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A General Treatment to Study Molecular Complexes Stabilized by Hydrogen-, Halogen-, and Carbon-Bond Networks: Experiment and Theory of $(\text{CH}_2\text{F}_2)_n \cdots (\text{H}_2\text{O})_m$

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Abstract: Rotational spectra of several difluoromethane–water adducts have been observed using two broadband chirped-pulse Fourier-transform microwave (CP-FTMW) spectrometers. The experimental structures of $(\text{CH}_2\text{F}_2) \cdots (\text{H}_2\text{O})_2$, $(\text{CH}_2\text{F}_2)_2 \cdots (\text{H}_2\text{O})$, $(\text{CH}_2\text{F}_2) \cdots (\text{H}_2\text{O})_3$, and $(\text{CH}_2\text{F}_2)_2 \cdots (\text{H}_2\text{O})_2$ were unambiguously identified with the aid of 18 isotopic substituted species. A subtle competition between hydrogen, halogen, and carbon bonds is observed and a detailed analysis was performed on the complex network of non-covalent interactions which stabilize each cluster. The study shows that the combination of stabilizing contact networks is able to reinforce the interaction strength through a cooperative effect, which can lead to large stable oligomers.

The importance of non-covalent forces cannot be over-emphasized, as they are at the origin of the existence of any condensed phase. Among the different types of interactions which may occur at the intermolecular level, the hydrogen bond (HB) is by far the most widely known. It is able to stabilize static structures and mediate dynamic processes, and plays a key role in many chemical processes and biologically

relevant functions.^[1] Broadly speaking, the HB takes place whenever a D–H \cdots Y–Z interaction can be established, where the atoms D (donor) and Y (acceptor) are more electronegative than the H atom. This general definition not only refers to strong HBs, formed when both D and Y are strong donors or acceptors (for example, O or N), but can be extended to include weak hydrogen bonds (WHB) in which the binding partners only have a modest electronegativity. This can arise when either a weak donor (for example, C–H or S–H), a weak acceptor (halogens or π -systems), or both kinds of species are involved.^[2] In the same context, other non-covalent weak interactions such as halogen bonds,^[3] carbon interactions,^[4] or beryllium bonds^[5] have emerged in recent years.

From the experimental point of view, high-resolution spectroscopic techniques are the only methods that provide unequivocal and accurate information to characterize any type of interaction. In the past two decades, a deeper insight into WHBs and halogen bonds has been achieved by successfully combining experimental techniques, in particular Fourier-transform microwave spectroscopy (FT-MW), with computational approaches.^[6–10] The unique sensitivity of rotational spectroscopy allows an accurate characterization with nuclear resolution of (W)HBs or halogen bonds, providing the assignment of single conformers, even when geometric variations are only minor. However, its applicability has been limited to 1–3 subunits with few stabilizing interactions.^[10,11] The recent progress of quantum-mechanical (QM) methods together with the development of chirped Fourier-transform microwave (CP-FTMW) spectroscopy opens the possibility of studying larger oligomers. Very few systems in which several subunits and a large number of weak interactions are involved^[12–16] have been studied to date. Certainly, the rotational assignment of this type of oligomer to a high level of resolution is a challenge that can only be completed with the help of state-of-the-art calculations.

From a computational point of view, two major challenges have to be faced when dealing with weak interactions: the capability to efficiently explore complex interaction potential energy surfaces (IPESs), often characterized by shallow, quasi-degenerate local minima whose number markedly increases with the dimensions of the cluster,^[17–25] and the accuracy required for a reliable and balanced estimate of non-covalent interactions. One of the best molecular benchmarks regarding weak interactions is difluoromethane (CH_2F_2 , DFM hereafter), which has a pair of weak proton donors and a pair of weak proton acceptors, so it can encompass a large variety

of intermolecular arrangements.^[26–28] Aside from their importance in critical processes such as atmospheric ozone depletion, freons (halocarbon products) are molecular species of fundamental interest in the context of WHB and halogen bonding.^[29,30]

In this work, the competition between different classes of stabilizing interactions is shown using CP-FTMW spectroscopy. For the first time, trimers and tetramers of DFM and water, in the form of stable gas-phase oligomers, are investigated. In 1999, Caminati et al. first studied the interaction of water with DFM^[31] and a DFM dimer^[27] using the Stark-modulated free-jet absorption millimeter-wave spectrometer.^[32,33] Since then, a way to the study of larger adducts has been opened: after 8 years, the DFM trimer,^[28] and another 7 years later, the tetramer were detected by means of FTMW spectroscopy.^[6,7,34] The subunits of both oligomers are held together by a WHB network, giving rise to a cyclic arrangement in the trimer and a rhomboid form for the tetramer. Exploiting the potential of CP-FTMW spectroscopy, we have extended the study of the interaction between DFM and water, analyzing the trimers $(\text{CH}_2\text{F}_2)\cdots(\text{H}_2\text{O})_2$ and $(\text{CH}_2\text{F}_2)_2\cdots(\text{H}_2\text{O})$, labelled DW2 and D2W, respectively, hereafter, and two tetramers $(\text{CH}_2\text{F}_2)\cdots(\text{H}_2\text{O})_3$ and $(\text{CH}_2\text{F}_2)_2\cdots(\text{H}_2\text{O})_2$, named DW3 and D2W2, respectively. Unraveling the structure of heteroclusters composed by more than two moieties is interesting, because it highlights the types of competitive interactions that stabilize each complex, making it possible to assess if other interactions might have a key role. In fact, the whole range of possible HBs is achievable, from moderately strong ($\text{OH}\cdots\text{O}$) HBs between two water molecules to WHBs of different types such as strong-donor-weak-acceptor ($\text{O}-\text{H}\cdots\text{F}$), weak-donor-strong-acceptor ($\text{C}-\text{H}\cdots\text{O}$), and the most elusive yet efficient weak-donor-weak-acceptor bond ($\text{C}-\text{H}\cdots\text{F}$). Additionally, more exotic interactions such as halogen-halogen contacts ($\text{C}-\text{F}\cdots\text{F}$) or halogen bonds ($\text{C}-\text{F}\cdots\text{O}$) could be present in this type of large oligomers. Such complexes should be stabilized by a subtle interplay of all the aforementioned contributions and could yield a wealth of structural and dynamical information, allowing for a step forward in the comprehension of non-covalent bonds. Moreover, the coexistence of single and bifurcate interactions could lead to further stabilization patterns.

The first step required for approaching such a large variety of possible non-covalent interactions concerns the choice of an accurate theoretical strategy that is able to identify the most stable conformers for the two trimers DW2 and D2W, and the two tetramers DW3 and D2W2. The conformational flexibility of these systems is enormous, since the oligomers can be stabilized by several types of weak interactions that coexist with very similar stabilization energies. When trimers and tetramers are considered, the presence of cooperative networks makes it very difficult to evaluate an evident preference a priori, since differences are very subtle and many oligomers are almost isoenergetic. It is clear then that conventional transferrable force fields, used routinely in molecular mechanics, encounter many difficulties in the prediction of this kind of system. Even if the force field is parameterized specifically for each system (with a non-

negligible computational burden), the limitation of the classical model potentials constituting the force field makes further refinement based on higher-level QM methods necessary.^[3,4] As far as intermolecular interactions are concerned, it is well known that the best compromise between accuracy and computational cost is offered by density functional theory (DFT), compared to more accurate yet expensive wave-function-based techniques such as second-order Møller-Plesset perturbation theory (MP2) or Coupled Cluster. Nonetheless, the accuracy of the results obtained by a specific DFT functional is well known to significantly depend on the investigated system, especially when WHBs are involved.^[20,24,35–37] Recently,^[3,4] the identification of homo-clusters of two, three, and four DFM units obtained with the dispersion-corrected DFT functional B97D^[38] was found to be in good agreement with both experimental data and, as far as the dimer and the trimer are concerned, with QM predictions previously obtained at the MP2 level.^[27,34] Unfortunately, to our knowledge, the performance of the B97D functional for the DFM and water molecules was never extensively benchmarked, so it should be used carefully. Conversely, despite being computationally more expensive and aside from the good agreement found with B97D for the aforementioned DFM clusters, MP2 was successfully applied in several studies to describe WHBs,^[2] in particular the $\text{DFM}\cdots\text{H}_2\text{O}$ interaction.^[31]

To circumvent these issues, we here resort to a two-step computational screening protocol based solely on QM calculations, exploiting both the benefits of DFT and the accuracy of MP2. For all investigated species, a preliminary exploration of the IPESs of the clusters is carried out with the B97D functional first. Specifically, a number of different starting points, prepared in consideration of the possible symmetry and WHB networks that could be established, is subjected to a geometry optimization, where the binding energy (BE) is evaluated.

The second step, computationally more expensive, is then only performed on a selection of the most stable clusters. It consists in a further geometry optimization, carried out at the MP2 level, which is known to yield reliable results for non-covalent complexes^[21,39] and used in similar systems.^[29,30,34] Additional DFT calculations carried out using the popular B3LYP functional with the empirical D3(BJ)^[40] correction with two different basis sets are then performed to verify the quality of these calculations. Further details on the whole screening protocol can be found in the Supporting Information (Figures S1–S9 and Tables S1–S4). The most stable predicted conformations for each oligomer at the MP2 level are displayed in Figure 1 and were used as a starting point for the experimental analysis.

The rotational spectra were recorded with two different CP-FTMW spectrometers covering the frequency ranges 2–8 GHz (equipment at the University of Virginia)^[41] and 6–18 GHz (equipment at the University of the Basque Country),^[42] and the details are reported in the Supporting Information. Both spectra have a similar S/N ratio and are fairly crowded (Figure 2). First, the transitions and frequencies already observed in the previous works for $(\text{DFM})_2$, $(\text{DFM})_3$, $(\text{DFM})_4$, and $(\text{DFM})\cdots(\text{H}_2\text{O})$ with S/N ratios of 9250,

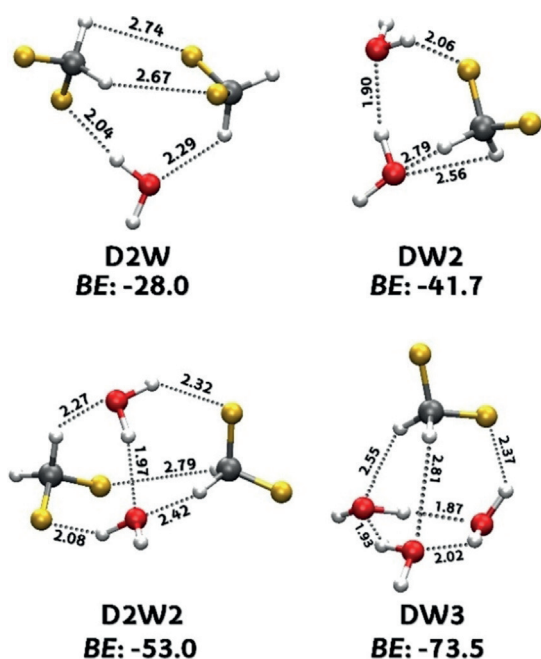


Figure 1. Most stable predicted conformations of D2W, DW2, D2W2, and DW3 complexes, calculated at the MP2/6-311++G(d,p) level. Binding Energies (BE) are given in kJ mol^{-1} . The most important intermolecular interactions are highlighted and the corresponding distances are given in Å.

1325, 25, and 1250, respectively, were removed. In the lower panel of Figure 2, it can be seen that after removing the already-known species, a significant amount of rotational transitions remained in the spectra. Based on our predictions, the oligomers DW2, D2W, DW3, and D2W2 could be successfully assigned. In particular, 43 different frequencies ($S/N \approx 230$) were assigned to DW2 μ_a -R type transitions with a splitting pattern (Supporting Information, Table S1). Regarding the heavier oligomers D2W ($S/N \approx 450$), DW3 ($S/N \approx 200$), and D2W2 ($S/N \approx 100$), their presence in the spectra is still noticable. 121, 103, and 158 different frequencies were measured for D2W, DW3 and D2W2, respectively. In the case of D2W and DW2, the rotational transitions exhibit a splitting pattern due to large amplitude motions of the water molecule. All rotational frequencies were fitted with a Watson S -reduced Hamiltonian in the I^r representation.^[43] The obtained spectroscopic parameters (Table 1) along with the types of dipole-moment transition patterns point out that the observed oligomers correspond to the most stable structures of each species. However, several compositions of clusters have similar rotational constants due to the flexibility of the systems. To confirm the assignments and achieve a straightforward and unequivocal identification, a third experiment was performed in Bilbao. A mixture of $\text{H}_2\text{O}:\text{D}_2\text{O}$ (1:1) instead of pure H_2O was added to the DFM cylinder. In this way, the analysis of various isotopologues was carried out. The spectra of a total of 3, 10, and 5 different isotopologues species were fitted using the same procedure as before for DW2, D2W, and D2W2, respectively (Tables S9–S11). The comparison between the substitution structures (r_s ,

Kraitchmann method^[44]) and the equilibrium structures (r_e , theoretical) validated the assignments. All spectroscopic constants and principal-axes coordinates are given in Supporting Information (Tables S5–S7 and S9–S11). It should be highlighted that the theoretical estimates are not very accurate for these kinds of weakly bound complexes, where many weak interactions and motions are involved. Hence, the assignment of these clusters becomes a difficult task, especially when light hydrogen atoms are involved in weak interactions. Furthermore, the presence of tunneling effects that involve different hydrogen atoms of the water molecules affect the corresponding coordinates, increasing the deviation from the predictions.

To deepen the knowledge about the different kinds of interactions and understand the driving forces responsible for their aggregation, we performed a quantitative and qualitative analysis. In particular, the quantum theory of atoms in molecules (QTAIM) by Bader was applied, supported by the non-covalent-interactions (NCI) method.^[45,46] The first approach makes it possible to evaluate the presence or absence of bonds stabilizing the complexes, identifying the bond-critical points (BCPs) and bond paths for each cluster. In this analysis, the 1:1 adduct of DFM (DW hereafter) and the DFM dimer (D2) were also considered. The second approach, NCI analysis, makes it possible to visualize and verify non-covalent interactions based on the electron density (ρ), its gradient (s), and its derivatives (λ). The colored iso-surfaces reveal the attractive and repulsive nature of each interaction. The results are summarized in Figure 3. We know that the analysis is affected by intrinsic limitations, but combining the two approaches is useful in order to extend the interpretation of the results. Considering the observed dimers, it is clear that the presence of an oxygen atom represents the strongest driving force. In fact, while the DW complex is stabilized by two HBs ($\text{O}-\text{H}\cdots\text{F}$ and $\text{C}-\text{H}\cdots\text{O}$), the homodimer needs up to four weaker interactions (two times $\text{C}-\text{F}\cdots\text{H}$ as well as $\text{C}-\text{H}\cdots\text{F}$ and $\text{C}-\text{F}\cdots\text{F}$). It should be noted that, in addition to the three HBs that were already determined, the QTAIM method reveals a halogen–halogen contact ($\text{C}-\text{F}\cdots\text{F}$; -6.8 kJ mol^{-1}) and its stabilization energy is in the same order of magnitude as the WHBs. Furthermore, the attractive character is also confirmed in the corresponding NCI plot (Figure 3). The total stabilization in D2 is higher than in DW, -24.6 (D2) vs. $-18.1 \text{ kJ mol}^{-1}$ (DW), despite the absence of an oxygen atom that could create stronger HBs.

Adding a molecule of water does not alter the observed trend. Hence, the DW2 complex is characterized by a lower number of interactions with respect to D2W. In particular, in DW2, the predominant interaction is a HB ($\text{O}-\text{H}\cdots\text{O}$) between the two water molecules. This allows to obtain a more compact and bound cluster, characterized by a cyclic triangular arrangement that includes the other two WHBs ($\text{O}-\text{H}\cdots\text{F}$ and $\text{C}-\text{H}\cdots\text{O}$). Regarding the D2W trimer, the cyclic-triangular arrangement is maintained, but only WHBs can be formed, so the oligomer requires four weaker interactions ($\text{O}-\text{H}\cdots\text{F}$, $\text{C}-\text{H}\cdots\text{O}$, $\text{F}-\text{C}\cdots\text{F}$, and $\text{C}-\text{H}\cdots\text{F}$). One of these interactions (BCP #3) is represented by an unexpected $\text{F}-\text{C}\cdots\text{F}$ contact. This unusual stabilizing interaction has already been characterized in the literature^[4] as a carbon

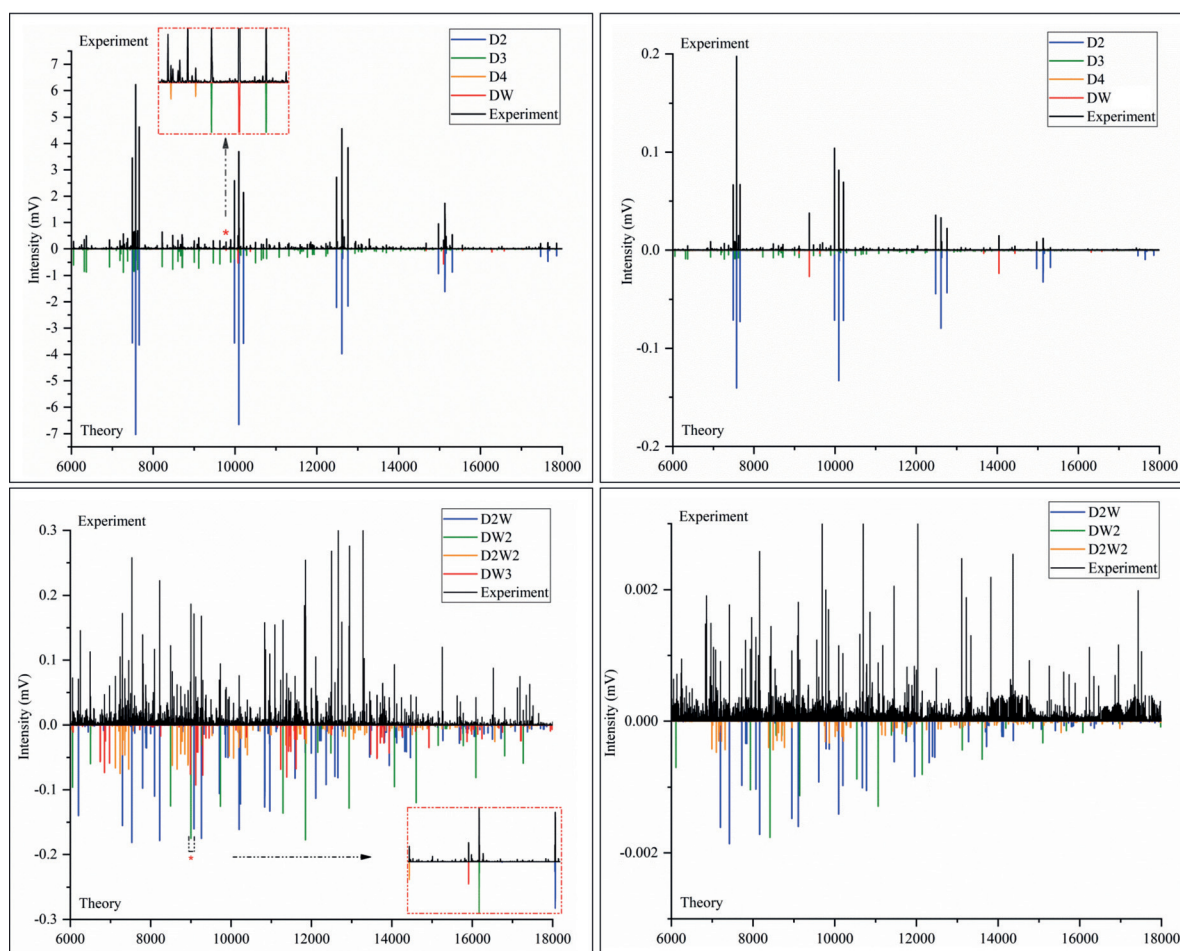


Figure 2. Broadband rotational spectra of DFM with water (in MHz). The experimental spectra are represented by the black trace, while the simulated spectra created from the fitted parameters of each species are represented by colored traces. In the top left panel, the spectrum of DFM with H_2O is displayed; while the spectrum of DFM with D_2O is shown in the top right panel. In the bottom panel, the spectra of DFM with H_2O (left) and DFM with D_2O (right) are shown after cutting all the lines of species analyzed in previous works.^[6,27,28,31,34]

Table 1: Experimental and theoretical rotational constants of the observed clusters, calculated at the MP2/6-311++G(d,p) level. The states $\nu=0$ and $\nu=1$ refer to the tunnelling motion involving the hydrogen atoms of D2W and DW2.

	D2W Exp. $\nu=0$	$\nu=1$	Theo.	DW2 Exp. $\nu=0$	$\nu=1$	Theo.	D2W2 Exp.	Theo.	DW3 Exp.	Theo.
A [MHz]	2248.046(7)	2248.189(7) ^[a]	2305	5249.79(8)	5249.99(9)	5560	1759.4166(4)	1744	2755.9026(8)	2801
B [MHz]	1096.505(1)	1096.513(1)	1103	1729.538(3)	1729.659(3)	1736	763.3093(1)	737	1182.2330(5)	1213
C [MHz]	860.5630(6)	860.5101(6)	873	1316.198(2)	1316.167(3)	1339	696.9655(1)	699	1105.3436(4)	1140
σ [kHz] ^[b]	10.1			9.9			5.8		8.1	
N ^[c]	121			43			158		103	

[a] Error in parentheses in units of the last digit. [b] Root-mean-square deviation of the fit. [c] Number of fitted transitions.

bond and it is preferred over other WHBs. The corresponding NCI plots also shows this stabilization.

The D2W2 complex has a net of six interactions and adopts a tetrahedral-like arrangement, showing a HB between the two water moieties ($\text{O}-\text{H}\cdots\text{O}$) which shortens the $\text{O}\cdots\text{O}$ distance (2.9 Å) and elongates the $\text{C}\cdots\text{C}$ distance (4.2 Å) between the two DFM units. The D3W complex adopts a pyramidal structure, with the three water molecules forming the base of the pyramid with three HBs ($\text{O}-\text{H}\cdots\text{O}$)

and difluoromethane at the top of the pyramid, stabilized by three WHBs ($\text{O}-\text{H}\cdots\text{F}$ and two times $\text{C}-\text{H}\cdots\text{O}$).

The defining factor to evaluate the stability of each cluster is the BE. The corresponding values computed at the MP2/6-311++(d,p) level can be also compared with the sum of the energies of each BCP, estimated with the QTAIM method. Both procedures have limits. However, it is possible to derive trends that can be considered more representative. In general, the values obtained by summing all BCP interactions are

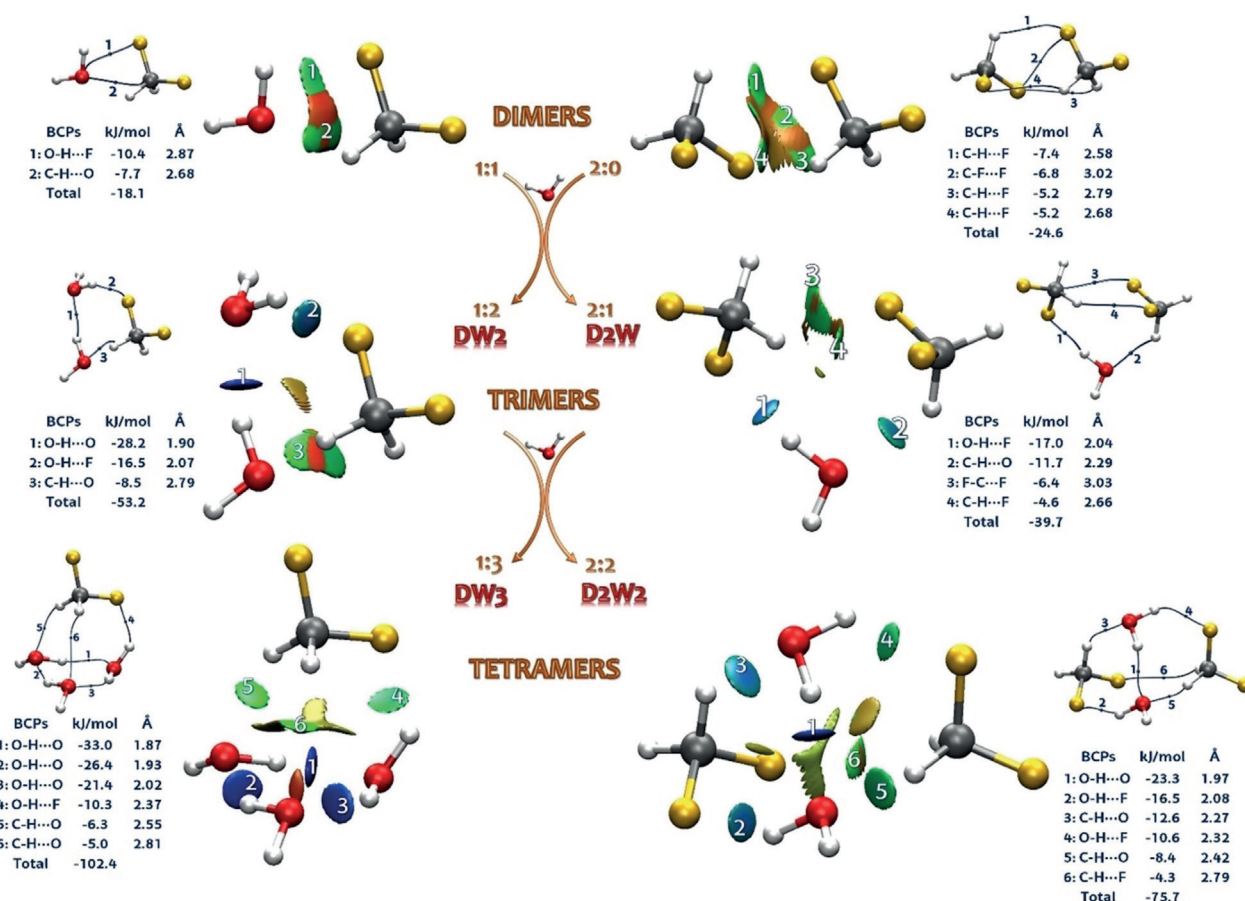


Figure 3. Quantitative analysis of attractive and repulsive interactions using the QTAIM procedure and NCI iso-surfaces. The energy values of attractive contacts (QTAIM) and interaction distances (MP2/6-311 + G(d,p)) are also reported. Blue- and green-colored areas indicate the presence of strong and weak attractive interactions, respectively. Red color signifies repulsive interactions. Bond-critical-point (BCP) paths are represented as blue lines. The iso-surface of the NCI analysis was built using $s=0.5$ and a blue-green-red color scale from $-0.02 < \text{sign}(\lambda_2) \rho(r) < +0.01$ a.u.

larger than the MP2 values (Table S8), but regarding the trimers, both methods are consistent in the prediction that DW2 is bound more strongly. As expected, a larger number of water molecules leads to stronger total interactions. Another interesting observation is the high stability of these oligomers with respect to the fragmentation. This is confirmed by comparing their BE to the sum of the values of the corresponding adducts out of which they are formed. In all cases, the interaction energy of the cluster is considerably higher. For instance, the interactions characterizing D2W2 can be related to the smaller adducts. In particular, if we consider all the intermolecular bonds present in the D2W2 tetramer and therefore its BE, it is quite similar to the sum of the different dimers D2, W2, and DW (Table S8 and Figure S10). As expected, since the number of interactions increases, the WHB network that keeps the tetramer together is more stabilizing than the sum of interactions in the separated dimers. In general, the computed BEs are consistent with the average values found in the literature.^[1,2,47]

In summary, the combination of rotational spectroscopy with CP-FTMW spectrometers and accurate computational screening protocols based on QM calculations has allowed the

first observation of four different heteroclusters of DFM and water (D2W, DW2, D2W2, and DW3). Moreover, 18 substituted isotopologues confirmed the observed clusters. The study shows the subtle balance and competition between different stabilizing interactions such as hydrogen, halogen, and carbon bonds. The analysis of how these two moieties interact to form larger aggregates highlighted the oxygen atom with its good electron-donor character. This is reflected in the higher BE of the clusters with the larger number of water molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: difluoromethane · molecular clusters · non-covalent interactions · quantum-chemical calculations · rotational spectroscopy

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