On the energetic and geometric description of the interaction between the isonipecotic and 1,1-cyclobutanedicarboxilic acids

Alejandro Rojas\textsuperscript{a}, Luis E. Seijas\textsuperscript{b}, Lusbely M. Belandria\textsuperscript{b} and Rafael Almeida\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a}Laboratorio de Procesos Dinámicos en Química, Departamento de Química, Facultad de Ciencias, Universidad de Los Andes, Mérida, Venezuela
\textsuperscript{b}Laboratorio de Cristalografía, Departamento de Química, Facultad de Ciencias, Universidad de Los Andes, Mérida, Venezuela

Received 31 March 2011
Accepted /Revision 9 March 2012

Abstract. Recently, multi component crystals composed of two or more molecules that form a unique crystalline structure having unique phase and properties, where its components are bond together via hydrogen bonds, have been the subject of great deal of attention, in particular those where aminoacids participate in their structure. In this work we have studied a system formed by the acids 1,1-cyclobutanedicarboxilic and isonipecotic. We have analyzed the HB-network present in the crystallographic system and compared it with that found computationally. Next, we have studied the energetic of the system and the factors that lead to its stabilization. Finally a comparison between the geometry of the crystallographic packing and that obtained from the computational calculations has been carried out, looking for an understanding of the elements that lead to the observed relative distribution and orientations of the participant molecules, i.e. to the special arrangement of the reported crystallographic structure.

Keywords: Cocrystal, hydrogen bond, supramolecular structure

PACS: 81.16.Fg

1. Introduction

Hydrogen bonds have a great impact in our daily life. The particular properties of water, indispensable to life, respect to those shown by similar molecules formed by the same periodic group atoms are consequence of the formation of hydrogen bond (HB) networks. Since life has evolved in an aqueous environment, it is not surprising that the existence of HB plays a crucial role in the formation of biological structures, in the processes in which they participate, and also, due to their strong directionality, the HBs are considered important contributors to the selectivity present in biological interactions [1]. On the other hand, the aminoacids constitute the building blocks of peptides and proteins. In these biological systems, non covalent interactions play a key role in many of the process where they take part, in

\textsuperscript{*}Corresponding author: Rafael Almeida, Laboratorio de Procesos Dinámicos en Química, Departamento de Química, Facultad de Ciencias, Universidad de Los Andes, Mérida 5101, Venezuela. E-mail: mata@ula.ve.
their energetic behavior, and; therefore, in the stabilization of their structures. Among these non covalent interactions, HB is one of the most important and is responsible for several of the main characteristics of these systems, including their crystal packing, and some of the intermolecular interactions in which they are involved. Hence, it is not surprising that numerous studies have been performed to estimate the stabilization energy of these biological systems, and that among them; quantum chemically calculated energy variation analysis has been employed as a very important mean to understand and characterize hydrogen bonded systems [2–4]. This kind of analysis has proved to be particularly significant for characterizing molecular crystals constructed from discrete, individual molecules, as in the aminocid case, forming hydrogen bonded structures. Before continuing, it is important to mention that although the HB strength is about one order of magnitude smaller than that of the covalent bonds, their significant importance emerges from the fact that due to the HB polar nature, they strongly interact with each other; therefore, a HB integrated into a network of HBs will enhance its bond strength, which will also modify its geometry, vibrational frequencies, etc. This effect, known as cooperativity, makes the HB interactions strongly nonlinear, i.e. no additive.

Lately, thanks to its potential variety of applications, the developing of cocrystal has arisen a great deal of attention [5]. This is not surprising since applications have been reported in the fields of material science, i.e. improving of materials with energetic uses, and more widely in that of pharmaceutical drug design. There is not a uniquely accepted definition for the cocrystals, here we will adopt that stating that they are multi component crystals composed of two or more molecules that form a unique crystalline structure, having unique phase and properties, where its components are bonded together via non-covalent interactions, mainly hydrogen bonds [6]. Among their applications, it has been reported that cocrystals may incorporate pharmaceutical acceptable guest molecules into a crystal lattice along with the active pharmaceutical ingredient (API), without affecting its pharmacological activity, which makes them alternative attractive solid forms for drug development. Additionally, cocrystallization allows improving the physicochemical properties of pharmaceuticals (solubility, hygroscopicity, stability, bio-availability, etc.), and even allows the possibility of introducing two or more API into a solid drug. All this translates in new opportunities for diversifying drug substances that could exhibit improved balance of important properties [7]. One of the issues of great importance for understanding cocrystal formation, and eventually designing and predicting the activities of new drugs is the comprehension and characterization of the non-covalent binding networks that lead to the formation of the cocrystals. In this direction, recently a crystallographic and spectroscopic study of several cocrystals has been presented [8]. Among them, the cocrystal formed by the acids 1,1-cyclobutanedicarboxilic and isonipecotic was considered. In this work, we will study the HB-network present in this system; we will analyze the cocrystal energetic and geometrical properties, looking for an understanding of the factors that lead to the relative distribution and orientations of the participant molecules, that is to the three dimensional arrangement of the reported structure.

2. The system

The 1,1-cyclobutanedicarboxilic acid: isonipecotic acid cocrystal was recently characterized employing infrared spectroscopy, thermo gravimetric analysis, differential scanning calorimetry and X-ray diffraction [8]. The results of these studies lead to conclude that the cocrystal asymmetric unit is formed by a positively charged molecule of the isonipecotic acid and a negatively charge molecule of acid 1,1-cyclobutanedicarboxilic. The positive charge on the isonipecotic acid, results from the bonding of the nitrogen atom to two hydrogen ones. This molecule has a chair conformation with the carboxylic
A. Rojas et al. / On the energetic and geometric description of the interaction

Fig. 1. Partial packing view of the crystal structure for the cocrystal constituted by the acids 1,1-cyclobutanedicarboxilic and isonipecotic.

group in the axial position. It was also found that the ciclobutane of the 1,1-cyclobutanedicarboxilic acid is not planar. A partial packing view of the crystal structure through the bc plane is illustrated in Fig. 1. From there, one observes the existence of zig-zag supramolecular chains, oriented along the c-axis Fig. 6(b(I)). These chains, described by a first order C(6) graph set, are constituted by molecules of the 1,1-cyclobutanedicarboxilic acid and are consequence of the formation of consecutives HB of the type O—H···O, with the cyclobutane rings oriented toward the same side of the chain. From that figure, it is also clear that these chains interact among themselves through molecules of aminoacids. On one side, the amino group acts as a double proton donor. There, one of the hydrogens interacts with the oxygen of one carboxylic group of the acid molecule, while the other amino-hydrogen forms a HB with the carboxylate oxygen of a neighbor acid molecule on the same chain. On the other side of the molecule, the amino acid carboxylic group also acts as a proton donor, forming HBs with one of the oxygen atom of an acid molecule at the other chain. In addition to this HB, this oxygen is also hydrogen bonded to one of the amino hydrogen of a neighbor bridge aminoacid molecule. The result is a supramolecular ring, of the interaction of four molecules, described by a $R_2^2(18)$ graph Fig. 6(a(I)). These interactions lead to the formation of a complex and efficient crystal packing, with a percentage of occupy space of 70.8%.

3. Semi-empirical calculations

The previous section shows that the considered system displays a complex crystalline packing, as a consequence of this, a detailed and exact characterization of the studied cocrystal involves intensive and exigent calculations and requires expensive computational tasks. Thus, after taking these facts into account, together with the computational resources available for carrying out this kind of study; we have decided to utilize approximated semi-empirical methods instead. It has been reported [9,10] that for the kind of molecules participating in the system, which are interacting through HB, the AM1 [11] renders results comparable with those obtained at the Hartree Fock level of calculation or obtained.
A. Rojas et al. / On the energetic and geometric description of the interaction

Fig. 2. In the first row, the optimized structures of the neutral and positively charged isonipecotic acid molecules are displayed. The second row corresponds to the neutral and charged 1,1-cyclobutanedicarboxilic acid molecules. The dashed lines represent the intra molecular HBs.

Fig. 3. Optimized Geometry of the six-member cluster formed through the interaction of three 4-piperidinic acid molecules and three 1,1-cyclobutanedicarboxilic acid molecules.

experimentally. This has been tested by us [12], for a system formed by the 1-aminocyclopentano-1-carboxilic acid interacting with oxalic acid and water, through calculations employing the AM1 and PM3 semi-empirical methods, together with Hartree Fock level calculations. We found that the AM1 and Hartree Fock qualitative trends are the same, while their numerical results are comparable. This was not the case for the results obtained from the PM3 calculations. Additionally, recently the new PM6 method [13] was augmented with a transferable H-bonding correction, PM6-DH2, which was reported to achieve large improvements in accuracy for interaction energies of systems similar to those studied here [14]. Thus, here we have performed the calculations employing both, the AM1 and the PM6-DH2 methods.

In this work, we compute the stabilization energy, due to the formation of the clusters, per participating molecule, this is:

\[ \Delta E = \frac{ET - (nE_{an} + mE_{dn})}{n + m} \]  

Here \( ET \) is the total energy for the cluster, \( E_{an} \) is the energy of the optimized molecule of isonipecotic acid with a chair conformation and the carboxylic group in the axial position, \( n \) is their number in the cluster, \( E_{dn} \) is the energy of the optimized molecule of 1,1-cyclobutanedicarboxilic acid and \( m \) is the number of them in the cluster. The calculation of \( \Delta E \) allows evidencing the cooperative enhancement in the formation energy of the clusters [15–17]. Additionally, this quantity is well suited for extrapolations toward \( (n + m) \rightarrow \infty \), which is the case of extended chains. This extrapolation is useful for obtaining estimates of the stabilization energies of extended systems, as the ones considered in this work [18].

3.1. Small cluster geometries and hydrogen bond networks

The geometry of the optimized monomers is exhibited in Fig. 2, all these molecules have intra molecular HBs, which are represented as dashed lines in the figure. For both of the employed methods, at the
Fig. 4. (a) Variation of the stabilization energy per participating molecule with the number of monomers in the cluster, $\Delta E$. (b) Variation of $\Delta E$ in function of the inverse of the number of monomers, $1/n$. Continuous green and dotted red lines correspond to the neutral specie cluster at AM1 and PM6-DH2, respectively. Purple and blue dashed lines correspond to the charged system at AM1 and PM6-DH2 respectively, while the black dotted lines represent the extrapolation to infinite monomers.

scale displayed in the figure, the geometrical results are undistinguishable from each other. The calculated values of $E_{an}$ and $E_{dn}$ are, respectively, $-40792.27$ and $-49830.11$ Kcal/mol for the AM1 method, and $-38323.23$ and $-46748.36$ Kcal/mol for the PM6-DH2 one. Before continuing, let us mention that similar relative qualitative behavior between the PM6-DH2 and AM1 results was already reported [14] for hydrogen-bonded complexes. The optimized geometry of the dimer is found starting from optimized monomers at several intermolecular relative orientations. Once this structure was obtained, a monomer is randomly placed close to it, and optimization of the trimer is carried out. This procedure is repeated many times and the result reported corresponds to the obtained minimum having the smallest energy. For larger clusters two methodologies are employed to generate the initial geometry. The first follows similar steps than those explained for the trimer, while in the second, the optimized structures corresponding to smaller size clusters are randomly placed close to each other. For the cases involving several unit cells, the initial geometry is constructed from the result obtained for one unit cell, which is repeated following the crystallographic pattern, after which the optimization is performed. For all the cases, the AM1 optimized structures are taken as the initial geometries for the PM6-DH2 optimization. The result obtained for the six molecule cluster is presented in Fig. 3. Notice that in spite of the cluster size, the aminoacids, as in the crystallographic result, act as bridges between the diacid molecules, which have the ciclobutane rings approximately oriented to the same side. For all the studied clusters, the AM1 method renders HB distances approximately 10% larger than those computed from the PM6-DH2 one, while all the angles and bond distances are approximately the same for both methods. It is important to mention that, in average, regardless of the employed method the HB-distances decrease with cluster size, which could be taken as an indication of the presence of cooperative effects.

3.2. Energetic analysis

For the fully optimized clusters, the variation of the stabilization energy per participating molecule ($\Delta E$) is displayed in Fig. 4. Looking to explore the role of the charges in the structure stabilization, we have carried out a numerical experiment: we have repeated the whole procedure explained so far, but instead of employing charged molecules, as the ones reported experimentally, we have started from neutral ones. For both of the employed semiempirical methods, the results indicate that the geometry and HB
network are quite similar to that obtained for the charged species; nevertheless, from the energetic point of view there are some differences. The energy results, displayed in Fig. 4, show that the AM1 method renders for the charge specie structure, absolute values of $\Delta E$ that are approximately an order of magnitude larger than those of the fictitious neutral one. On the other hand, the PM6-DH2 results also indicate that the charged systems are the most stable ones; however, in this case the additional stabilization only amounts to approximately 50% of the values of $\Delta E$ for the fictitious neutral systems. In spite of this quantitative difference, it is also observed that both methods display the same qualitative behavior: the stabilization grows faster for the charged molecule clusters. If the dependence of $\Delta E$ with the cluster size is considered in terms of the inverse of $(n + m)$, nearly perfect linear behaviors are obtained. This fact, allows us to perform an extrapolation to the asymptotic limit of infinite structures, $(n + m) \to \infty$, which for the AM1 method leads to an estimate of $-4.73$ and $-63.46$ kcal/mol for the neutral and charged molecule cases, while for the PM6-DH2 one, the results are $-11.94$ and $-17.93$ kcal/mol, respectively. The trends represented by these results, together with the average geometrical tendencies, evidence the existence of cooperative effects in the cluster formation; furthermore, they also show the importance of the electrostatic interactions in the structure formation. Looking to get more insights on the role of each of the cocrystal participants in the structure stabilization, we have performed several additional fictitious numerical experiments, and for each case we have obtained the values of $\Delta E$ for $(n + m) \to \infty$. In the first one, we have considered clusters only formed by each of the individual components of the cocrystal in their neutral form. For the 1,1-cyclobutanedicarboxilic acid clusters, the asymptotic value of $\Delta E$ is $-6.83$ and $-9.84$ kcal/mol for the AM1 and PM6-DH2 methods respectively, while for the 4-piperidinic acid clusters, those asymptotic values are $-4.73$ and $-8.24$ kcal/mol. Let us point out that these last results are close (especially for the AM1 method) to that obtained for the fictitious neutral cocrystal cluster, which seems to agree with the crystallographic finding Figs 1 and 6(a) that the aminoacid mediated HB interactions are determinant in the energetic of this system. Next, one of the molecules is charged, aminoacid or diacid, and is allowed to interact with neutral molecules. This can be thought as a salvation experiment, where the charged specie is surrounded by neutral molecules interacting with it through the formation of HBs, which lead to the stabilization of the system. If a charged 4-piperidinic acid molecule is allowed to interact with other neutral aminoacid molecules, the asymptotic stabilization energy is $-12.97$ kcal/mol for the AM1 method and $-13.77$ for the PM6-DH2 one. On the other hand, if it interacts with neutral diacid molecules these energy values are $-12.83$ and $-15.05$ kcal/mol. For the charged 1,1-cyclobutanedicarboxilic acid molecule interacting with neutral diacid ones, the asymptotic stabilization energy is $-10.54$ kcal/mol for the AM1 method and $-14.96$ for the PM6-DH2 one, while the interaction with neutral aminoacids leads to an stabilization energies of $-9.34$ and $-11.47$ kcal/mol. These results lead us to think that, for all these cases, the value of the stabilization energy is mostly dependent on the kind of charged molecule, and is less dependent on the type of molecules interacting with it. At this point, it is important to emphasize the fact that, with the charge on the molecules also increases the number of HB in which they may participate (in the aminoacid case, there is an additional hydrogen bonded to the nitrogen, while in the diacid molecule there is one extra free-pair of electrons on one of the carboxilate oxigens), which would explain the previous results regarding the stabilization of the charged clusters and would reflect the importance of the HB-interactions in the studied cocrystal clusters.

3.3. Comparison with the crystallographic results

Next, we compare the result obtained for the optimized structure corresponding to the crystal unit cell (Fig. 5) with that reported crystallographically (Fig. 1). We first notice that, coarsely, both results contain
Table 1

<table>
<thead>
<tr>
<th>Angle</th>
<th>Crystallographic (°)</th>
<th>Computational AM1 (°)</th>
<th>Computational PM6-DH2 (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₄-C₅-C₆</td>
<td>88.5</td>
<td>89.4</td>
<td>89.2</td>
</tr>
<tr>
<td>C₃-C₄-C₆</td>
<td>88.7</td>
<td>90.2</td>
<td>90.2</td>
</tr>
<tr>
<td>C₃-C₆-C₅</td>
<td>89.4</td>
<td>90.1</td>
<td>90.3</td>
</tr>
<tr>
<td>C₆-C₅-C₃</td>
<td>88.2</td>
<td>90.2</td>
<td>90.2</td>
</tr>
</tbody>
</table>

The same type of supramolecular structures, responsible for the existence of the extended system. In spite of
the same type of supramolecular structures, responsible for the existence of the extended system. In spite
that these interactions, responsible for the formation of these supramolecular structures, were discussed
in Section 2, let us here summarize their main features, details of which are displayed in Fig. 6:

a) The aminoacids molecules act as bridges between the diacid ones forming four member supramolecular ring units, in a sandwich kind arrangement, described by a R²₄(18) graph Fig. 6(a).

b) The molecules of the 1,1-cyclobutanedicarboxilic acid are hydrogen bonded among themselves leading to the formation of zigzag supramolecular chains, with the cyclobutane rings oriented toward the same side, opposite to the center of the supramolecular ring. These chains are approximately directed along the c-axis and are described by a first order C(6) graph set Fig. 6(b).

Fig. 5. Optimized Geometry of the cluster corresponding to the unit cell of the cocrystal constituted by the 4-piperidin-1,1-cyclobutanedicarboxilic acids.

From the results represented by Figs 5 and 6, it is first noticed that the HB network responsible for the
formation of the crystallographic structure (Fig. 1) is essentially the same than that obtained in the computa-
tional results. Also, by inspecting these figures, one may conclude that the main differences appear for the chain supramolecular structure. Thus, as a first step, we will compare the geometrical characteristics of the participating diacid molecular units. Figure 7 displays the structures of these molecules entering into the extended structure (crystallographic case) and in the isolated unit cell (computational results), and Table 1 shows the values of their internal angles. From this Table one first notice that, as mentioned before, the two employed semiempirical methods render approximately the same geometrical results, also, it is clear that for all the sets, the results are close to 90°, and the largest difference between them is of about 2°. Nevertheless, by inspecting Fig. 7 one can observe that in the cocrystal, the cyclobutane ring departed from the planarity, which is not the case for the computational result. Thus, as is illustrated in Fig. 8(a), for the cocrystal, the angle formed between the C₄-C₅-C₆ and the C₃-C₄-C₆ planes is 24, 3°; while the equivalent result found for the computational case is 2, 3° for the AM1 method and 1, 4° for the PM6-DH2 one. The difference becomes even clearer if the Newman projections along the C₃-C₄ bonds are compared. Figure 8(b) shows that for both cases, the C₁-H₁ and C₂-H₂...
Fig. 6. Comparison between the supramolecular structures obtained crystallographically (I) and computationally (II). (a) cyclic four-member supramolecular units in a sandwich kind arrangement; (b) 1,1-cyclobutanedicarboxilic acid molecule zigzag chain extending along the c-axis.

Fig. 7. Crystallographic (left) and computationally optimized (right) structures of the molecules of the 1,1-cyclobutanedicarboxilic acid in the chains along the c-axis.

are not eclipsed. However, for the cocrystal the dihedral angles between these bonds are 18°, and 22° respectively, whereas those obtained from the AM1 method are 1° and 4°, and from the PM6-DH2 one are 0.7° and 4°.

Since the zigzag chain extends throughout the crystal, one may think that these differences, together with those in the relative orientation of the cycobutane are mainly due to the border effects, consequence of the small size of the considered unit cell, or to the lack of consideration of the stacking effects, due
Table 2

<table>
<thead>
<tr>
<th>Angle</th>
<th>Crystallographic (°)</th>
<th>Computational (°) Unit Cell (AM1)</th>
<th>Computational (°) Unit Cell (PM6-DH2)</th>
<th>Computational (°) Stacking of Unit Cell (AM1)</th>
<th>Computational (°) Stacking of Unit Cell (PM6-DH2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₄-C₃-C₅</td>
<td>88.5</td>
<td>89.4</td>
<td>88.4</td>
<td>88.4</td>
<td>87.9</td>
</tr>
<tr>
<td>C₃-C₄-C₆</td>
<td>88.7</td>
<td>90.2</td>
<td>90.2</td>
<td>90.2</td>
<td>87.8</td>
</tr>
<tr>
<td>C₄-C₆-C₅</td>
<td>89.4</td>
<td>90.1</td>
<td>90.3</td>
<td>90.3</td>
<td>89.5</td>
</tr>
<tr>
<td>C₆-C₅-C₃</td>
<td>88.2</td>
<td>90.2</td>
<td>90.2</td>
<td>86.0</td>
<td>89.0</td>
</tr>
</tbody>
</table>

Fig. 8. Geometrical results for the ring of the 1,1-cyclobutanedicarboxilic acid molecule: Crystallographic at the left and computationally optimized at the right. (a) Molecular conformations, where should be noticed the difference between the values of the angle formed between the C₃-C₅-C₆ and the C₃-C₄-C₆ planes; (b) Newman projections along the C₃-C₄ bond. Here, notice the difference between the values of the C₁-H₁ and C₂-H₂ dihedral angles for each of the different kind of results. For all the cases, the results obtained from the PM6-DH2 method is shown in parenthesis.

In order to explore the first of the previous possibilities, we have carried out a calculation where, following the crystallographic pattern, we have placed 9 optimized unit cells (3 x 3) in the b-c plane. Figure 9 exhibits the results obtained for the central part of this cluster, where the border effects are not expected to be of importance. From there, one again can observe the existence of the HB network responsible for the structure formation, and whose characteristics have been already described. But, additionally, after inspection one notices that the relative orientation of the cycobutanes in the diacid zigzag chains becomes similar to that found in the crystallographic results, indicating that the relative orientation differences observed in Fig. 6(b) arise as a consequence of not taking into account the crystal extended structure. Nevertheless, this inspection also shows that the cycobutanes remain approximately planar. Looking for some more clues to solve this piece of the puzzle, we have considered the crystallographic stacking by simulating a system where several unit cells are piled up along the a-axis, again following the crystallographic pattern. The results obtained for the central diacid molecules in this computational experiment are displayed in Table 2 and Fig. 10. From Fig. 10(a) is clear that in this case the cyclobutane rings depart from the planarity. Thus, as is illustrated...
Fig. 9. Optimized Geometry of the cluster of the 4-piperidinic acid-1,1-cyclobutanedicarboxilic acid cocrystal, corresponding to 9 unit cells ($3 \times 3$) placed in the crystallographic b-c plane. In the figure is only displayed the central part of this cluster, where the border effects are not expected to be important.

Fig. 10. Geometrical results for the ring of the 1,1-cyclobutanedicarboxilic acid molecule corresponding to the simulation of the stacking of several unit cells. (a) Structure of the diacid molecules; (b) Molecular conformation, noticed the value of the angle formed between the $C_3$-$C_5$-$C_6$ and the $C_3$-$C_4$-$C_6$ planes; (c) Newman projections along the $C_3$-$C_4$ bond. Here, notice the increasing in the values of the $C_1$-$H_1$ and $C_2$-$H_2$ dihedral angles respect to that found for one unit cell. Angles values in parentheses correspond to the PM6-DH2 results.

In Fig. 10(b), under these conditions the angle formed between the $C_3$-$C_5$-$C_6$ and the $C_3$-$C_4$-$C_6$ planes is 30, 8° for the AM1 method and 25, 64° the PM6-DH2 one; while the equivalent result found for the crystallographic measure is 24, 33°. Finally, Fig. 10(c) displays the Newman projections along the $C_3$-$C_4$ bonds, showing that the dihedral angles between $C_1$-$H_1$ and $C_2$-$H_2$ in the cocrystal are 18° and 22° respectively, whereas the AM1 computational results are 24° and 22°, and the PM6-DH2 ones are 22° and 18° respectively. Table 2, shows that for all the cases, the values of their internal angles are approximately 90° and the largest difference between them remain at about 2°. Let us mention that for these cases, in comparison with the crystallographic measures, the PM6-DH2 method performs slightly
better than the AM1 one. The outcome of this last group of numerical experiments confirms that the previously obtained discrepancies between the results corresponding to the unit cell and those rendered by the crystallographic data are consequence of only considering a small size cluster for describing the cocrystal structure.

4. Summary and comments

In this work, through semi-empirical calculations, we have reproduced and characterized the HB network present in the cocrystal constituted by the acid 4-piperidinic and the acid 1,1-cyclobutanedicarboxylic. It has been found that even in the small clusters the main features responsible for the formation of the cocrystal are present. The results of the energetic analysis, together with the average geometrical tendencies, evidence the existence of cooperative effects in the cluster and in the cocrystal formation; furthermore, they also show the importance of the presence of charged species in the cocrystal structure, which increases the stabilization energy of the system respect to the fictitious neutral structure. Additionally, the performed computational experiments indicated that the presence of a charged molecule is enough to enhance appreciably the stabilization energy, respect to the values obtained for the equivalent neutral systems. This could be understood if we realized that along with the charge on the molecules also increases the number of HB in which they may participate, which reflect the importance of this kind of interactions in the cocrystal stabilization. Finally when comparing the results obtained for the unit cell and those corresponding to the crystallographic analysis, one concludes that even this crude modeling of the cocrystal is capable to reproduce its main features and interactions, responsible for the formation of these supramolecular structures. The remaining differences are accounted for when border effects, due to the finite size of the unit cell, and stacking effects present in the crystal packing are taking into consideration. Finally is important to point out the fact that approximated methods, as the one employed here, turn out to be very useful, and in some cases even necessary, when complex and large systems need to be studied. Thus, even though the results are not expected to be quantitative, they are able to explain the interactions or process present in the systems and the understand the obtained trends.

Acknowledgments

This work has been supported by the CDCHT of the Universidad de los Andes (grant No C-1618-08-08-AA). The authors are grateful with Prof. Luis Rincon for his valuable computational advice.

References