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Influence of Dispersive Forces in the Final Shape of a Reverse Micelle

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Micelles are interesting self-organized structures with multiple applications in chemistry and related with the formation of biological structures. Their final shape depends on a subtle equilibrium between several weak forces: namely, van der Waals and hydrogen bond interactions. In order to address the influence of each type of interaction, the aggregation of cyclohexanol molecules was studied in the gas phase. The geometry of the clusters formed with sizes from 2 to 6 cyclohexanol molecules was elucidated by an IR double resonance technique that combines fs and ns lasers. Comparison of the structures obtained with those from previous works demonstrates that hydrogen bond plays a central role defining the general shape, but that its contribution to the overall stabilization energy may be lower than expected in systems with multiple C-H···π interactions

Introduction

Since the introduction of supersonic expansions as a cold, high-density molecular source and to simplify the spectra of atom and molecules,[1-4] the study of molecular aggregates has been a hot topic, due to the relevance of the data that such studies offer. Certainly, the non-covalent interactions that drive molecular aggregation in the jets are also responsible for very fundamental phenomena as the non-ideal behaviour of real gases, but they also drive the formation of important structures for life, such as ice or the macromolecular ensembles in the cells.[5]

Among the key phenomena driven by non-covalent interactions, nucleation, the process by which a new phase is formed inside another,[6;7] is one of the most difficult to describe accurately,[8;9] as aggregation is triggered by the fluctuation of just a few molecules inside the mother phase,[10;11] and therefore, it has a strong chaotic component.

From a molecular point of view, we can divide the long-range forces that drive the aggregation of those first molecules into hydrogen bond and van der Waals interactions.[12-16] The main difference between the two groups is the strongly directional nature of hydrogen bond, which looses strength very fast as the three atoms implicated in the interaction move away from linearity. In previous works,[17;18] using supersonic expansions and mass-resolved spectroscopy, we demonstrated that during formation of aggregates of molecules with amphiphilic character, the hydrogen bond interactions define a frame, on top of which the rest of the interactions give the final shape to the cluster. Even if the hydrogen bond contribution to the total cluster binding energy is small compared with the rest of the interactions, its strong dependence with the angle, convinces the molecules to adopt a geometry that favours linear X-H···Y interactions. In that work, we also demonstrated that the molecules are able to re-arrange to form reverse micelles, even in the absence of any solvent, and we postulated that it may be a general ability of amphiphilic molecules in cold environments.

Following the previous works,[17;18] and aiming at generalizing the conclusions we reached, we present here a study on the formation of cyclohexanol aggregates containing up to six molecules. The absence of an aromatic ring in cyclohexanol allowed us to evaluate the importance of the dispersive and C-H···π interactions in the formation of reverse micelles. However, development of a new, unconventional methodology was necessary to tackle the mass-resolved spectroscopy of cyclohexanol aggregates, as the molecule lacks of a chromophore, which is required to run REMPI (resonance-enhanced multiphoton ionisation) and IR/UV double resonance experiments. In order to circumvent this difficulty, we use a combination of IR ns and fs lasers to obtain the mass-resolved IR spectrum of each of the species.[19;20] As it will be demonstrated below, the absence of an aromatic group has a strong influence in the overall stabilisation energy, but the cluster's shape resemble the general characteristics found in propofol aggregates.

Methods

Experimental

The experimental set up was described in detail in ref 19. Briefly, the experiments are carried out in a linear Time-of-Flight mass spectrometer (Jordan Inc.). The cyclohexanol vapour (Sigma-Aldrich, 99%) kept at room temperature was seeded in 1-2 bar of He and expanded trough the nozzle of a pulsed valve (Jordan Inc.) to form a supersonic expansion. The supersonic jet was collimated by a 1 mm skimmer before entering the ionization region, where interacts with the ns/fs laser beams. The ultra-short pulses used as ionizing probe were generated by a commercial Ti:sapphire oscillator-regenerative amplifier laser system (Coherent, 1 kHz,40 fs pulses, 800 nm). A portion of the amplifier output (~300 µJ) was focused into the ionization region by a 35 cm lens reaching intensities of the order of 10^{13} W/cm^2.

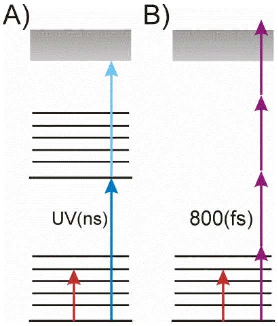

Figure 1. Schematic of the laser arrangement in a) IR/UV double resonance experiments and b) the technique used in this work to record mass-resolved IR spectra of molecules without chromophore.

A schematic of the laser arrangement employed in the experiments is shown in Fig.1b. The 800 nm femtosecond ionizing laser was preceded by a spatially overlapped ns IR beam, fired 100-400 ns earlier. Scanning the IR along the O-H stretching region of the targeted species, the spectrum is recorded as dips in the signal intensity from the fs laser

A commercial Nd:YAG/Dye/LiNbO$_3$ laser system (Quantel Brilliant B/Fine Adjustment Pulsare Pro) with 0.1 cm^{-1} line with and an OPO system (Laser Vision) with 10 cm^{-1} line with were used as ns IR laser sources.

Calculations

A full description of the calculation protocol may be found in ref 21. Briefly, data interpretation was guided by the calculations carried out using Maestro and Gaussian 09,[22] installed in the the supercomputer available at the University of the Basque Country. A thorough exploration of the conformational landscape was carried out using the molecular mechanics algorithms (MMFFs force field)[23] implemented in Maestro (Schrodinger Inc). A minimum of 100.000 cycles were employed for each species, resulting in thousand of candidate structures for the largest clusters. As optimization of all the structures is not possible, they were grouped into families and at least the lowest energy structures in each family were subjected to full optimisation at M06-2X/6-311++G(d,p) level. All the calculated structures, together with their energetics and their predicted IR spectra may be found in the supplemental information.

Results and discussion

Compared with phenol, the closest aromatic molecule, cyclohexanol is a complicated system, as it can adopt several different conformers (Fig. 1).[24] On the one hand, the cycle can be in boat or chair conformations, although the latter are significantly less stable, and on the other hand, the OH moiety can be in axial or equatorial position with *trans* or *gauche* orientations. Taking into account the small energy difference between the structures, one would expect to find at least the three most stable conformers in the expansion. Likewise, the clusters may contain monomers in several different conformations, stressing the importance of performing an exhaustive conformational exploration in this kind of systems.

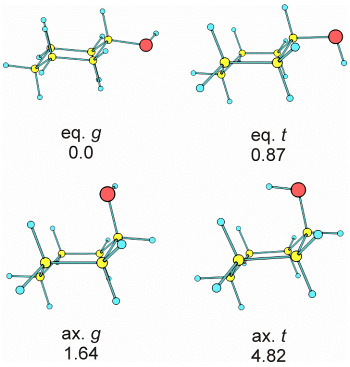

Figure 2. The four lowest energy conformers of cyclohexanol

The mass-resolved IR spectra of cyclohexanol clusters obtained using a combination of ns and fs IR lasers are collected in Figure 3, together with the simulated spectra for the structures that better reproduce the experimental observation. Such structures are depicted in Figure 4.

Cyclohexanol only has an OH group, and therefore a single band is expected for each molecule in the region scanned. Thus the spectrum of the dimer presents two bands: a sharp one at 3650 cm^{-1} corresponds to a free OH stretch, while the broad one at 3510 cm^{-1} corresponds to the bonded OH. In a previous work, the unexpectedly broad width of the bonded OH stretch band was attributed to an experimental artefact caused by the contribution of hot species to the blue tail of the band, due to an increase in ionization efficiency with temperature.[20] On the other hand, one cannot rule out the contribution of several conformational isomers to the broadening of the IR bands, especially in systems of such a large size. Indeed, at least three isomers of cyclohexanol are expected to be populated in the expansion (Figure 2) and therefore, there are six possible combinations of structures in the dimer, all of them with very similar vibrational frequencies (See Figures S1 and S2 of the supplemental information). Nevertheless, all of them present the same O-H···O interaction, and since this is the relevant aspect of this study, the conclusions extracted may be generalized to the rest of the isomers which may contribute to the final experimental spectrum.

As more cyclohexanol molecules are added to the cluster, the band due to the free OH stretch disappears, indicating that all the OH groups are establishing hydrogen bonds. Furthermore, the band due to the stretches of the bonded OHs increases in width and shifts to the red, which is the signature of the formation of cyclic hydrogen bond networks, as demonstrated in previous studies.[17] Such conclusion is reinforced by the comparison with the spectra predicted for the calculated structures. In all the cases only those conformers in which all the OH moieties participate in a cyclic hydrogen bond network are able to reproduce the experimental IR spectra.

It is important to note that each experimental spectrum in Figure 3 is not assigned to a single isomer but to a family of conformers with similar structure. Due to the low signal intensity it was not possible to run IR/IR/IR^{fs} experiments to determine the real number of isomers contributing to each stoichiometry. However, as stated above, the conclusions extracted in this work would not be modified by the presence of several isomers with similar structures.

It is also worthy to note the influence of the entropy in the stability of these systems. Tables S7-S10 collect the ΔH and ΔG for the twenty most stable structures, according to their relative enthalpy. Clearly, introduction of the entropic term alters significantly the energetic order. Nevertheless, the new most stable structures are of the same family of those previously assigned as the most stable ones when the enthalpy alone was taken into account.

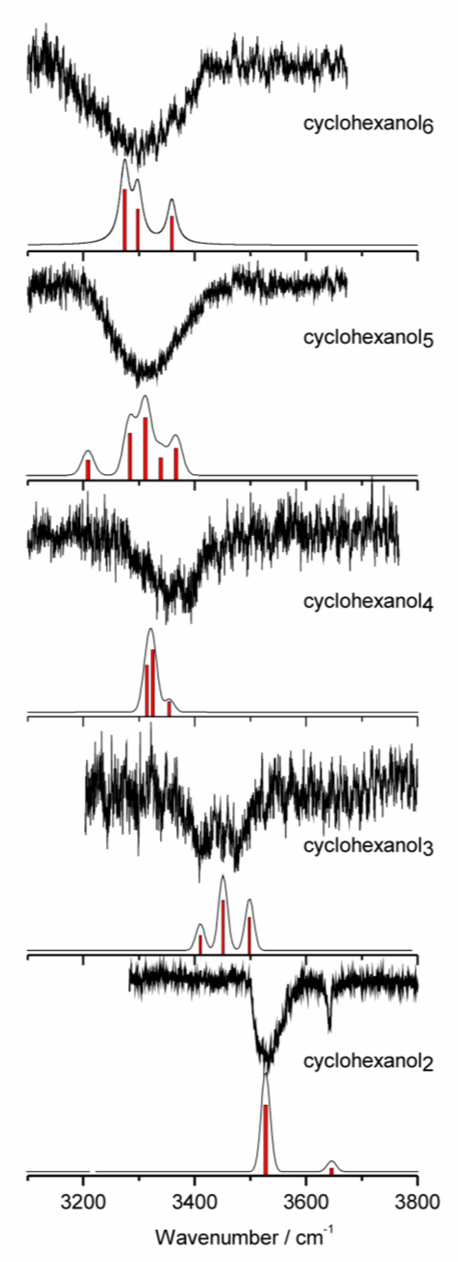

Figure 3. Comparison between the mass-resolved IR spectra of cyclohexanol aggregates of selected size and the simulated spectra that better resembles the experimental observation. The corresponding structures are shown in Figure 4.

Figure 4 collects the calculated structures whose simulated spectra are shown in Figure 3. The structures of propofol aggregates of similar size[17] and of cycloalkanes are also shown for comparison.

The differences found between cyclohexanol and propofol dimer stress the influence of the aromatic ring, and therefore, of the C-H···π interactions, in the aggregation process: while cyclohexanol dimer clearly maximizes the O-H···O hydrogen bond as indicated by the almost linear OHO angle, aggregation of propofol is mainly driven by the interaction between the rings and the isopropyl groups, and the dipole-dipole interaction between OH moieties contribute with a marginal stabilization energy to the whole cluster stability.

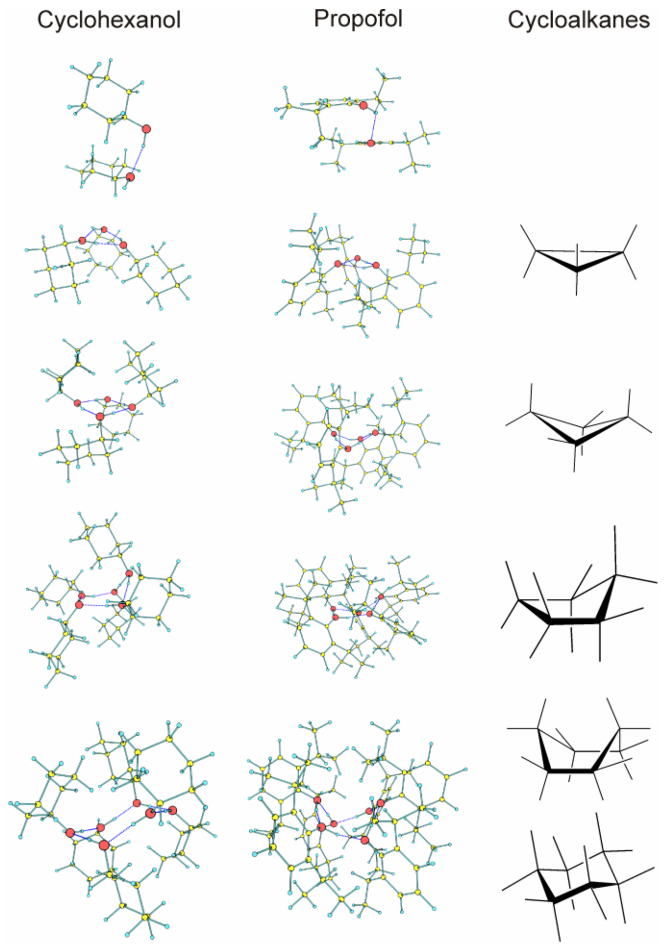

Figure 4. Comparison between the structure of cyclohexanol aggregates determined in this work and propofol aggregates adapted from ref 7. The structure of cycloalkanes is also included for comparison.

The trimer is a special case in the series, as the structures of cyclohexanol and propofol trimer are very alike: all three OH groups are engaged in a hydrogen bond network that defines a plane, placing the "substituents" of the OH groups below such plane. The difference between propofol and cyclohexanol is that for the former, direct interactions between the CH_3 groups of each molecule and the aromatic rings of the other two molecules are found, while in cyclohexanol aggregate, the alkylic rings try to stay away from each other.

Such effect is more pronounced in the tetramer, where two of the alkylic rings are above the plane defined by the hydrogen bond network, while the other two are below. Conversely, the propofol molecules try to maximize the contacts between the methyl groups and the neighbouring aromatic rings. It is interesting to point out that the cyclic hydrogen bond formed in propofol tetramer closely resembles the shape of cyclobutanol, in which all four carbons are not in the same plane, while the cyclic hydrogen bond structure in cyclohexanol tetramer is planar, probably due to the repulsion between the alkylic rings.

Incorporation of the fifth molecule into what looks like a reverse micelle, gives enough room to cyclohexanol to position the alkylic rings away one from each other, while forming a cyclic hydrogen bond that is very similar in shape to cyclopentane. However, propofol prefers to maximize the contacts between methyl groups and aromatic rings and therefore the hydrogen bond network is distorted respect to the “ideal” cyclopentane shape. Once again the main contribution to propofol’s cluster stability is, instead of the hydrogen bond network, the interaction with the aromatic ring, although the directionality of the latter imposes a general structural frame (a hydrogen bond skeleton) to the superstructure.

A remarkable difference is found between cyclohexanol and propofol hexamers: a cyclic hydrogen bond network is formed in both clusters, but while it adopts a chair conformation in cyclohexanol, it is closer to a boat conformation in propofol cluster. Actually, the first structures of cyclohexanol hexamer with boat-like shape are ca. 13.8 kJ/mol above the global minimum and therefore their presence in the expansion may be ruled out.

The chair conformation is the most stable structure of cyclohexane, because it allows cyclohexane to position its hydrogen atoms in alternated configurations. The preference of cyclohexanol hexamer for such conformation stresses that it is also energetically favourable for the cluster to have all the alkylic rings away one from each other, as if they were “gigantic” hydrogen atoms. Conversely, propofol adopts a boat conformation that seems to permit the monomers to continue with the trend observed in the smaller clusters: each methyl group interacts with the aromatic ring of the neighbouring molecule, adding valuable extra stabilization energy to the superstructure.

Interestingly, while the chair conformation adopted by cyclohexanol hexamer is almost identical to the cyclohexane chair conformer, leaving aside the longer hydrogen bond distances, the boat shape of the hydrogen bond network of propofol is distorted, probably because such distortion allows the cluster to maximize the rest of the interactions.

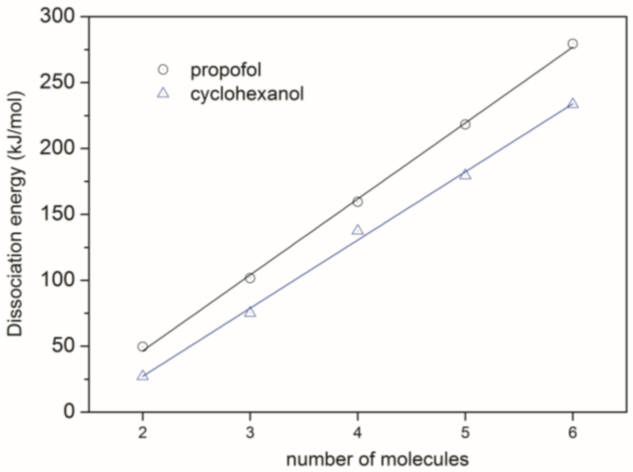

Figure 5. Dissociation energy of the structures assigned in this work to cyclohexanol clusters and of the propofol structures in ref 17.

Regarding the interaction energy, Figure 5 shows a comparison between the increase in the cluster’s dissociation energy with the number of molecules for propofol and cyclohexanol clusters. Surprisingly, a linear relationship is found between the number of molecules and the dissociation energy, while one would expect a larger increasing, due to many-body effects, specially in cyclohexanol, where the hydrogen bonds play a central role in cluster formation. However, a careful analysis of the structures shows that there are many forces at play and that the observed behaviour is the result of several positive and negative interactions.

Formation of propofol dimer has an unusually high dissociation energy. As stated above, the main intermolecular force is the interaction between the isopropyl groups and the aromatic rings, while there is only a marginal dipole-dipole interaction between the OH moieties. On the other hand, cyclohexanol dimer is almost purely formed by an O-H···O hydrogen bond. Thus, the energy difference between the two dimers gives an estimation of the relative importance of the C-H···π interactions in propofol, compared with the intermolecular hydrogen bond in cyclohexanol.

Surprisingly, formation of the trimer does not result in a huge increase in the dissociation energy of propofol$_3$ compared to cyclohexanol$_3$. The main aggregation force in the trimer is formation of a cyclic hydrogen bond arrangement. However, to adopt such configuration, the hydroxyl moiety of propofol has to rotate to be perpendicular to the plane of the aromatic ring. Otherwise, the isopropyl groups would not allow the system to establish the hydrogen bond network. Thus, the stabilization that propofol trimer obtains from the hydrogen bond network is not very high, but due to the directional nature of the hydrogen bond, it is still able to define the general structure of the cluster. Thus, most of the interaction energy of propofol trimer comes from the C-H···π contacts. One must take into account that a propofol trimer formed exclusively by such kind of interactions is not possible, due to the rotation of the isopropyl groups required to maximize the C-H···π contacts.

Conversely, cyclohexanol does not have obstacles to form a strong hydrogen bond network, and the OH moiety is relatively loose, as the oxygen’s lone pairs are not coordinated with an aromatic ring. Still, the repulsion or steric effects compensate for the extra stabilization energy gained by the ring formation process. The existence of repulsion forces between the cycloalkanes is highlighted in higher-order clusters, where they try to position as far as possible one from each other.

As more molecules enter the cluster, the hydrogen bond network is reinforced due to many body effects. If a larger increase in dissociation energy is not observed, is probably due once more, to the repulsion between the alkylic rings in cyclohexanol clusters and to the relatively weakness of the hydrogen bond network in propofol clusters, whose main aggregation force is the isopropyl-aromatic ring interactions.

Thus, both the structure and the dissociation energy of the clusters studied in this work are the result of a subtle balance between the several interactions at play.

Conclusions

Here, we present for the first time the mass-resolved IR spectra of cyclohexanol aggregates containing up to six molecules, recorded using a combination of ns and fs lasers. The aggregates present a hydrophilic core in which all the OH moieties are forming a cooperative hydrogen bond network, while the cycloalkane moieties position in such a way that repulsive forces are minimized. When compared with previous results on propofol aggregates, the influence of the aromatic ring is stressed: in propofol aggregates, the cluster tends to maximize the contacts between methyl groups and aromatic rings, as they significantly contribute to the stabilization of the cluster. Comparison of the hydrophilic core in the hexamers highlight the influence of such extra interactions, as they are able to tune the shape of the hydrogen bond network, shifting it towards a boat conformation in propofol$_6$, compared to the chair conformation adopted in cyclohexanol$_6$.

We also confirm for cyclohexanol aggregates the previous observation of a signature in the IR spectra for the formation of reverse micelles, as all the OH stretches appear grouped in a very narrow spectral region. Such signature may be useful to identify the appearance of this kind of aggregates in other molecular systems. Our group is currently running experiments on other similar systems to explore such behaviour further.

Acknowledgements

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Notes and references

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Electronic Supplementary Information (ESI) available: all the calculated structures, tables with dissociation energy values and predicted IR spectra. See DOI: 10.1039/b000000x/

(1) A. Kantrowitz, J. Grey, *Review of Scientific Instruments* 1951, **22,** 328-332.

(2) G. B. Kistiakowsky, W. P. Slitcher, *Review of Scientific Instruments* 1951, **22,** 333-337.

(3) D. H. Levy, *Science* 1981, **214,** 263-269.

(4) C. Pérez, M. T. Muckle, D. P. Zaleski, N. A. Seifert, B. Temelso, G. C. Shields, Z. Kisiel, B. H. Pate, *Science* 2012, **336,** 897-901.

(5) W. A. Herrebout, M. A.; Suhm, *Phys .Chem. Chem. Phys.* 2011, **13,** 13858-13859.

(6) S. Liang, P. G. Kusalik, *Chem. Sci.* 2011, **2,** 1286-1292.

(7) A. Laaksonen, V. Talanquer, D. W. Oxtoby, *Annu. Rev. Phys. Chem.* 1995, **46,** 489-524.

(8) M. Kumala, K. E. J. Lehtinen, A. Laaksonen, *Atmospheric Chemistry and Physics* 2006, **6,** 787-793.

(9) J. Kazil, P. Stier, K. Zhang, J. Quaas, S. Kinne, D. O'Donnell, S. Rast, M. Esch, S. Ferrachat, U. Lohmann, J. Feitcher, *Atmospheric Chemistry and Physics* 2010, **10,** 10733-10752.

(10) A. A. Manka, J. Wedekind, D. Ghosh, K. Höler, J. Wölk, R. Strey, *J. Chem. Phys.* 2012, **137,** 054316.

(11) S. H. S. Salk, C. K. Lutrus, D. E. Hagen, *Journal of the Atmospheric Sciences* 1988, **45,** 2979-2986.

(12) L. Pauling, *The Nature of the Chemical Bond*; Cornell University Press: Ithaca, New York., 1960.

(13) A. J. Stone, *The theory of intermolecular forces*; Oxford University Press: Oxford, 2013.

(14) I. G. Kaplan, I. G. *Intermolecular Interactions: Physical Picture, Computational Methods and Model Potentials*; John Wiley and Sons: Sussex, 2006.

(15) A. G. Jeffrey, *An introduction to hydrogen bonding.*; Oxford University Press: Oxford, New York., 1997.

(16) G. Gilli, P. Gilli, *The Nature of the Hydrogen Bond: Outline of a Comprehensive Hydrogen Bond Theory*; Oxford University Press: Oxford, New York, 2009.

(17) I. León, J. Millán, E. J. Cocinero, A. Lesarri, J. A. Fernández, *Angew. Chem. Int. Ed.* 2013, **52,** 7772-7775.

(18) I. León, J. Millán, E. J. Cocinero, A. Lesarri, J. A. Fernández, *Angew. Chem. Int. Ed.* 2014, in press. DOI: 10.1002/anie.201405652.

(19) I. León, R. Montero, F. Castaño, A. Longarte, J. A. Fernández, *J Phys Chem A* 2012, **116,** 6798-6803.

(20) I. León, R. Montero, A. Longarte, J. A. Fernández, *Journal of Chemical Physics* 2013, **139**.

(21) I. León, E. J. Cocinero, J. Millán, S. Jaeqx, A. Rijs, A. Lesarri, F. Castaño, J. A. Fernández, *Phys. Chem. Chem. Phys.* 2012, **14,** 4398.

(22) M. Frisch, et al. Gaussian 09, Rev. A02. 2009. Wallingford CT, Gaussian, Inc.

(23) T. A. Halgren,. *J. Comput. Chem.* 1999, **20,** 730-748.

(24) K. S. Pitzer, W. E. Donath, *J. Am. Chem. Soc.* 1959, **81,** 3213-3218.

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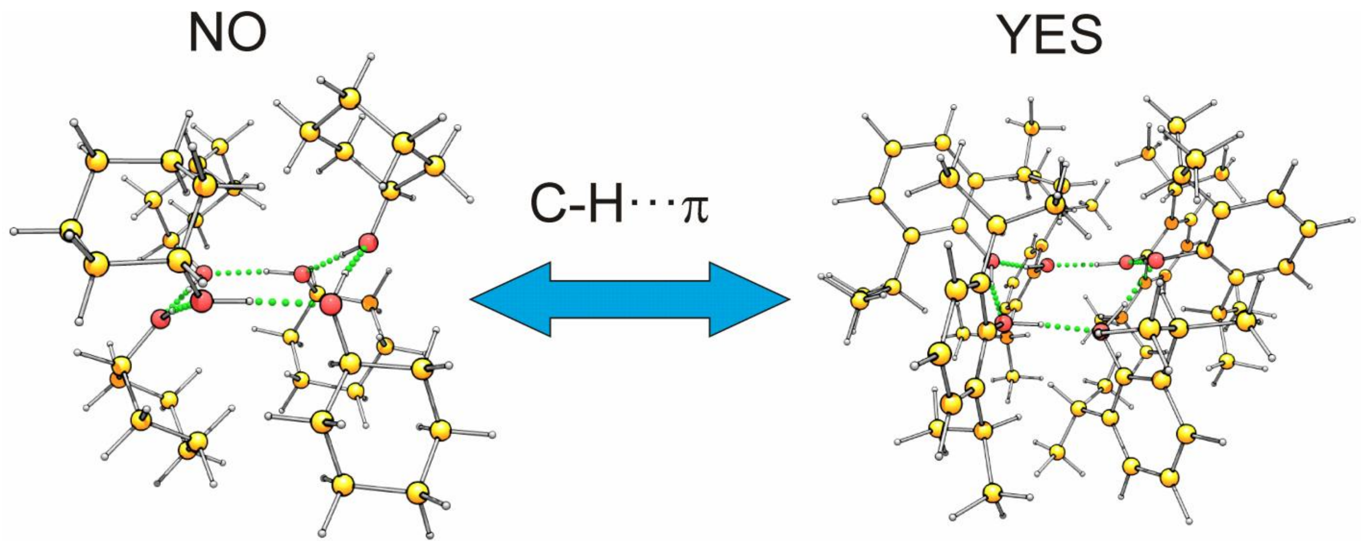

Despite that they are comparatively weaker, C-H···π interactions have a strong influence in the final shape of molecular aggregates.