However, their single point calculation at the MP2/aug-cc-pVTZ//MP2/6-31G\*\* level of theory pre-

dicts a dimerization BSSE corrected energy at 15.3 kcal/mol,<sup>[18]</sup> whereas our corresponding value at geometry optimized calculation at the MP2/aug-cc-pVTZ level of theory corrected for BSSE or with BSSE geometry optimization is 14.1 kcal/mol. By analogy, the above 16.0 kcal/mol value<sup>[18]</sup> is considered to be an overestimation, which would be expected if the inclusion of the fragment relaxation energy terms in the estimation of the BSSE correction has not been applied. See for instance Ref. [30].

All methods used in this work result in similar geometries for the dimers with the exception of the hydrogen bond lengths, where differences up to 0.1 Å are observed, see Table 1 and Supporting Information, Table 15. The larger differences are observed for the (HCOOH)<sub>2</sub> dimer and the smallest ones for the (HCONH<sub>2</sub>)<sub>2</sub> dimer. As shown, the hydrogen bond lengths obtained with the smaller basis set are not very good. On the contrary, the M06-2X/6-311+G(d,p) method predicts hydrogen bond lengths which are in agreement with those of the MP2/aug-cc-pVTZ when the geometry is optimized with respect to the BSSE. Thus, the M06-2X/6-311+G(d,p) method is a very good choice. Experimentally, the hydrogen bond lengths of the **A<sub>H</sub>•C<sub>H</sub>** and **C<sub>H</sub>•C<sub>H</sub>** dimers have been measured. For the first one, the experimental OH...O and O...HN hydrogen bond lengths are 1.78 and 1.80 Å,<sup>[14]</sup> whereas our corresponding MP2/aug-cc-pVTZ values are 1.634(1.667) Å and 1.859(1.890) Å; the number in parenthesis corresponds to the BSSE geometry optimization. The difference between experiment and theory is about 0.1 Å. However, in the case of the **C<sub>H</sub>•C<sub>H</sub>** dimer, the agreement between theory and experiment is very good. The experimental value is 1.667 Å,<sup>[12]</sup> whereas our MP2/aug-cc-pVTZ values of 1.660(1.693) Å.

#### R = methyl

In the case of the methyl substituted amides and carboxylic acid homodimers and heterodimer, the dimerization energies are 16.5, 16.0, and 14.3 kcal/mol for the **C<sub>Me</sub>•C<sub>Me</sub>**, **A<sub>Me</sub>•C<sub>Me</sub>**, and **A<sub>Me</sub>•A<sub>Me</sub>** dimers, respectively, at the M06-2X/6-311+G(d,p) level of theory corrected for BSSE or with BSSE geometry optimization, see Figure 1 and Table 1. These values are slightly larger



**Figure 2.** Dimerization energies and hydrogen bond lengths of the **C•C**, **A•C**, and **A•A** dimers with respect to the size of the R substituents at the M06-2X/6-31G(d,p) [open symbol] and M06-2X/6-311+G(d,p) [solid symbol].

than those of the unsubstituted amides and carboxylic acid dimers, that is, with  $R = H$ . The hydrogen bond lengths of the dimers for the case of  $R = \text{methyl}$  are shorter by about  $0.02 \text{ \AA}$  than for the dimers with  $R = H$  at the same level of theory.

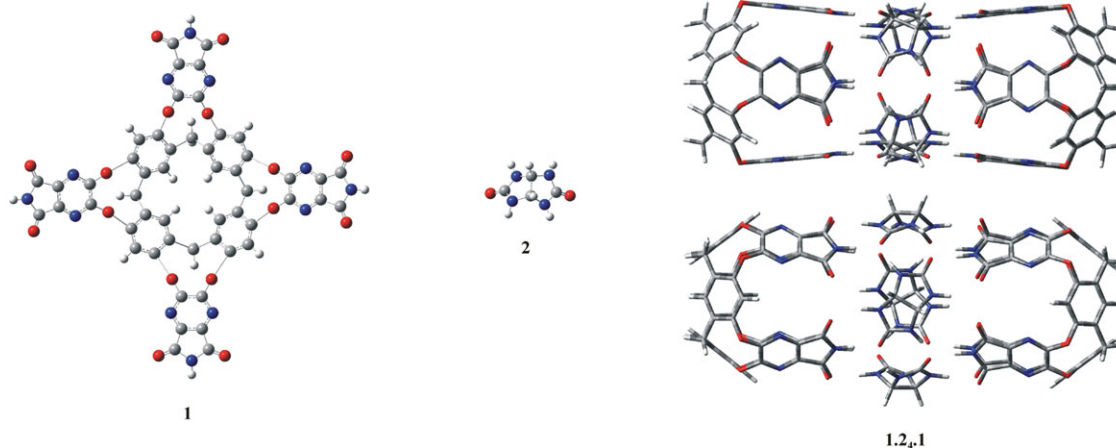
For the dimers with  $R = \text{methyl}$ , as with  $R = H$ , the M06-2X/6-31G(d,p) method predicts similar BSSE corrected dimerization energies ( $\Delta E$ ) with the M06-2X/6-311+G(d,p) method. The differences between the corresponding  $\Delta E$  range from 0.3 to 0.6 kcal/mol. Again, the MP2/6-311+G(d,p) method predicts dimerization energies smaller by up to 5 kcal/mol.

### R = phenyl and p-ethylphenylene

As expected, the phenyl and the *p*-ethylphenylene substituents of amides and carboxylic acid homodimers and heterodimers present nearly the same dimerization energies and geometries, see Table 1 and Supporting Information Table 15. The dimerization energies are 17.1, 16.0, and 13.8 kcal/mol for the **C<sub>p</sub>•C<sub>p</sub>**, **A<sub>p</sub>•C<sub>p</sub>**, and **A<sub>p</sub>•A<sub>p</sub>** dimers (with phenyl substituents) at the M06-2X/6-311+G(d,p) level of theory, and 17.2, 16.0, and 13.7 kcal/mol for the corresponding *p*-ethylphenylene substituents.

We observe a slight increase in the dimerization energy of the carboxylic acid homodimer by 0.7 kcal/mol, a slight decrease in the dimerization energy of the amide homodimer by 0.6 kcal/mol, whereas for the heterodimers, the dimerization energy remains the same when the substituent is changed from methyl to phenyl or *p*-ethylphenylene. Finally, the hydrogen bond length is shorter by  $0.03 \text{ \AA}$  in the carboxylic acid homodimers, shorter by about  $0.01 \text{ \AA}$  for the heterodimers and the same for the amide dimers in the phenyl or *p*-ethylphenylene substituted systems compared to the methyl substituted systems. The trends in the hydrogen bond lengths and the dimerization energies with the size of the substituent are depicted in Figure 2.

The effect of encapsulation for the case of the *p*-ethylphenylene derivatives on the dimerization energies and hydrogen bond lengths is considered here, where the capsule used is the **1.2<sub>4</sub>.1** which consists of two cavitands **1** and four glycoluril molecules **2**, see Figure 3. The encapsulation has been investigated by geometry optimization at the M06-2X/6-31G(d,p) level of theory. The encapsulated dimers are depicted in Figure 4 viewed from two different angles.



**Figure 3.** Structures of the cavitant **1** and glycoluril **2** components and the optimized structure of the **1.2<sub>4</sub>.1** cage viewed from two different angles. (H atoms = white spheres, C = gray spheres, O = red spheres, and N = blue spheres).



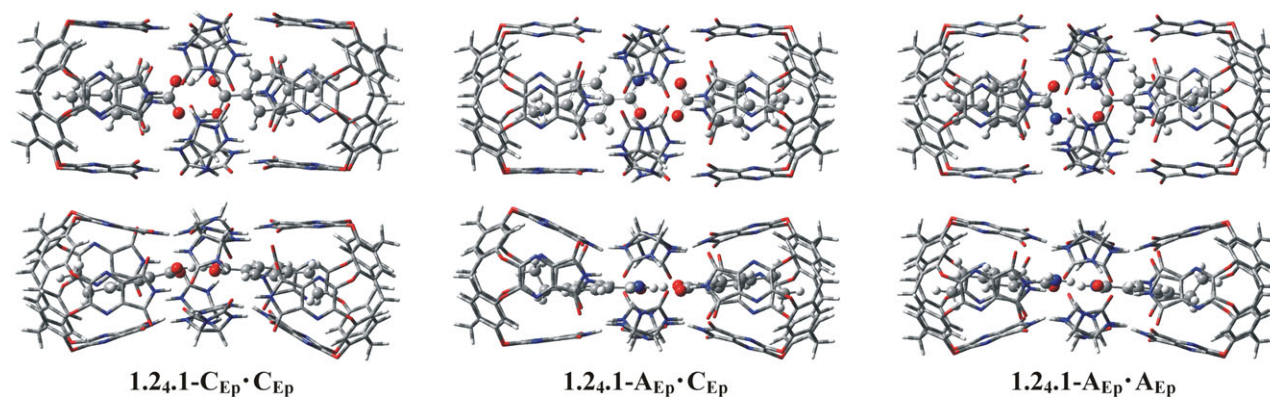


Figure 4. Optimized structures of encapsulated dimers,  $\text{C}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$ ,  $\text{A}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$ , and  $\text{A}_{\text{Ep}}\bullet\text{A}_{\text{Ep}}$  viewed from two different angles. (H atoms = white spheres, C = gray spheres, O = red spheres, and N = blue spheres). The atoms of the capsule are designed with stick bonds for clarity.

As we mentioned above, the M06-2X/6-311+G(d,p) method is a very good choice for the present calculated system, however, if this method is not practical due to the size of the molecules, the alternative M06-2X/6-31G(d,p) method is a good choice for the calculation of the dimerization energies. For the encapsulated systems, which are more than 300 atoms, the M06-2X/6-31G(d,p) method is the only choice. The dimerization energies inside the capsule are decreased by about 2 kcal/mol with respect to the corresponding values of the free dimers in the gas phase. In the homodimers, the hydrogen bond lengths are increased by about 0.04 Å. The interaction energy,  $\Delta E_3$  values, between the cage and the dimers ranges from 38.7 kcal/mol for the carboxylic acid dimer ( $\text{C}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$ ) to 41.7 kcal/mol for the amide dimer ( $\text{A}_{\text{Ep}}\bullet\text{A}_{\text{Ep}}$ ), see Table 2. The

Dimer	$\Delta E_1^a$	$\Delta E_2^a$	$\Delta E_3^a$	$\Delta E^a$
$\text{C}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$	208	56.2	38.7	15.5
$\text{A}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$	209	56.8	40.8	13.7
$\text{A}_{\text{Ep}}\bullet\text{A}_{\text{Ep}}$	208	55.4	41.7	11.6

[a] BSSE corrected interaction energies.

interaction energy,  $\Delta E_2$  values, between the cage and the monomers ranges from 55.4 kcal/mol for the amide dimer ( $\text{A}_{\text{Ep}}\bullet\text{A}_{\text{Ep}}$ ) to 56.8 kcal/mol for the carboxylic acid-amide dimer ( $\text{A}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$ ). Finally, the total interaction energy,  $\Delta E_1$  values, of the encapsulation complexes with respect to the six separate components of the cage and the two monomers is about 208 kcal/mol at the M06-2X/6-31G(d,p) level of theory, see Table 2.

The % dimer distribution of the  $\text{C}\bullet\text{C}$ ,  $\text{A}\bullet\text{C}$ , and  $\text{A}\bullet\text{A}$  dimers is given in Table 3 and Supporting Information, Table 2S. The distributions were calculated taking into account statistical factors, namely, the occurrence of the heterodimer is twice as probable as that of the homodimers. We observe that different methods predict nearly the same distributions even though there are dif-

ferences up to 5 kcal/mol in their corresponding dimerization energies. Moreover, the BSSE correction barely changes the dimer % distribution. The relative amount of the  $\text{C}\bullet\text{C}$  dimer increases slightly, of the  $\text{A}\bullet\text{A}$  dimer decreases slightly, whereas the distribution of the  $\text{A}\bullet\text{C}$  dimer remains the same as the size of the substituent increases. The values are about 26–27, 51, and 22–23% for the free  $\text{C}\bullet\text{C}$ ,  $\text{A}\bullet\text{C}$ , and  $\text{A}\bullet\text{A}$  dimers, respectively. For the encapsulated *p*-ethylphenylene substituent dimers, the % distribution is 28( $\text{C}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$ ), 50( $\text{A}_{\text{Ep}}\bullet\text{C}_{\text{Ep}}$ ), and 22( $\text{A}_{\text{Ep}}\bullet\text{A}_{\text{Ep}}$ ). The corresponding experimental % distributions are 36, 53, and 11%,<sup>[25]</sup> in agreement with the theoretical ones.

## Conclusions

The homodimers and heterodimers of four amides  $\text{RCONH}_2$  and four carboxylic acids  $\text{RCOOH}$ , where R = H, methyl, phenyl, *p*-ethylphenylene have been calculated via DFT(M06-2X)

R	Methods	$\text{C}\bullet\text{C}$	$\text{A}\bullet\text{C}$	$\text{A}\bullet\text{A}$
H	M06-2X/6-31G(d,p)	26.2	51.1	22.7
	M06-2X/6-311+G(d,p)	25.8	51.2	23.0
	MP2/6-311+G(d,p)	25.0	51.3	23.7
	MP2/aug-cc-pVTZ	25.5	50.9	23.6
	MP2/aug-cc-pVTZ <sup>a</sup>	25.5	51.0	23.5
	MP2/aug-cc-pVQZ <sup>b</sup>	25.6	50.9	23.5
Me	RCCSD(T)/aug-cc-pVTZ <sup>b</sup>	25.4	50.8	23.8
	M06-2X/6-31G(d,p)	26.5	50.9	22.6
	M06-2X/6-311+G(d,p)	26.3	51.0	22.8
	M06-2X/6-311+G(d,p) <sup>a</sup>	26.3	51.0	22.8
	MP2/6-311+G(d,p)	26.1	50.2	23.7
	MP2/6-311+G(d,p)	26.3	50.9	22.7
Ph	M06-2X/6-31G(d,p)	27.7	50.7	21.6
	M06-2X/6-311+G(d,p)	27.2	50.9	21.9
	MP2/6-311+G(d,p)	26.3	50.9	22.7
EthPh <sup>c</sup>	M06-2X/6-31G(d,p)	27.7	50.7	21.6
	M06-2X/6-311+G(d,p)	27.3	50.9	21.8
	M06-2X/6-311+G(d,p) <sup>a</sup>	27.3	50.9	21.8
EthPh <sup>c,d</sup>	M06-2X/6-31G(d,p)	28.4	50.3	21.3
	Expt <sup>e</sup>	36	53	11

[a] BSSE optimized geometry. [b] At the optimized MP2/aug-cc-pVTZ geometry. [c] *p*-ethylphenylene. [d] Coencapsulated dimers in the 1.24.1 cage. [e] Ref. [24].

methodology and MP2 and CCSD(T) methods in conjunction with the 6-31G(d,p), 6-311+G(d,p), aug-cc-pVTZ, and aug-cc-pVQZ basis sets. The aim is to find out how the size of the substituent R influences their dimerization energy and their hydrogen bond length. Moreover, the coencapsulation of the dimers was also considered. Our main conclusions are:

1. The dimerization energy values and the geometries at the M06-2X/6-311+G(d,p) functional are in very good agreement with the corresponding values at the MP2/aug-cc-pVQZ and CCSD(T)/aug-cc-pVTZ.

2. The calculated dimerization energy values range from 14 to 17 kcal/mol for the different dimers in the gas phase, with the ordering carboxylic homodimers  $\geq$  amide-carboxylic dimers  $>$  amide homodimers. Only, for the unsubstituted dimers, the carboxylic homodimer has the same dimerization energy with the amide-carboxylic dimer.

3. For the **C•C** dimers, the hydrogen bond length decreases and the dimerization energy increases as the size of the R group increases.


4. For the **A•C** dimers, the hydrogen bond length decreases and the dimerization energy remains nearly the same as the size of the R group increases.

5. For the **A•A** dimers, the hydrogen bond length at first decreases and then increases; the dimerization energy at first remains the same and then decreases.

6. The dimer % distributions taking into account statistical factors are nearly the same for different methods. The values are about 26–27, 51, and 23–22% for the free **C•C**, **A•C**, and **A•A** dimers, respectively, for the four groups of dimers. For the encapsulated dimers, the % distribution in agreement with the experimental distributions.

**Keywords:** formic acid • carboxylic acid • formamide • amide • calculations • DFT • homodimers • heterodimers-encapsulation • cages

How to cite this article: D. Tzeli, I. D. Petsalakis, G. Theodorakopoulos, D. Ajami, J. Rebek, Jr, *Int. J. Quantum Chem.* **2013**, *113*, 734–739. DOI: 10.1002/qua.24062

 Additional Supporting Information may be found in the online version of this article.

- [1] Recent Theoretical and Experimental Advances in Hydrogen Bonded Clusters; S. S. Xantheas, Ed.; Kluwer Academic Publishers, NATO ASI Series C: Mathematical and Physical Sciences, **2000**, 561.
- [2] G. R. Desiraju, T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: New York, **1999**.
- [3] G. A. Jeffrey, W. Saenger, *Hydrogen Bonding in Biological Structures*; Springer: Berlin, **1991**.
- [4] G. Gilli, P. Gilli, *J. Mol. Struct.* **2000**, *552*, 1.
- [5] R. W. Gora, S. J. Grabowski, J. Leszczynski, *J. Phys. Chem. A* **2005**, *109*, 6397.

- [6] H. Pašalić, A. J. A. Aquino, D. Tunega, G. Haberhauer, M. H. Gerzabek, H. C. Georg, T. F. Moraes, K. Coutinho, S. Canuto, H. Lischka, *J. Comput. Chem.* **2010**, *31*, 2046.
- [7] R. García-Fandiño, L. Castedo, J. R. Granja, S. A. Vázquez, *J. Phys. Chem. B* **2010**, *114*, 4973.
- [8] J. M. Briggs, T. B. Nguyen, W. L. Jorgensen, *J. Phys. Chem.* **1991**, *95*, 3315.
- [9] L. Leiserowitz, *Acta Crystallogr. B* **1976**, *32*, 775.
- [10] (a) M. J. Krische, J.-M. Lehn, *Struct. Bonding* **2000**, *96*, 3; (b) L. J. Prins, D. N. Reinhoudt, P. Timmerman, *Angew. Chem., Int. Ed.* **2001**, *40*, 2383; (c) P. Rodríguez-Cuamatzi, O. I. Arillo-Flores, M. I. Bernal-Uruchurtu, H. Höpfl, *Cryst. Growth Des.* **2005**, *5*, 167.
- [11] A. Fernandez, T. R. Sosnick, A. Colubri, *J. Mol. Biol.* **2002**, *321*, 659.
- [12] J. E. Bertie, K. H. Michaelian, *J. Chem. Phys.* **1982**, *76*, 886.
- [13] B. Lucas, G. Grégoire, F. Lecomte, B. Reimann, J. P. Schermann, C. Desfrancois, *Mol. Phys.* **2005**, *103*, 1497.
- [14] A. M. Daly, B. A. Sargus, S. G. Kukolich, *J. Chem. Phys.* **2010**, *133*, 174304.
- [15] M. K. Hazra, T. Chakraborty, *J. Phys. Chem. A* **2005**, *109*, 7621.
- [16] L. F. Pacios, *J. Comput. Chem.* **2005**, *27*, 1641.
- [17] E. Sánchez-García, L. A. Montero, W. Sander, *J. Phys. Chem. A*, **2006**, *110*, 12613.
- [18] P. Dediková, M. Pitoňák, P. Neogrady, I. Černušák, M. Urban, *J. Phys. Chem. A* **2008**, *112*, 7115.
- [19] A. Mardyukov, E. Sánchez-García, P. Rodziewicz, N. L. Doltsinis, W. Sander, *J. Phys. Chem. A* **2007**, *111*, 10552.
- [20] S. J. Grabowski, *J. Phys. Org. Chem.* **2008**, *21*, 694.
- [21] (a) A. Bende, S. Suhai, *Int. J. Quantum Chem.* **2005**, *103*, 841; (b) L. E. Fernandez, A. C. G. Marigliano, E. L. Varetto, *Vib. Spectrosc.* **2005**, *37*, 179; (c) I. Wolfs, H. O. Desseyn, *J. Mol. Struct. (Theochem)* **1996**, *360*, 81.
- [22] J. F. Lu, Z. Y. Zhou, Q. Y. Wu, G. Zhao, *J. Mol. Struct.-Theochem.* **2005**, *724*, 107.
- [23] (a) J. Czernek, *J. Phys. Chem. A* **107**, **2003**, 3952; (b) P. Hobza, Z. Havlas, *Collection Czechoslovak Chem. Commun.* **1998**, *63*, 1343.
- [24] D. Tzeli, G. Theodorakopoulos, I. D. Petsalakis, D. Ajami, H. Dube, J. Rebek, Jr., *J. Am. Chem. Soc.* **2011**, *133*, 16977.
- [25] D. Ajami, H. Dube, J. Rebek, Jr., *J. Am. Chem. Soc.* **2011**, *133*, 9689.
- [26] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215; (b) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157.
- [27] L. A. Curtiss, M. P. McGrath, J. -P. Blaudeau, N. E. Davis, R. C. Binning, Jr., L. Radom, *J. Chem. Phys.* **1995**, *103*, 6104.
- [28] T. H. Dunning, Jr., *J. Chem. Phys.* **1989**, *90*, 1007.
- [29] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.
- [30] S. S. Xantheas, *J. Chem. Phys.* **1996**, *104*, 8821.
- [31] (a) B. Jeziorski, R. Moszynski, K. Szalewicz, *Chem. Rev.* **1994**, *94*, 1887; (b) D. Tzeli, A. Mavridis, S. S. Xantheas, *J. Phys. Chem. A* **2002**, *106*, 11327.
- [32] Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Menonucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision A.1, Gaussian: Wallingford CT, **2009**.
- [33] D. Tzeli, I. D. Petsalakis, G. Theodorakopoulos, *J. Phys. Chem. A* **2011**, *115*, 11749.
- [34] D. Tzeli, I. D. Petsalakis, G. Theodorakopoulos, *Phys. Chem. Chem. Phys.* **2011**, *13*, 11965.

Received: 15 December 2011  
Revised: 15 December 2011  
Accepted: 30 January 2012  
Published online on 29 March 2012