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ARTICLE TYPE

Molecular Hydration of Propofol Dimer in Supersonic Expansions: Formation of Active Centre-Like Structures

Iker León,^a Judith Millán,^b Emilio Cocinero,^a Alberto Lesarri^c and José A. Fernández^{*a}*Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX*

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Spectroscopic studies of molecular aggregates are a powerful tool to understand the weak interactions between molecules. Here, Propofol₂(H₂O)_{6,7} clusters were formed in supersonic expansions and its electronic and infrared spectroscopy was explored using several mass-resolved laser-based spectroscopic techniques. Using REMPI, their S₁←S₀ electronic spectrum was obtained with vibrational resolution, while the UV/UV hole burning revealed the presence of a single isomer of propofol₂(H₂O)₆ and of two isomers of propofol₂(H₂O)₇. Employment of IR/UV double resonance yielded the IR spectrum in the OH stretch region. Comparison with the spectra predicted for the structures calculated at the M06-2X/6-31+G(d) level demonstrated that the two propofol molecules interact mainly through C-H...π contacts between the lipophilic sides of the molecules, while the hydroxyl moieties are in close contact, forming a kind of "active centre" with which the water molecules interact, forming polyhedral structures.

INTRODUCTION

The introduction of the supersonic expansions as a method to obtain spectra of cold molecules constituted a revolution in gas phase spectroscopy, as they enabled obtaining the spectra of (what was considered at that time) very large systems (aniline, phenol... etc) with unprecedented resolution and S/N (signal-to-noise) ratio.¹⁻³ But at the same time, a new and exciting possibility opened: the cold and isolated environment of the supersonic expansion was the ideal medium to study molecular aggregation.⁴ Certainly, the weak forces that drive such processes (van der Waals and hydrogen bond) require of an absolute absence of interferences, such as those found in crystal structures, to be mapped and characterized. Thus, pioneering works in the formation of molecular aggregates appeared.^{5, 6} Combination of the supersonic expansions with mass spectrometry resulted in a second revolution: MRES (mass-resolved excitation spectroscopy), which allowed one to discriminate between the spectra of aggregates with different stoichiometry.⁷⁻¹¹ Indeed, the spectroscopy of aggregates is, in fact, the spectroscopy of a chromophore whose electronic, vibrational and rotational levels are perturbed by the non-covalent interaction with the rest of the cluster, and therefore, the spectra of aggregates of different stoichiometry overlap in the same spectral region. Thanks to the introduction of REMPI (resonance-enhanced multiphoton ionisation),¹² it was possible to tackle the spectroscopy of systems of increasing complexity, always trying to fill the gap between gas phase and solution. The pioneering work of Zwier's group on the solvation of benzene deserves special attention, as they were able to demonstrate that water forms ice cubes that coordinate with the benzene molecule.^{13, 14} It

is also worthy to mention the outstanding work by Kleiner's group on the solvation of phenol, in which they unravelled the spectroscopy of phenol clusters containing up to 12 water molecules and to propose a structure for the clusters up to phenol(H₂O)₈.^{11, 15, 16}

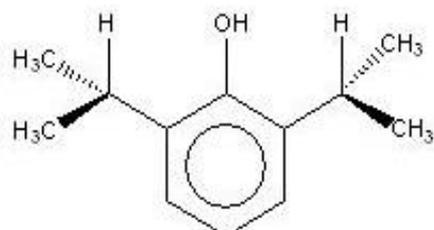
In recent times, the fascinating work by Asuka Fujii and col. on large phenol-water¹⁷ and protonated water clusters^{18, 19} and by Masaaki Fujii and col. on several systems, but especially on the spectroscopy and structure of phenol/ammonia clusters²⁰ have contributed to build a bridge between gas phase and solvation. The great success achieved in the structural elucidation of clusters is mainly due to the introduction of double resonance techniques, which allow to extract isomer-selective electronic (hole burning) and IR (IR/UV double resonance) spectra.⁷ Such physical observables can be compared directly with the predictions from quantum chemistry using the available software.

Our group is also engaged in the study of molecular aggregates,²¹⁻²⁵ and especially of the solvation of molecules with biological activity.²⁶⁻³² Within this research line, we started a rather exhaustive work on the solvation of propofol (scheme 1), a widely used general anaesthetic, exploring the formation of pure propofol clusters,²⁶ propofol/water clusters^{26-29, 33-35} and the interaction with the residues of the amino acids conforming the active centre of the GABA_A receptor, where it exerts its action.^{31, 36} Here we extend such knowledge to the study of the solvation of propofol dimers with six and seven water molecules. The study of the solvation of organic dimers constitutes an important step forward towards understanding real solutions, but it also involves a significant increase in complexity. In water clusters containing a single organic molecule, the cluster formation is largely controlled by the hydrogen bonds between the water molecules and the most hydrophilic groups of the chromophore. However,

introduction of a second aromatic molecule, produces an exponential increase in the system's complexity (number of possible conformers) and in the type of interactions driving the cluster formation: while the hydrophilic sites will still form hydrogen bonds, the hydrophobic (lipophilic) interactions may become even more important, depending on the side of the system, tipping the final cluster structure towards very different geometries.

Aside from the excellent paper by Gruenloh et al on the solvation of benzene dimer,³⁷ very little studies exist in the literature on the solvation of aromatic dimers,³⁸ probably due to the difficulty of forming such species in a controlled way. Indeed, a very narrow window of experimental conditions allow for the formation and detection of systems containing a dimer of an organic molecule and such a large number of water molecules. Furthermore, powerful computers are required to carry out the calculations needed to interpret the experimental results. Such computational resources were not available until recently. As we will demonstrate in this work, thousands of possible structures are possible for the systems here studied, within a reduced stability window and a high calculation level is required to obtain accurate-enough predicted spectra for the calculated structures.

Thus, in this work we put together several mass-resolved spectroscopic techniques and computational chemistry predictions to propose plausible structures for propofol₂(H₂O)_{6,7}. Also, comparison with previous studies on similar systems will be presented, to increase the knowledge on the solvation of organic molecules.



Scheme 1 propofol (2,6-diisopropylphenol)

METHODOLOGY

Experimental methods

The methodology used here was exhaustively described previously,²⁹ and therefore, a very short summary will be offered here. Propofol (2,6-diisopropylphenol) was purchased from Sigma-Aldrich and used without further modifications. Due to its relatively high vapour pressure, no further heating was required to achieve enough concentration in gas phase. Water was added in a different sample holder and was also kept at room temperature. He was used as buffer gas at typical pressures of 1-2 bar. The propofol/water ratio was critical and was adjusted adding water to the sample compartment and allowing the buffer gas to dry it until maximizing the signal from the desired stoichiometry.

REMPI and double resonance experiments (UV/UV and IR/UV) were carried out using a two-colour detection scheme, to avoid fragmentation from higher-order clusters. A detailed description

on how the experiments were performed may be found in ref. 29.

Calculations

Detailed description of the computational procedure may be found in ref 34. Briefly, special care was taken to carry out a thorough exploration of the potential energy surface, using fast molecular mechanics. In this first step, thousands of structures were obtained in a 25 kJ/mol stability window, most of them with small, non-relevant differences in the relative position of the water molecules. Therefore, they were grouped into families, and several representative structures of each family were subjected to full optimisation at M06-2X/6-31+G(d) level. In this way, 77 and 60 fully optimised structures were obtained for propofol₂(H₂O)₆ and propofol₂(H₂O)₇ respectively. These structures were used for spectra interpretation. Their dissociation energy was also estimated, using the zero-point energy (ZPE) from a normal mode analysis and the basis set superposition error (BSSE) value was obtained using the counterpoise procedure. All the structures, together with their predicted IR spectra and the dissociation energy values may be found in the supplemental material. The calculated structures are named as PPF2W_n-S_m, where n = 6,7 refers to the number of water molecules and m = 1, 2... refers to the energetic order of the structure, starting with m = 1 for the global minimum.

RESULTS

As it was demonstrated in previous works,³⁴ propofol presents a rich electronic spectroscopy, due in part to the four conformations that it can adopt in supersonic expansions. Interconversion between propofol isomers was previously reported, when Ar or even Ne was used instead of He, facilitated by the existence of paths between the isomers with low energy barriers.³⁴

Figure 1 shows the 2-color REMPI spectrum of propofol₂(H₂O)_{6,9}. The REMPI spectra of propofol and propofol dimer are also included for comparison. While formation of the homodimer results in a small shift to the red in the 0₀⁰ transition, aggregation of six water molecules shifts the spectrum almost 200 cm⁻¹ to the red, placing the band origin at 36009 cm⁻¹. Despite that the spectrum presents a limited number of bands, it is difficult to perform an assignment; the two first bands appear at 23.4 and 27.9 cm⁻¹ from the 0₀⁰ transition and may be safely identified as the two lowest vibrational modes (calculated harmonic frequencies of 25 and 38 cm⁻¹). Also, the spacing between the rest of the peaks seem to indicate the presence of a progression on ν₂, which seems to be an active mode. This mode roughly corresponds to a stretching of the two C-H...π intermolecular interactions. Very likely, there is a change in such distance upon electronic excitation. Aside from such observations, extraction of further conclusions would be too speculative.

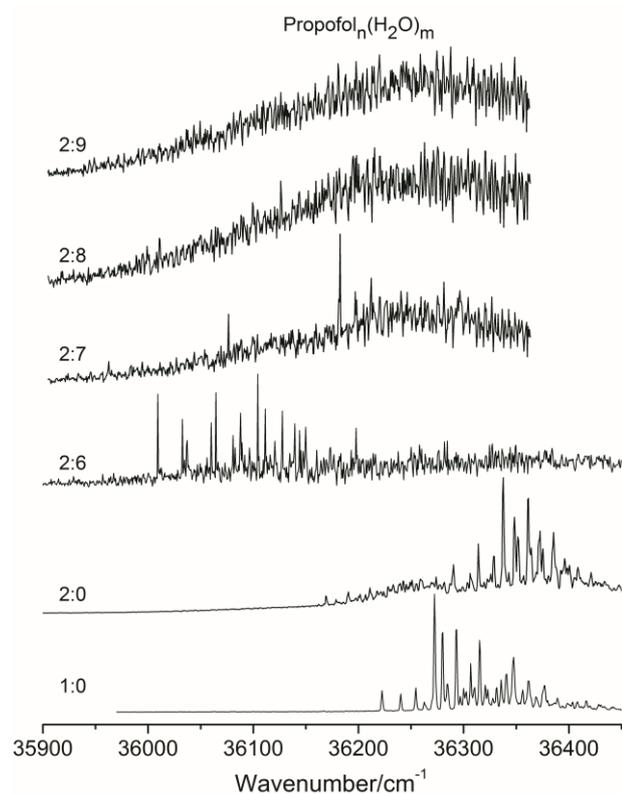


Fig. 1 two-colour REMPI spectra of propofol, propofol dimer and propofol₂(H₂O)_n, n = 6-9. No discrete spectrum was found for clusters containing more than 7 water molecules.

The spectrum of propofol₂(H₂O)₇ is significantly different. Most of the vibrational structure is lost and only two discrete features are clearly visible over a broad absorption. It is difficult to locate the 0₀⁰ transition, but it may lie around 35950 cm⁻¹. The overall shape of the spectrum points to an important change of geometry upon excitation, perhaps due to a floppy structure. Whatever the reason is, the effect is clearly reinforced in the clusters containing eight and nine water molecules, where a complete lack of vibrational structure is found. Attempts to obtain structural information from such species were carried out running double resonance experiments, tuning the probe laser at several different transitions within the continuum, without success. Thus, it seems that propofol₂(H₂O)₇ is the largest species from which spectral information may be extracted.

To determine the number of isomers contributing to each stoichiometry, hole burning (UV/UV double resonance spectroscopy) experiments were carried out, tuning the probe laser to several transitions in the spectrum. The results are shown in Figure 2, together with the corresponding 2-color REMPI spectra for comparison. The spectra indicate that while a single isomer contribute to the spectrum of propofol₂(H₂O)₆, at least two isomers of propofol₂(H₂O)₇ were detected. A single discrete transition was found in the hole burning spectrum of the red-most isomer (isomer 1), but at least three discrete transitions are clearly visible in the spectrum of the blue-most isomer (isomer 2).

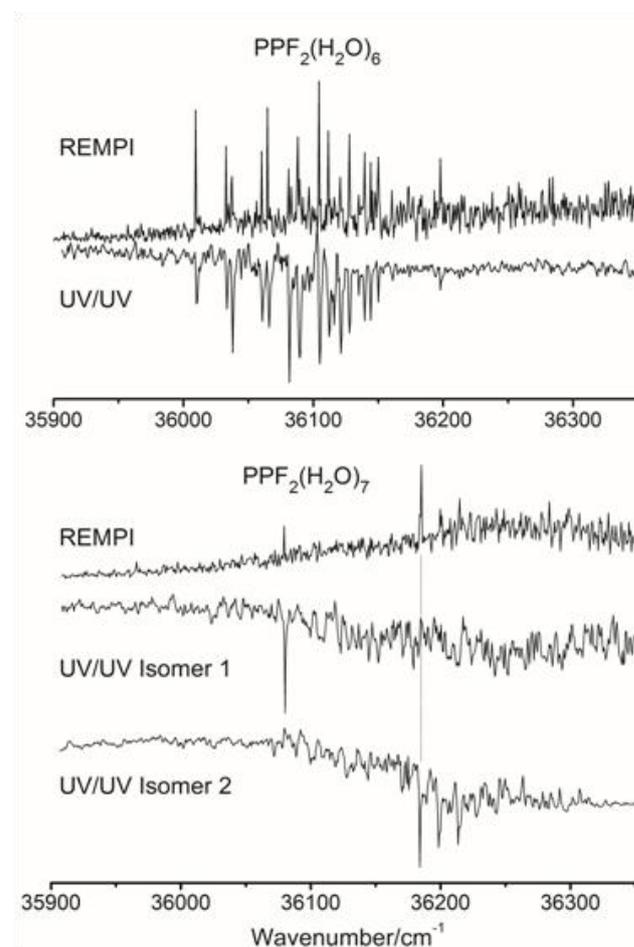


Fig. 2 Hole burning traces obtained probing the transition at 36009 cm⁻¹ of propofol₂(H₂O)₆ and the transitions at 36078 and 36184 cm⁻¹ of propofol₂(H₂O)₇.

In order to obtain structural information from the detected species, an IR/UV double resonance experiment was carried out, probing the transition at 36009 cm⁻¹ of propofol₂(H₂O)₆ and the transitions at 36078 and 36184 cm⁻¹ of propofol₂(H₂O)₇ (Figures 3 and 4). Only OH stretch bands are expected in the spectral region scanned, and therefore at least 14 bands are expected to appear in the spectrum of propofol₂(H₂O)₆ and 16 in the spectrum of each isomer of propofol₂(H₂O)₇. However, when equivalent OH exist (i. e., when the environment of two OH bonds is similar) their stretching frequencies usually overlap. That is the case, for example, of the stretches of free (non-hydrogen bonded) OH moieties. The spread of the bands in the spectra of propofol₂(H₂O)₆ and propofol₂(H₂O)₇ through ~ 700 cm⁻¹ point to formation of 3D structures in which most of the OH groups are non-equivalent.

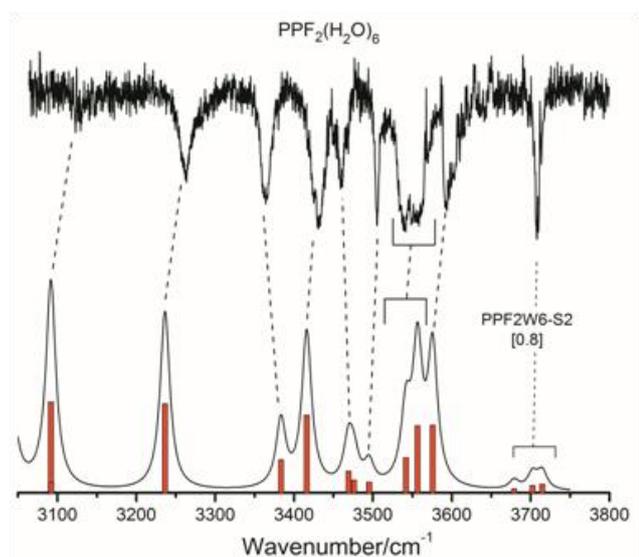


Fig. 3 IR/UV double resonance of propofol₂(H₂O)₆ obtained tuning the probe laser at 36009 cm⁻¹. The simulated spectrum that better reproduces the experimental trace is also shown for comparison. A correction factor of 0.955 was applied to account for anharmonicity. The relative stability of the assigned structure is also given in kJ/mol.

As explained above, 77 structures of propofol₂(H₂O)₆ were fully optimized at M06-2X/6-31+G(d) level. For the sake of brevity, only the simulated spectrum that better reproduces the experimental trace is shown in Figure 3, but the rest of the predicted spectra may be found in the supplemental material, together with the calculated structures.

The structures found using the calculation procedure described above (Fig. S1 of the supplemental material) can be classified, according to the shape of the hydrogen bond network formed. The most stable structures present a network that resembles the cubic structure formed by eight water molecules in pure water clusters. Around 3.5 kJ/mol from the global minimum, structures with hydrogen bond networks resembling the pure water book structure may be found. Interestingly, these structures present a relatively large *window region* in the IR spectrum (3200-3500 cm⁻¹), and all the OH stretches appear grouped in a narrow region, apart from those corresponding to the stretches of free OH groups. A representative spectrum may be found in Figure S2 of the supplemental material.

If the network presents a book-like structure but the two propofol molecules are not in close contact (for example, PPF2W6-S15, see Fig. S2), the spectrum changes significantly and the vibrational transitions are spread through a broader region. Also, the energy of the system increases to at least 8.7 kJ/mol.

Isoenergetic with the latter, the first structure in which the water molecules form a distorted prism may be found (PPF2W6-S14). The spectra of this kind of structures present no window region and the transitions cover a broad range: from ~3710 cm⁻¹ (free OH stretches) to ~3200 cm⁻¹, due to the low symmetry of the structure, in which almost every OH experiences a very different environment.

As one goes higher in energy, more complex structures appear, such as *butterflies* (PPF2W6-S18) *extended books* (PPF2W6-S25), bicyclic (PPF2W6-S30) or hexameric cyclic arrangements

(PPF2W6-S66). Each kind of structure presents a characteristic spectrum that is the result of the particular environments that each OH bond experiences. An example of each kind of structure, together with its simulated spectrum may be found in Figure S2. The simulated spectrum in Figure 3, and that reproduces reasonably well the experimental trace, corresponds to structure PPF2W6-S2 which is 0.8 kJ/mol above the global minimum, and therefore its energy difference with the global minimum is within the calculation error. In this isomer, the aromatic ring of each propofol is interacting with an isopropyl group of the other one. Both hydroxyl moieties form a sort of hydrophilic site, with which the water molecules interact (Figure 5). Such structure correlates well with the observation of a progression in ν_2 , which corresponds to the intermolecular stretching along the coordinate separating the two aromatic rings. Very likely, both rings approach to each other upon electronic excitation, activating that particular vibrational coordinate.

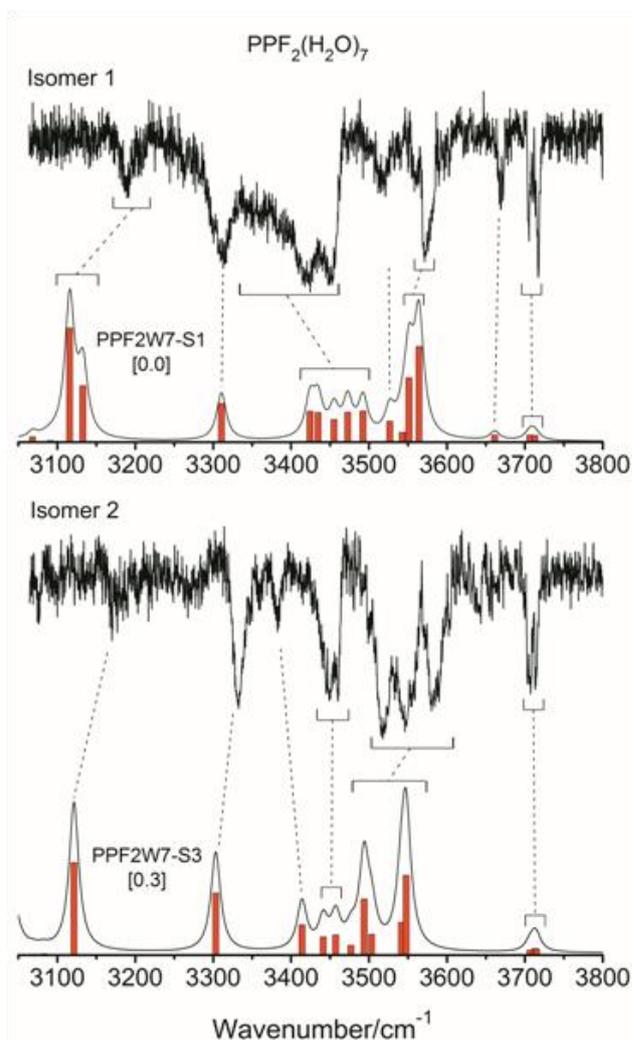


Fig. 4 IR/UV double resonance of the two isomers of propofol₂(H₂O)₇ obtained tuning the probe laser at 36078 and 36184 cm⁻¹ respectively. The simulated spectrum that better reproduces each of the experimental traces is also shown for comparison. A correction factor of 0.955 was applied to account for anharmonicity. The relative stability of the assigned structures is also given in kJ/mol.

Introduction of the seventh water molecule results in very complex structures, some of them with no equivalence in the pure water clusters. Despite the strong hydrophobic environment, the global minimum still presents a distorted cube hydrogen bond network. Actually, no other kind of structure is found until 3.6 kJ/mol, where a *butterfly*-like structure may be found. Such structure is not very different from the distorted cube, as one transforms into the other by moving a single water molecule and rearranging the network. Accordingly, the predicted spectrum is not very different from those of the cubic structures: it still presents a window region, but some transitions are shifted to the far red-end of the observed region (PPF2W7-S6, Fig. S5 of the supplemental material), indicating the reinforcement of some hydrogen bonds.

Higher in energy, more complex (lower symmetry) structures may be found, some of them difficult to describe. For example, what can be considered as PPF2W6-S8 with an additional water molecule is now at 8.1 kJ/mol above the global minimum (PPF2W7-S12, Fig. S5). Its spectrum also resembles that of PPF2W6-S8: all the bands are grouped in the central part of the spectrum, except those from the free OH stretches. However, no window region between both groups of bands is present this time. Assignment of the two detected isomers of propofol₂(H₂O)₇ is not straightforward. Apparently, both spectra are very different. However, a careful inspection shows significant similarities: both spectra present two free OH stretches, strong transitions around 3675, 3450 and 3300 cm⁻¹, and a weaker transition around 3150 cm⁻¹. The most notable difference between the spectra is the presence of a broad absorption around 3350 cm⁻¹ in the spectrum of isomer 1, which becomes a well-resolved band at higher frequencies in the spectrum of isomer 2. Additionally, the presence of a band at 3660 cm⁻¹ in the spectrum of isomer 1, may indicate the presence of an O-H...π interaction.

The simulated spectra that better reproduce the experimental traces are also shown for comparison. In this case, they correspond to PPF2W7-S1 and PPF2W7-S3, which are almost isoenergetic, and representative structures of very (structurally) similar families.

DISCUSSION

Once the structure of the detected isomers was determined, it is

possible to put them in perspective, by comparison with the structures reported for similar systems. Figure 5 collects the structures of the isomers detected in the present work, together with those from similar systems.

It is well known that the water octamer forms a very stable cubic structure, which is maintained in benzene/water clusters.^{37, 39} Such structures benefit from a large cooperative effect, in which each hydrogen bond reinforces the rest of the hydrogen bonds in the network.

Following such trend, phenol₁(H₂O)₇ may be envisioned as a water octamer in which a hydrogen atom of one of the water molecules was replaced by a phenyl group. Certainly, the cubic structure does not seem to be very much affected by the presence of the aromatic ring. Likewise, the cubic structure is not very much affected in one of the isomers of propofol₁(H₂O)₇. However, in the second one, the cube closes over the ring, instead of with the hydroxyl moiety of propofol. Such observation seems to indicate that either both O-H...O and O-H...π interactions present similar strengths in this particular cluster, or that the latter interaction allows the whole water superstructure to relax some structural stress imposed by the cubic structure, compensating for the loss of stabilization energy resulting from switching to a less favourable O-H...π interaction. Apparently, the extra electron density accumulated in the aromatic ring, due to the two electron-donating isopropyl groups, is enough to stabilize this second family of structures.

Formation of propofol₂(H₂O)₆ seems to follow the same trend, but in this case the second propofol molecule replaces the hydrogen which had the interaction with the aromatic ring in propofol₁(H₂O)₇. At the same time, the two propofol molecules establish several C-H...π interactions, which result in a significant increase in the cluster's stability.²⁹

On the other hand, the cluster may be observed from the point of view of the propofol dimer. From that perspective, the main aggregation forces are the C-H...π interactions, which force the two molecules to group their OH moieties, forming a localized hydrophilic spot, to which the water cluster attaches, and therefore, propofol₂(H₂O)₆ somehow resembles the formation of active sites in proteins and peptides, although at a reduced scale.

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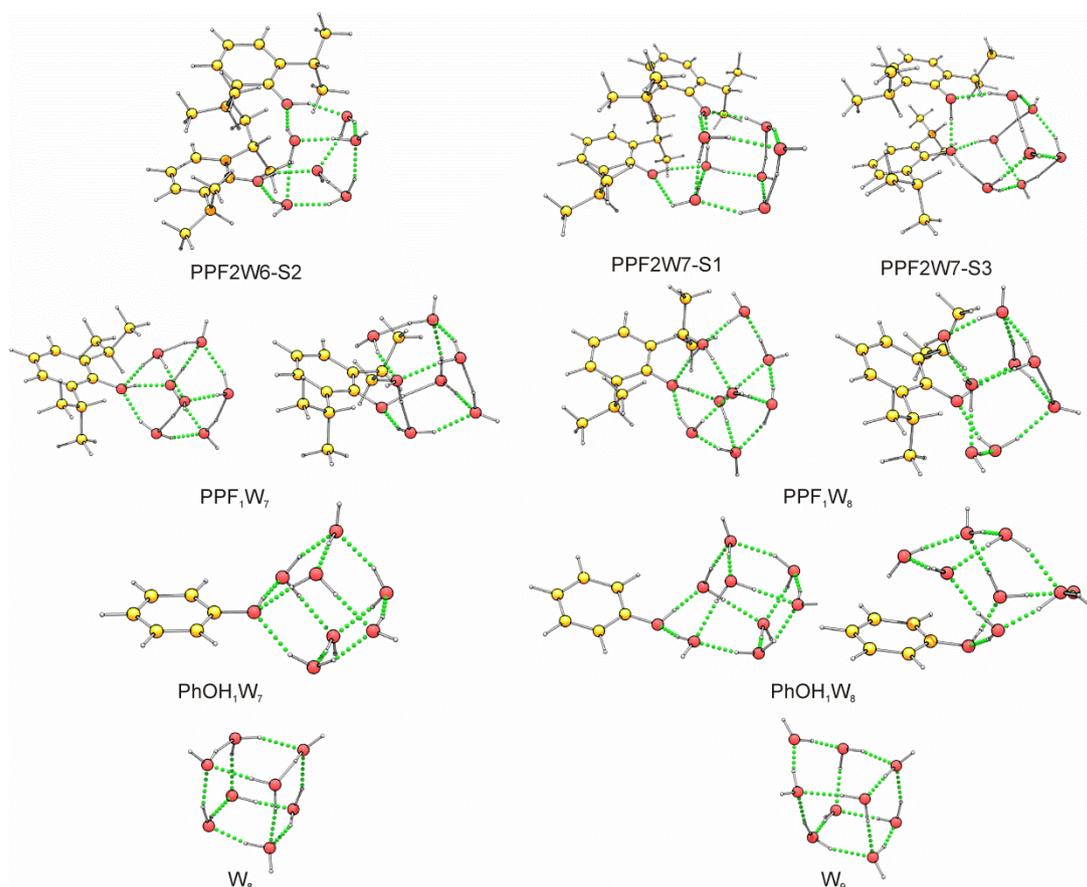


Fig. 5 Comparison between the structure of the isomers of propofol₂(H₂O)_{6,7} detected in the present work and those from the literature in similar systems. propofol₁(H₂O)_{7,8} were taken from ref. 35, while phenol₁(H₂O)_{7,8} structures were taken from ref. 40, 41 and those from pure water clusters were taken from refs. 13, 39, 42, 43. All the structures taken from the literature were recalculated at M06-2X/6-31+G(d) level.

Similar observations may be done for the water nonamer → phenol₁(H₂O)₈ → propofol₁(H₂O)₈ → propofol₂(H₂O)₇ ladder, although the lower symmetry of the pure water structure allows for the existence of two isomers of phenol₁(H₂O)₈, one of them with a clearly distorted hydrogen bond network that is lost in propofol clusters. In the latter, the original cubic structure of the water nonamer is somehow recovered.

Formation of an special hydrophilic centre in a highly hydrophobic structure was also observed in propofol₃(H₂O)₁ or even propofol₄(H₂O)₁, where the water molecule was completely encapsulated inside the hydrophobic superstructure, like in the interaction between signalling molecules and receptors. Extrapolation of these observations, may lead to conclude that the formation of active sites in proteins and other biomolecules may be driven by the natural tendency of the hydrophobic lateral chains to group together, while maintaining their hydrophilic moieties in close contact, thus creating localized regions of different philicity.

Conclusions

Here, we analyzed the spectroscopy of propofol clusters with six and seven water molecules. Using a combination of mass-resolved laser spectroscopy and calculations, it was possible to determine the structure of the singly detected isomer of propofol₂(H₂O)₆ and of the two isomers of propofol₂(H₂O)₇ detected in the jet. A careful inspection of the structures confirms the trends observed in previous works: the high aggregation energy of the water molecules force the clusters to follow a geometry that resembles that of pure water clusters. But at the same time, the two propofol molecules position with the hydroxyl moieties forming a localized hydrophilic site, that resembles the change of philicity observed in the active site of proteins and receptors. Generalization of these observations points to the natural tendency of lipophilic groups to cluster together and grouping their hydrophilic moieties as the driving force behind

the formation of the active sites.

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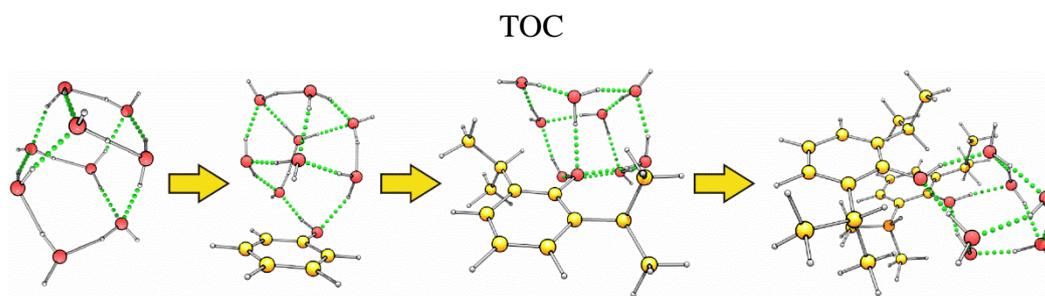
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Notes and references

- ¹⁰ ^a Dep. of Physical Chemistry, Fac. of Science and Technology, University of the Basque Country (UPV/EHU), B^o Sarriena s/n, Leioa 48940, Spain.
- ¹¹ ^b Dep. of Chemistry, Fac. of Science, Agricultural Studies and Informatics, University of La Rioja, Madre de Dios 51, Logroño 26006, Spain.
- ¹² ^c Dep. of Physical Chemistry and Inorganic Chemistry, Fac. of Science, University of Valladolid, Valladolid 47011, Spain.
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5