

# Water-Induced Structural Changes in Crown Ethers from Broadband Rotational Spectroscopy.

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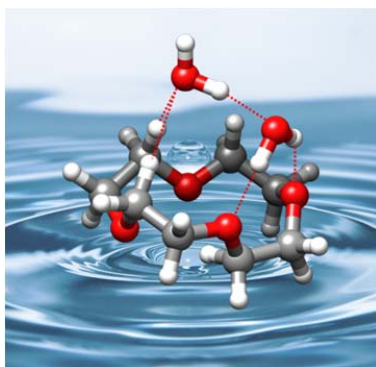
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ABSTRACT The complexes of 12-crown-4 ether (12C4) with water, generated in a supersonic jet, have been studied using broadband Fourier transform microwave spectroscopy. Three 1:1 and one 1:2 clusters have been observed and their structures unambiguously identified through the observation of isotopologue spectra. The structures of the clusters are based on networks of O-H $\cdots$ O and C-H $\cdots$ O hydrogen bonds. The most abundant 1:1 cluster is formed from the most stable S<sub>4</sub> symmetry conformer of 12C4, even though it is not the energetically favored water complex. Interestingly, the structures of the most stable water cluster and the other remaining observed 1:1 and 1:2 complexes are formed from the third or the fifth most abundant conformers of 12C4. This shows the existence of a mechanism that changes the configuration of 12C4 so that the host-guest interactions can be maximized, even for a “soft” ligand like water.

## TOC GRAPHICS



Crown ether (CE) chemistry has contributed to important advances in the area of molecular recognition and to the introduction of new concepts such as host-guest chemistry and supramolecular chemistry.<sup>1</sup> These compounds have many remarkable properties, but the most important attribute, known since their discovery,<sup>2</sup> is the ability to selectively form complexes with metal cations<sup>1,3</sup> or with other cationic molecular species like protonated primary and secondary amines.<sup>4</sup> Neutral molecular guest species were also identified to form solid-state inclusion compounds with CEs as observed by Pedersen in his second paper on macrocycles.<sup>5</sup>

The capability of CEs to form complexes can be related to their great flexibility to adopt different configurations, making it possible for the cooperation of the oxygen atoms lone pairs to create a high electronic density region inside the ring cavity. Because of the rich conformational panorama of CEs<sup>6,7</sup> and the respective low barriers associated with them, a mechanism that changes the configuration to maximize host-guest interactions can be assumed. Furthermore, CEs are amphiphilic. They can transport their guests from a hydrophilic solvent phase, such as water, to a hydrophobic solvent phase, where an organic reaction might take place. Since structural changes upon solvation of the CEs might influence the binding properties, one of the open questions is how the solvent and the host-solvent interactions influence the conformational stabilities of such flexible systems.<sup>8</sup> A useful way to quantify these interactions is to isolate the clusters formed by the host and solvent molecules in the gas phase. The isolation of CEs and their molecular clusters in a supersonic jet combined with high-resolution molecular spectroscopy can be an effective way to obtain their conformations and intrinsic properties in an environment free of intermolecular interactions or bulk solvent effects. Furthermore, individual water molecules can be added in a bottom-up approach to selectively study the effect of microsolvation.

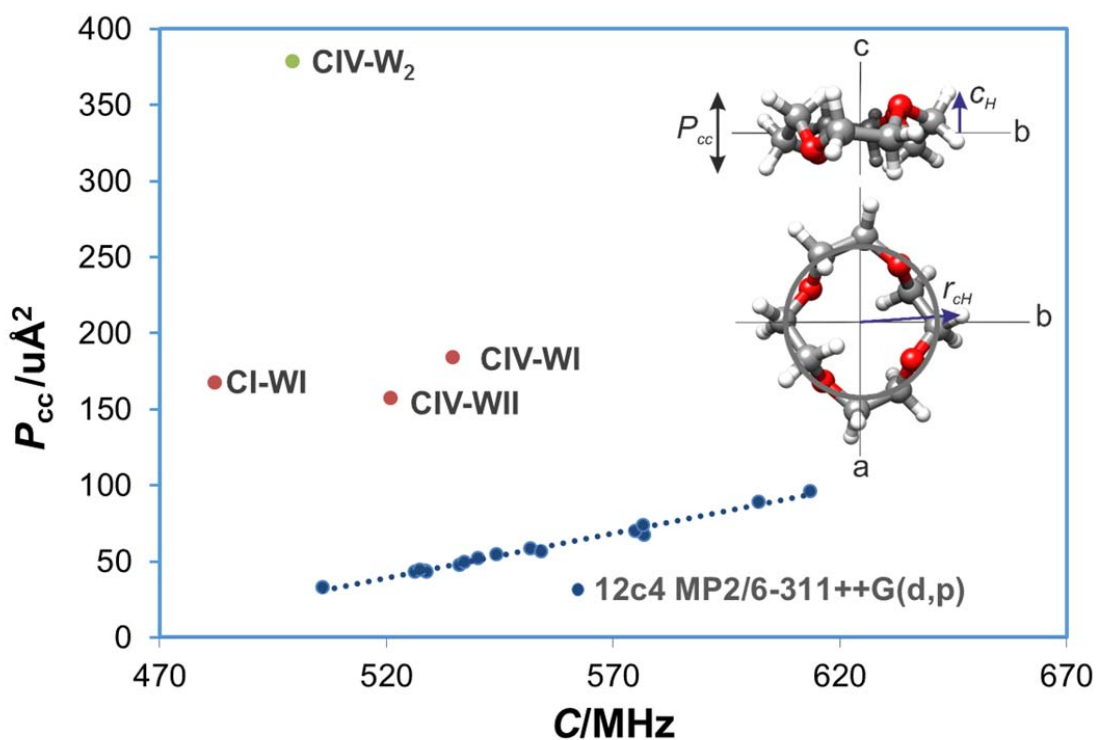
Up to now, only a limited number of gas-phase studies of CEs<sup>6,7,9</sup> and their complexes with water or other solvents can be found in the literature.<sup>10-13</sup> Pioneering work was performed on benzo-CE compounds, bearing a chromophore group, using IR-UV laser spectroscopy techniques.<sup>9-13</sup> It was found that for benzo-15-crown-5 – water complexes formed in a supersonic jet the addition of a single water molecule changed the energy order of the respective crown conformations tremendously. Interestingly, a second water molecule was found to bind to the opposite side of the crown ring and not, as one might intuitively assume, to the first water. Recently, a pure microwave (MW) spectroscopy study on the bare 15-crown-5 (15C5) was performed, identifying eight conformers.<sup>6,7</sup> Furthermore, using infrared multiple photon dissociation (IRMPD) vibrational spectroscopy, the complexes of 18-crown-6 (18C6) and 15C5 with hydronium and ammonium cations were investigated. It was found that in the complex, 15C5 took on an asymmetric pyramidal structure, while 18C6 remained more symmetric ( $C_{3v}$ ).<sup>14</sup>

In the present study, we use broadband chirped-pulse Fourier transform microwave spectroscopy (CP-FTMW)<sup>15</sup> to reveal the conformational flexibility of 12C4 and how it changes as water molecules are added, in a bottom-up approach. MW spectroscopy in supersonic jets offers one of the most powerful experimental methods to precisely determine the structure of an isolated molecule or cluster, and it provides access to molecules without chromophore groups.<sup>16-18</sup> Because of this, potential influences of the chromophores on the formation of water clusters, as studied in previous, UV-based spectroscopic studies (*vide supra*)<sup>9-13</sup> can be investigated. For MW spectroscopy, the molecules need to be polar and have to be brought into the gas phase. Using CP-FTMW spectroscopy, large areas of the spectrum can be covered while keeping the superior resolution and sensitivity known for MW spectroscopy. These features enable us to observe mixtures of low concentration species, such as CEs and their clusters.

For the experiments, the Hamburg CP-FTMW spectrometer COMPACT was used.<sup>19</sup> 12C4 was placed in a heatable reservoir close to the orifice of a pulse valve. The molecules were supersonically expanded into vacuum using neon as a carrier gas to provide low rotational temperatures (1-2 K). The molecules were excited using a low-frequency 2-8 GHz microwave chirp of 4  $\mu$ s duration. This low-frequency range is particularly suited for larger and heavier molecular systems like CEs that have large moments of inertia and thus small rotational constants. After the excitation pulse is over, the molecular response was recorded as a free-induction decay (FID) in the time domain. A Fast Fourier transformation to the frequency domain yielded the rotational spectrum of all polar species sufficiently abundant in our jet, such as conformers, clusters with different amounts of water molecules attached, or isotopologues.

Prior to analyzing the microwave spectrum, we extended previous ab initio calculations<sup>20</sup> to generate reasonable sets of rotational parameters, energies and relative populations of the most abundant conformers of 12C4.<sup>21</sup> Table S1 and Figure S1 of the supplementary material collect a summary of the results for the conformers within an energy range of 1000  $\text{cm}^{-1}$  relative to the global minimum. The two species expected to be the most abundant, according to their calculated Gibbs energies, are **CI** (the global minimum) and **CII**, which have  $S_4$  and  $C_i$  symmetries, respectively, and thus no dipole moment and no microwave spectrum. Therefore, for 12C4 only a weak microwave spectrum arising from the less populated, but polar higher-energy conformers would be expected. For the lowest energy conformers of 12C4 we also performed some preliminary predictions of the possible 1:1 clusters with water to evaluate possible water docking positions. The results are collected in Table S2 and Figure S2 of the supplementary material.

An interesting result derived from these calculations is the linear correlation found between the values of the planar momentum  $P_{cc}$  and the  $C$  rotational constant for the conformers of 12C4 (see Figures 1 and S3). This can be understood by taking into account that 12C4 is a ring. While  $C$  gives a measure of the average diameter of the ring,  $P_{cc}$  gives the mass extension out of the  $ab$  plane or thickness. Puckering of the ring leads to a reduction of the radius and increases the thickness, so both  $C$  and  $P_{cc}$  increase. On the contrary, an extended ring would have lower values of  $C$  and  $P_{cc}$  so a positive slope for the correlation line can be expected, as shown in Figure 1.



**Figure 1.** Scatter plot showing the correlation between the values of the planar moment  $P_{cc} = (I_a + I_b - I_c)/2 = \sum_i m_i c_i^2$  and the  $C$  rotational constant ( $C = h/8\pi^2 I_c$ ;  $I_c = \sum_i m_i (a_i^2 + b_i^2) = \sum_i m_i r_{ci}^2$ ) for a series of 12C4 forms predicted at the MP2/6-311++G(d,p) level. The planar moment  $P_{cc}$  can be associated to the thickness of the ring and  $C$  to its average diameter. Both the ring thickness ( $P_{cc}$ ) and the diameter ( $C$ ) depend on the degree of ring-puckering and should be strongly correlated. For a form with a small degree of puckering and thus extended the radius should be high ( $C$  small) and the

thickness low ( $P_{cc}$  small). On the contrary, a puckered ring would imply a low diameter ( $C$  high) and a high thickness ( $P_{cc}$  high). The points corresponding to the observed species **CI-WI**, **CIV-WI**, **CIV-WII** and **CIV-W<sub>2</sub>** indicate that these do not correspond to any 12C4 conformer.

The broadband spectrum recorded for 12C4, given in Figure S4, is extremely rich, with more than 2000 lines having a signal to noise ratio (S/N) of 3:1 or better. It exhibits rather intense lines, which is not what we initially expected based on the ab initio calculations. When adding a flow of water to the supersonic expansion of 12C4 and neon, the most intense lines increased in intensity so they can be attributed to clusters of 12C4 with water. The observation of several characteristic a- and b-type transition quadruplet patterns (see Figure 2) allowed for the identification of the most prominent species in the spectra. The analysis of its spectrum<sup>22</sup> yielded the rotational constants collected in the first column of Table 1. The observed values of  $C$  vs  $P_{cc}$  (Figure 1) suggest it to be a heterodimer of 12C4 with water. From comparison with ab initio calculations, we could initially assign it to the **CI-WI** form (see Tables 1, S1 and S2). The observed lines were intense enough to have observable spectra for the monosubstituted <sup>13</sup>C isotopologues in natural abundance (see Table S3 of the supplementary material). An experiment conducted with a 1:1 mixture of H<sub>2</sub><sup>18</sup>O and H<sub>2</sub><sup>16</sup>O allowed for the identification of its <sup>18</sup>O isotopologue (see Figure 2 and Table S3) and led to the determination of the structure of this species, as shown in Figure 3.

In the subsequent analysis of the broadband spectrum new species were identified. Their rotational constants are collected in Table 1. For the species lately identified as **CIV-WI** the spectrum of one water-<sup>18</sup>O was observed and the  $C$  vs.  $P_{cc}$  plot (Figure 1) identifies it as a heterodimer. The **CIV-WII** species was found to be rather weak, and no water-<sup>18</sup>O spectrum was observed. However, from its  $C$  vs.  $P_{cc}$  values it can also be identified as a heterodimer. The **CIV-W<sub>2</sub>** species was identified as a three-body cluster by the  $C$  vs.  $P_{cc}$  plot, and it exhibits the parent

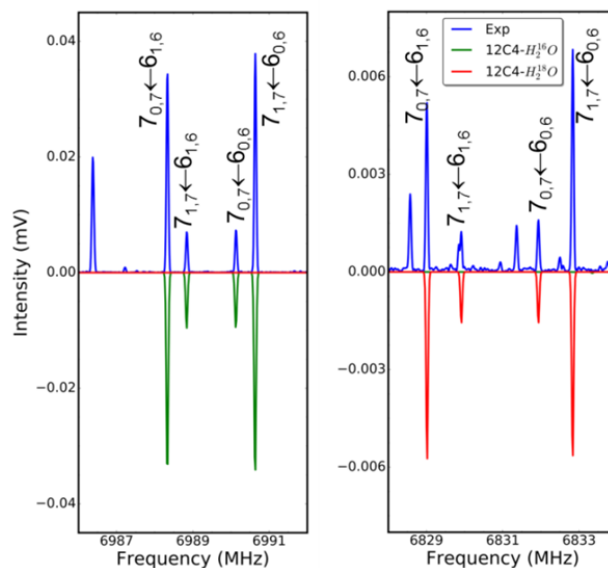
and two water  $^{18}\text{O}$  species spectra. The observed transition frequencies (Tables S11 to S22), the complete tables of rotational constants and the details of the analysis are given in the supplementary information (Tables S3 to S6).

**Table 1.** Rotational parameters obtained from the analysis of the spectrum of the 12-crown-4 ether $\cdots(\text{H}_2\text{O})_n$  ( $n=1,2$ ) clusters, **CI-WI**, **CIV-WI**, **CIV-WII** and **CIV-W<sub>2</sub>**, and their comparison with ab initio values (MP2/6-311++G(d,p)). (See also Table S2 for further information.)

Param. <sup>a]</sup>	<b>CI-WI</b>		<b>CIV-WI</b>		<b>CIV-WII</b>		<b>CIV-W<sub>2</sub></b>	
	obs.	calc	obs.	calc	obs.	calc	obs.	calc
$A/\text{MHz}$	859.605198(18) <sup>[b]</sup>	884.8	865.68041(57) <sup>b</sup>	889.2	858.65138(36) <sup>b</sup>	858.6	620.65214(33) <sup>b</sup>	639.7
$B/\text{MHz}$	634.96607(17)	641.0	692.14048(89)	699.1	726.04533(57)	716.7	528.67490(24)	537.9
$C/\text{MHz}$	482.06588 (15)	484.2	534.66454(78)	539.4	520.96955(55)	534.4	499.26754(26)	501.2
$P_a/\text{u}\text{\AA}^2$	628.17798(28)	630.5	545.8003(13)	545.7	538.78594(91)	531.2	576.95262(70)	709.6
$P_b/\text{u}\text{\AA}^2$	420.18290(28)	413.2	399.4260(13)	391.2	431.28805(91)	414.6	435.28825(70)	575.5
$P_c/\text{u}\text{\AA}^2$	167.73701(28)	157.9	184.3680(13)	177.2	157.28494(91)	174.0	378.98270(70)	214.8
$\Delta_J/\text{kHz}$	0.1675(18)		0.0555(99)		[ 0.] <sup>[c]</sup>		0.0339(32)	
$\Delta_{JK}/\text{kHz}$	-0.4604(52)		[ 0.]		[ 0.]		0.390(13)	
$\Delta_K/\text{kHz}$	0.7887(56)		[ 0.]		[ 0.]		-0.336(11)	
$\delta_J/\text{kHz}$	0.00954(77)		-0.0196(54)		-0.0815(81)		0.0086(16)	
$\delta_K/\text{kHz}$	0.0869(38)		[ 0.]		[ 0.]		-0.326(17)	
$\sigma/\text{kHz}$	4.3		4.0		5.2		4.6	
$n$	136		75		21		80	

<sup>[a]</sup> Analysis of the spectra have been done with the A-reduced semirigid rotor Hamiltonian of Watson<sup>[16]</sup> in the  $I'$  representation.  $A$ ,  $B$  and  $C$  are the rotational constants;  $\Delta_J$ ,  $\Delta_{JK}$ ,  $\Delta_K$ ,  $\delta_J$  and  $\delta_K$  are the quartic centrifugal distortion constants;  $\sigma$  is the rms deviation of the fit;  $n$  is the number of lines fitted. <sup>[b]</sup> Standard errors are given in parentheses in units of the last digit. <sup>[c]</sup> Values in square brackets were kept fixed.





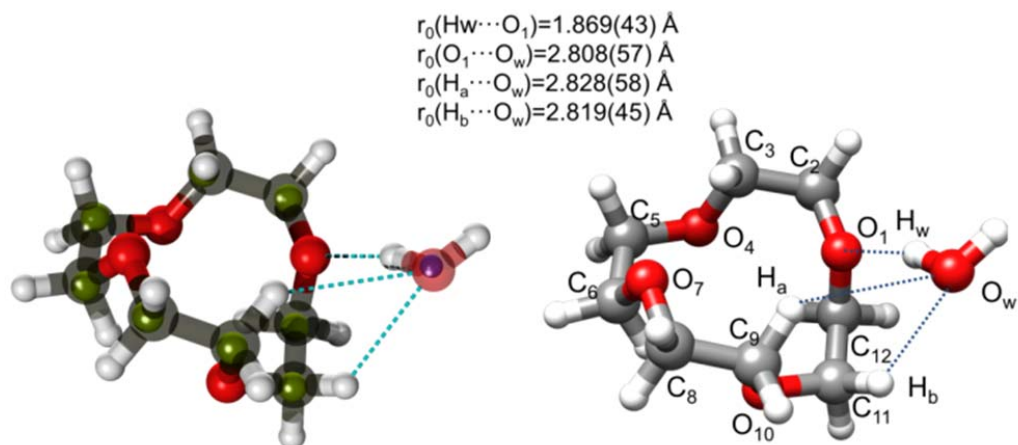
**Figure 2.** Sections of the spectrum of 12-crown-4 ether-H<sub>2</sub>O (conformer **CI-WI**) for H<sub>2</sub><sup>16</sup>O (left) and H<sub>2</sub><sup>18</sup>O (right) isotopologues showing the recognizable a-type vs. b-type transition patterns (e.g.  $7_{17}-6_{16}$  (a-type) vs.  $7_{07}-6_{16}$  (b-type)), which were very useful for the assignment of the spectra (see text for further explanations).

A simple look at the rotational parameters gives us some insight about the structures of the molecular complexes. In all cases, the value of  $P_{cc}$  increases upon <sup>18</sup>O substitution so the water molecule is located out of the *ab* inertial plane. The almost equal values of the  $P_{bb}$  planar moment for the parent and <sup>18</sup>O<sub>w</sub> species of **CI-WI** indicate that the water oxygen lies near the *ac* plane of the respective complex (Table S3). In the case of **CIV-WI** the *C* rotational constant,  $P_{aa}$  and  $P_{bb}$  are almost unchanged upon substitution (Table S4) indicating that the oxygen atom lies close to the *c* inertial axis.

The observation of the spectrum of monosubstituted isotopologues is primordial to precisely determining the structure of a molecular system using microwave spectroscopy. The rotational data of the parent and substituted species are the basis of the  $r_s$  and  $r_0$  methods, well established for structure determination. The  $r_s$  method uses the Kraitchmann equations<sup>23,24</sup> to give the

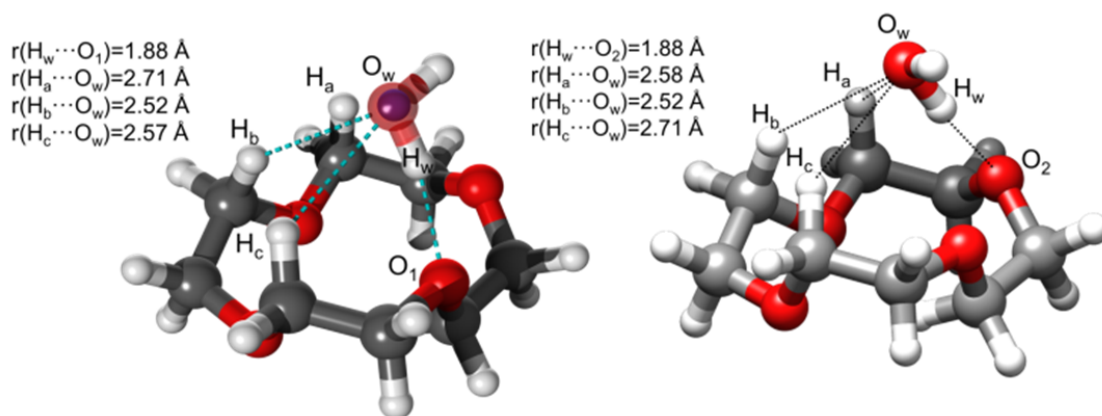
absolute values of the coordinates of the isotopically substituted atoms in the principal inertial axis system of the parent species. In the case of microsolvated molecules, this method may directly give us the location of the water molecule from the investigation of the  $^{18}\text{O}$  spectra.<sup>16,18,25</sup> In the  $r_0$  method<sup>26</sup> the effective structure of the ground vibrational state is totally or partially determined by fitting the complete set of rotational parameters. The application of the  $r_s$  method is limited to monosubstituted species and has serious limitations to determine the coordinates of atoms lying near the principal axes, which may result in imaginary coordinates. The signs of the coordinates can be chosen from a reasonable ab initio, $r_0$  structure, or from chemical intuition.

The  $r_s$  coordinates determined from the rotational parameters for the **CI-WI**, **CIV-WI** and **CIV-W<sub>2</sub>** rotamers are given in Table S7, and the details of the  $r_0$  calculation for species **CI-WI** are given in Table S8. The positions of all the carbon atoms and the water oxygen atom have been determined. These coordinates identify unambiguously its structure as conformer **CI-WI** (See Table S2 and figure S2) formed from the  $S_4$ -symmetric conformer **CI** of  $12\text{C}_4$  with water. This identification is clearly seen in Figure 3, which gives a comparison of the structure of this conformer from ab initio calculations (MP2/6-311G++d,p) and the positions of the substituted carbon and oxygen atoms. The oxygen atoms of the crown backbone structure point downwards and upwards in an alternating manner. A comparison of the experimental and calculated rotational constants is given in Table 1.



**Figure 3.** Comparison of the  $r_s$  structure of **CI-WI** (green balls) with the ab initio MP2/6-311++G(d,p) structure (left) and summary of the hydrogen bond  $r_0$  structure.

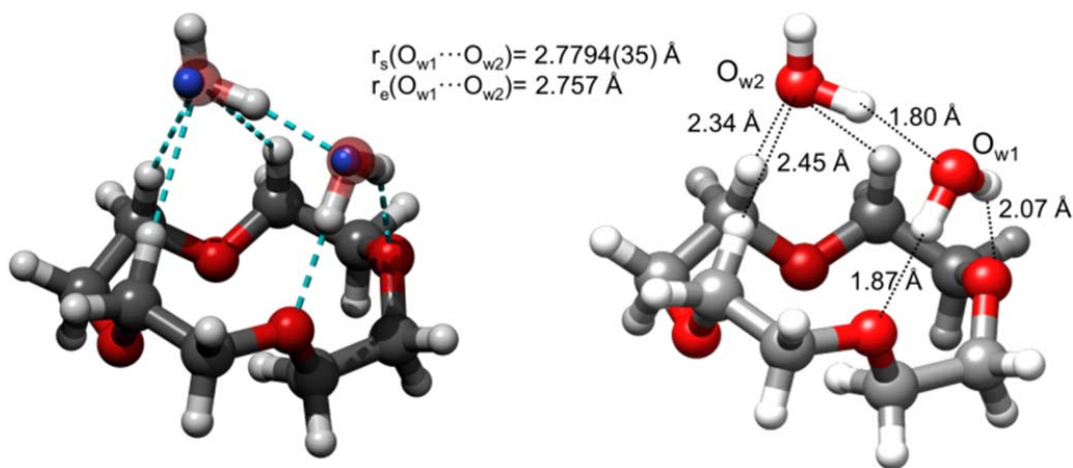
The structural assignment of the other species was not so straightforward. If we take into account the enormous flexibility of crown ethers and the many possible water docking sites, the observation of the  $^{18}\text{O}$  isotopologue was needed. We compared the rotational constants of the parent and  $^{18}\text{O}$  isotopologues and the coordinates of water oxygen with those calculated from the 12C4-w adducts formed from the lowest energy forms of 12C4 (see Tables S2 and S1). This procedure led to the identification of species **CIV-WI** shown in Figure 4, in which the 12C4 has almost the same structure as conformer **CIV** of the bare 12C4 (see also Table 1). Here, the oxygen atoms of the crown backbone are arranged in pairs, i.e., two pointing away from the water and two pointing towards the water. In the case of species **CIV-WII**, the tentative assignment of the structure was made by comparing the observed and calculated rotational constants (see Tables 1 and S2). The structure of this species is also shown in Figure 4. The main structural difference between **CIV-WI** and **CIV-WII** results from the different oxygen atom to which the water binds and, less importantly, from the different orientation of the water molecule with respect to the crown ether framework.



**Figure 4.** Comparison of the  $r_s$  coordinate of water oxygen (purple ball) calculated for the **CIV-WI** rotamer with the ab initio structure (MP2/6-311++G(d,p)) (left) as well as the ab initio structure of **CIV-WII**. Summary of the hydrogen bond ab initio structures (MP2/6-311++G(d,p)).

The identification of the 12C4- $w_2$  heterotrimer was challenging since the variety of conformers and docking positions made the approach of calculating all possible structures rather cumbersome, even if done automatically. In this case, we used a more practical approach. As discussed in more detail in the supplementary material (see Table S9), it is possible to calculate the rotational constants of the 12C4 backbone in the complex by subtracting the inertial contributions of the two water molecules from the rotational constants. This approach is applicable when the position of all water molecules have been determined to test changes in the structure of a monomer upon complexation.<sup>27,28</sup> Using this approach, we could identify the 12C4 backbone in the 12C4- $w_2$  rotamer as the **CIV-W<sub>2</sub>** form related to conformer **CIV** (Figure 5), as confirmed by the calculated rotational constants (see Table 1) and the experimentally determined oxygen atom positions (see Table S7). Using the same approach (see Table S10) it was possible

to identify conformers **CI** and **CIV** of 12C4 as the backbones of rotamers **CI-WI** and **CIV-WI**, respectively. Finally, based on further analysis, we could show that the structures of the three rotamers **CIV-WI**, **CIV-WII** and **CIV-W<sub>2</sub>** can be the outcome of geometry optimizations starting either from conformers **CII** or **CIV**. For bare 12C4 there is a small barrier between these conformers (see figure S11) that explains why the **CIV** form is not observed in the free jet due to collisional relaxation. This barrier is overcome and the potential energy surface is altered by the presence of water, which selects form **CIV** maximizing 12C4···water interactions. These results help to understand how the structure of 12C4 is modified to maximize host-guest interactions even in the case of a “soft” ligand like water.



**Figure 5.** Comparison of the  $r_s$  structure of the 12C4-w<sub>2</sub> observed rotamer with the ab initio structure for the **CIV-W<sub>2</sub>** form. The blue balls give the experimentally determined oxygen positions.

Another point of interest concerns the formation of the clusters in the supersonic jet, an event that happens in the first stages of the expansion where three body collisions exist. In this short period there is no time to reach equilibrium since the jet rapidly enters the collisionless regime with the concentrations of all species formed so far being diluted and cooled down. This points to a kinetic selection mechanism depending on the initial concentration of the “reactives”, to control the cluster abundances in the jet.<sup>29,30</sup> In fact, rotamer identified as **CI -WI**, which has the most intense spectrum, is formed from the most abundant 12C4 conformer **CI** (see Table S1). Rotamer identified as **CIV-WI** was the lowest energy conformer of all the 12C4-w clusters calculated so far but its relative population in the jet as measured from relative intensity measurements is about 0.66 with respect to rotamer **CI -WI**. The less intense **CIV-WII** rotamer has a relative abundance of about 0.13. As we have shown, both **CIV-WI** and **CIV-WII** rotamers can be formed from conformers **CII** or **CIV** of bare 12C4. The predicted initial concentrations, when summed up, give a relative abundance of *ca.* 0.7 with respect to **CI**, results which confirm the prevalence of a kinetic selection mechanism to control the cluster abundances in the jet. The heterotrimer **CIV-W<sub>2</sub>**, with a relative abundance of 0.33, can be formed by interaction of the 12C4-w **CIV-WI** and **CIV-WII** rotamers with a second water molecule or from the interaction of the 12C4 conformers **CII** or **CIV** with a water dimer. These results suggest that the experimental clusters abundances in the jet have a link to the calculated stabilities of the 12C4 monomer from which they are formed rather than to their own calculated stabilities.

It is interesting to note that the water molecules adapt to the topology of 12C4 to maximize host-guest interactions, and as we have shown this may lead to modifications of the 12C4 backbone structure. In all 12C4-w clusters the main interaction is an O-H $\cdots$ O hydrogen bond

(HB) from water to one endocyclic oxygen atom. The system is further stabilized by a network of weak C-H $\cdots$ O HBs from the neighboring methylene groups to water. The difference between the **CIV-WI** and **CIV-WII** rotamers lies on the oxygen atom to which water binds. **CIV-W<sub>2</sub>** shows more sophisticated interactions that might arise from the fact that it can be formed from either **CIV-WI** or **CIV-WII**. The water molecule initially bound to either O<sub>1</sub> or O<sub>2</sub> in **CIV-WI** and **CIV-WII**, respectively, (see Figure 4) now forms a bifurcated interaction to these oxygen atoms (Figure 5) in the heterotrimer. The second water molecule forms an O-H $\cdots$ O HB to the first water molecule and is further stabilized by a network of weak C-H $\cdots$ O interactions as shown in Figure 5. The O-O distance in the water-dimer substructure of 12C4-w<sub>2</sub> amounts to  $r_c=2.757\text{\AA}$ . The shortening of this distance with respect to the values reported for the free water dimer ( $r=2.98\text{\AA}$ )<sup>31</sup> or trimer ( $2.85\text{\AA}$ )<sup>32</sup>, can be attributed to HB cooperativity.

It is worth to compare the results for 12C4 microsolvated with individual water molecules with the previous results on benzo-15-crown-5 (B15C) – water systems. For B15C-w, a structure where water is simultaneously bonded to two oxygen atoms was concluded via a combination of IR/UV spectroscopy and ab initio calculations. In 12C4-w, structures showing two O-H $\cdots$ O HBs were not observed. They were predicted to be less stable than those showing a single O-H $\cdots$ O interaction. This might arise from the ring size and shape of the most stable conformers of the crown framework. For B15C-w<sub>2</sub> the two water moieties are located on opposite sides of the crown ring, contrary to our findings for 12C4-w<sub>2</sub>. The analysis of the <sup>18</sup>O isotopologue spectra allowed us to unambiguously determine the positions of the oxygen atoms of the water molecules that form a water dimer bound to the crown framework. One possible reason is that structures with water on both sides of the 12C4 ring would give rise to non-observable non-polar species if the ring keeps the *S*<sub>4</sub> or *C*<sub>i</sub> forms.

To summarize, we used CP-FTMW spectroscopy to investigate the 12-crown-4 ether...water system. We were able to identify a number of different clusters deducing the monomer backbone structure of 12C4 before and after complexation. We show that the complexes are formed from the most abundant non-polar forms of 12C4. When possible, 12C4 modifies its structure to maximize host-guest interactions. Our results indicate that only a single water molecule is able not only to drastically change the energies of the different conformers of 12C4 but also to alter its potential energy surface to allow such conformational changes to occur. It would be interesting to study 12C4 using other techniques such as IR-UV spectroscopy to provide new insights on its conformational distribution and the related water complexes.

#### ASSOCIATED CONTENT

**Supporting Information.** Rotational constants of all the observed species, figures and results from Kraitchman analysis as well as complete least squares structural fits, and line list of the experimental transitions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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##### Notes

The authors declare no competing financial interests.



## ACKNOWLEDGMENT

C.P. acknowledges a grant from the Alexander von Humboldt Stiftung. J.C.L and S.B. acknowledge the Ministerio de Economía y competitividad (Grant CTQ2013-40717-P) and the Junta de Castilla y León (Grant VA334U14) for financial support. J.C.L. acknowledges a Mobility Grant (PRX14/00695) of the Ministerio de Educación, Cultura y Deporte and Dr. M. Schnell for her kind hospitality. M.S. acknowledges support by the Deutsche Forschungsgemeinschaft within the framework of the priority program SPP1807 (SCHN1280/4-1) and support from the excellence cluster “The Hamburg Centre for Ultrafast Imaging“.

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