Hydration Clusters

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Direct Spectroscopic Detection of the Orientation of Free OH Groups in Methyl Lactate–(Water)$_{1,2}$ Clusters: Hydration of a Chiral Hydroxy Ester**

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Abstract: *Hydration of chiral molecules is a subject of significant current interest in light of recent experimental observations of chirality transfer from chiral solutes to water in solution and the important roles which water plays in biological events. Using a broadband chirped pulse and a cavity based microwave spectrometer, we detected spectroscopic signatures of the mono- and dihydrates of methyl lactate, a chiral hydroxy ester. Surprisingly, these small hydration clusters show highly specific binding preferences. Not only do they strongly prefer the insertion H-bonding topology, but they also favor specific pointing direction(s) for their non-H-bonded hydroxy group(s). We observed that the particular dihydrate conformer identified is not the most stable one predicted. This work highlights the superior capability of high-resolution spectroscopy to identify specific water binding topologies, and provides quantitative data to test state-of-the-art theory.*

It is known that a chirality recognition process is greatly influenced by water solvation and desolvation processes.[1–3] This is not surprising since the energy associated with these processes is comparable to the interaction energy between chiral contact pairs in a chirality recognition process. In recent years, distinct vibrational circular dichroism (VCD) signatures at the water bending band have been detected experimentally and attributed to specific chiral molecule–water clusters formed in solution.[4–6] Because of the complexity of the condensed phase and the uncertain reliability of theoretical calculations in capturing the most stable conformations of these chiral solvated clusters, there have been debates about the existence and significance of these specific clusters. Detailed knowledge about the chiral molecule–water interactions at the molecular level is crucial to achieve a comprehensive understanding of the observed phenomena.

Unlike the condensed-phase measurements, jet-cooled high-resolution spectroscopy can differentiate conformations of isolated chiral-molecule–water clusters with subtly different structures and provide accurate structural and relative stability information about them. Although jet-cooled high-resolution spectroscopy has been successfully used to study small (organic) molecule–water adducts, such as nitric acid–water,[7] formamide–(water)$_{1,2}$,[8] glycine–(water)$_{1,2}$,[9] and trifluoroacetic acid–(water)$_{1,2,3}$,[10] studies of only a handful of chiral molecule–water clusters, such as alaninamide–water,[11] 3-hydroxytetrahydrofuran–water,[12] glycidol–water,[13] and propylene oxide–(water)$_{1,2}$[14] have been reported.

Herein, we report rotational spectroscopic and high-level ab initio computational studies of methyl lactate (ML)–(water)$_{1,2}$ clusters. ML is an α-hydroxy ester with multiple functional groups, offering multiple hydrogen-bonding sites. First, we focus on the delicate competition between intra- and intermolecular H-bonding in the ML–(water)$_{1,2}$ clusters. Second, subtle conformational changes resulting from different orientations of the non-H-bonded, that is, free water OH groups in these clusters were recently reported to generate drastically different VCD signatures.[4–6] Such dangling OH groups at interfaces are subjects of intense current interest.[15] We therefore aim to utilize the advantages of high-resolution spectroscopy to identify such subtly different conformations.

The dominant ML conformer, also the only one detected in a jet expansion,[16] is stabilized by an intramolecular H-bonded ring formed between the OH and C=O groups. We identified seven monohydrate conformers based on this dominant ML monomer by ab initio calculations and confirmed them to be true minima without negative harmonic vibrational frequencies. This includes four *insertion* and three *addition* conformations, where water is inserted into the existing intramolecular H-bonded ring of ML or where water serves as an H-donor to one of the oxygen atoms of ML without breaking the existing intramolecular H-bonded ring, respectively. For the dihydrate clusters, a total of 16 ternary conformers were found using the binary conformers as starting points. Among those, seven are *insertion* only conformers and the others are mixed *insertion–addition* or *addition* only conformers. All the lowest energy ternary ML–(water)$_2$ conformers have an *insertion* only topology. The geometries and the spectroscopic constants of the mono- and dihydrates are summarized in Table S1 and S2, respectively, in the Supporting Information, together with details about the ab initio computations. Monohydrate conformers are named i-I, i-II, etc, while those of dihydrate are labeled as ii-I, ia-VII, etc. The Roman number indicates the relative stability in their respective class (with I being the most stable), while "i" or "a" indicate that water takes on the *insertion* or *addition* topology,

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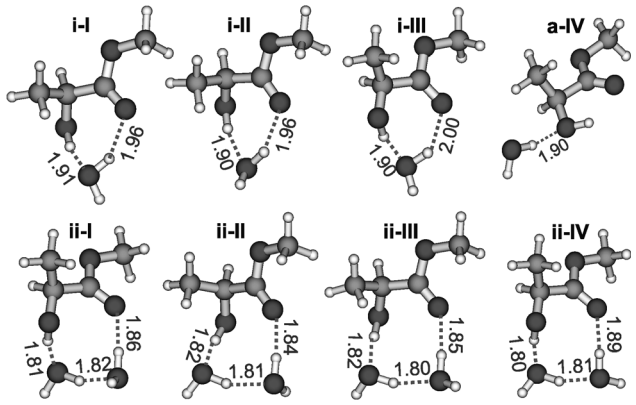


Figure 1. Geometries of the most stable conformers of the mono- and dihydrates of ML.

respectively. Geometries of some of the most stable conformers are shown in Figure 1.

Spectroscopic searches for the mono- and dihydrates of ML were carried out using a newly constructed broadband chirped pulse FTMW spectrometer.[17] Experimental details and an example broadband spectrum are provided in the Supporting Information and Figure S1. The final frequency measurements were performed with a cavity based FTMW spectrometer.[18] Transitions of *a*-, *b*-, and *c*-type were observed for the monohydrate conformer, while only *a*-type transitions could be observed for the dihydrate. Despite considerable efforts, no *b*- and *c*-type transitions were detected in this case.

Extensive isotopic studies were also performed. For the monohydrate, rotational spectra of ML–D_2O, ML–DOH, ML–HOD, MLOD(deuterated at the OH of ML)–DOH, and MLOD–HOD were measured and analyzed, in addition to that of ML–$H_2{}^{18}O$. For the dihydrate, three additional isotopologues were investigated, namely ML–$(H_2{}^{18}O)_2$, ML–$H_2{}^{18}O$–$H_2{}^{16}O$ and ML–$H_2{}^{16}O$–$H_2{}^{18}O$. The measured line frequencies were fitted with the internal rotator program XIAM,[19] using Watson's semi-rigid rotor Hamiltonian in the S-reduction and I^r–representation.[20] A brief summary of the resulting spectroscopic parameters of the mono- and dihydrate isotopologues is given in Table 1, while the complete lists are provided in Tables S3 and S4. The measured transition frequencies along with their quantum number assignments for all isotopologues are given in Tables S5–S15.

While the four *insertion* monohydrate conformers look very similar structurally, their relative dipole moment magnitudes are quite different, depending sensitively on the direction the free hydroxy group is pointing. The experimental rotational constants obtained are similar to the calculated ones of both i-I and i-II. From the optimized microwave pulse widths and transition intensities, it can be estimated that $\mu_a \approx 2\mu_b \approx 2\mu_c$. This trend agrees with what was predicted for i-I and is in contrast to i-II which has essentially zero *b*-dipole moment component. We therefore assign the observed monohydrate to i-I. A potential-energy scan as a function of the dihedral angle C=O−OH (of water) was performed at the MP2/6-311++G(d,p) level of theory (see Figure S2) to estimate the conversion barrier from conformer i-II into i-I. This barrier is rather low and can be easily overcome in a jet expansion.

Kraitchmann's substitution[21] coordinates of the water subunit are compared with the corresponding ab initio values of i-I and i-II in Table S16. Clearly, i-I provides better agreement with the experimental coordinates, thus supporting the above conformer assignment. The experimental rotational constants were used to provide a partially refined effective structure (Table 2). The bond lengths, angles, and dihedral angles related to the position of the water molecule relative to ML were fitted to the experimental rotational constants of all isotopologues, while the remaining structural parameters were kept at their ab initio values. The *insertion* nature of the intermolecular H-bonds can be clearly identified from the parameters in Table 2. A complete list of the coordinates is provided in Table S17.

For the dihydrate of ML, the situation becomes even more complex. Initially, the set of assigned transitions was tentatively identified as belonging to ii-I, the most stable conformer predicted. However, the failure to observe *c*-type

Table 1: Experimental spectroscopic constants of the observed isotopologues of i-I and ii-II.[a]

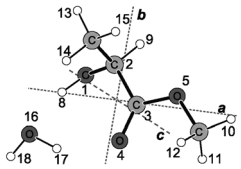
Parameter[a]	i-ML–H_2O	i-ML–$H_2{}^{18}O$	i-ML–DOD	i-ML–DOH	i-ML–HOD	i-MLOD–DOH	i-MLOD–HOD
A [MHz]	2566.4940(6)	2511.3532(5)	2478.541(1)	2529.399(1)	2511.849(1)	2529.862(1)	2512.3057(8)
B [MHz]	1278.7597(2)	1238.8016(1)	1241.9619(7)	1271.2273(5)	1249.2938(6)	1257.7016(4)	1236.4447(2)
C [MHz]	1011.8730(2)	979.5511(1)	975.8648(5)	1001.7533(4)	985.2618(5)	994.9089(4)	978.7656(2)
V_3 [kJ mol^{-1}]	5.12(2)	5.05(2)	5.12(1)	5.071(9)	5.11 (1)	5.125(8)	5.11(3)
N	106	104	49	62	62	68	85
σ [kHz]	4.0	3.3	6.8	6.8	7.4	7.2	4.6

Parameter[a]	ii-ML–2 H_2O	ii-ML–$H_2{}^{18}O$-$H_2{}^{18}O$	ii-ML–$H_2{}^{18}O$-$H_2{}^{16}O$	ii-ML–$H_2{}^{16}O$-$H_2{}^{18}O$
A [MHz]	1703.2142(53)	1647.0764(32)	1694.604(13)	1656.6878(58)
B [MHz]	915.85211(37)	872.66301(30)	887.98776(72)	898.66724(78)
C [MHz]	681.15852(31)	650.40411(23)	666.26735(51)	664.31504(56)
V_3 [kJ mol^{-1}]	5.1887(79)	5.1944(83)	5.187(18)	5.223(18)
N	64	61	44	51
σ [kHz]	3.5	3.2	4.8	5.8

[a] Complete lists of the spectroscopic constants of i-I and ii-II are given in Table S3 and S4, respectively. *N* is the number of transitions included in the fit and σ is the standard deviation of the fit. Standard errors in parenthesis are expressed in units of the least significant digit.

Table 2: Partially refined geometry of i-I conformer.

Parameter[a]	Exp.[b]	Theo.[c]
O16-H8	1.968(4)	1.9102
O16-H18-O1	162.2(1)	163.1
O16-H8-O1-C2	−55.3(5)	−44.8
H17-O16-H8	78.2(19)	87.4
H17-O16-H8-O1	−2.5(11)	−11.9
H17-O16	1.038(44)	0.968
H18-O16	0.964(33)	0.960
H8-O16	1.968[d]	1.910
H17-O4	1.846[d]	1.958



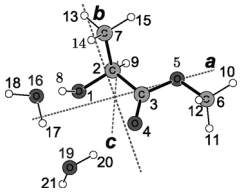
[a] Distances in [Å] and angles in [°]. [b] See the text for details. Values in parentheses are errors in units of the least significant digit. [c] At the MP2/6-311++G(d,p) level. [d] Calculated from the fitted parameters.

transitions was puzzling since ii-I was predicted to have a sizeable dipole moment component in the *c*-direction. Further extensive computational searches for other conformers with subtly different structures revealed a number of other possibilities (Table S2). We note that all the predicted *insertion*-only conformers, except ii-II, have either strong *b*- or *c*-type transitions. Consequently, the observed transitions were identified as belonging to ii-II based on the comparison of the observed and predicted rotational constants and dipole moment components.

For the dihydrate conformer, the substitution coordinates of the oxygen atoms of the two water subunits are given in Table 3, along with the related ab initio values of the

Table 3: Substitution coordinates [Å] of the O atoms of water in ML–$(water)_2$ and the related MP2/6-311++G(d,p) values for ii-I and ii-II.

Atom	Exp.	ii-I	ii-II
O16			
a	±2.857	−2.370	2.748
b	±0.455	0.239	0.438
c	±0.767	1.469	−0.871
O19			
a	±2.269	−2.632	2.289
b	±2.091	1.104	−2.065
c	±0.142	−1.126	0.147



dihydrate conformers ii-I and ii-II. Clearly, the experimental coordinates are in good agreement with those of ii-II, whereas they disagree with those of ii-I. This further supports our assignment of the observed ML dihydrate conformer to ii-II.

Several attempts to detect other *insertion* ML–$(water)_{1,2}$ conformers were not successful. In retrospect, this is not surprising for the monohydrate because of conformational relaxation in the jet expansion or negligible population to begin with. Furthermore, all unassigned lines observed in the broadband scan were checked using the cavity spectrometer with sample mixtures of ML + $H_2{}^{16}O$ and ML + $H_2{}^{18}O$ separately. Most of these lines could be ruled out as belonging to hydrated ML clusters since they were observed with both samples, while transitions of ML-$H_2{}^{16}O$ or ML-$H_2{}^{18}O$ could only be observed with either the ML + $H_2{}^{16}O$ or ML + $H_2{}^{18}O$ sample, respectively. We therefore conclude that the two conformers observed are the most stable ones for the mono- and dihydrate.

It is interesting to note that in the hydrated chiral clusters studied, a particular orientation of the free OH group(s) of water is strongly favored over the other possibilities, as suggested by our assignments to specific ab initio structures This is somewhat surprising since in acid–water complexes with "planar symmetry", such as HNO_3–H_2O[7] and CF_3COOH–H_2O[10] with a similar intermolecular H-bonded ring, large amplitude and tunneling motions associated with the water subunits were commonly reported. For example, the H-tunneling motion responsible for the observed tunneling splittings was hypothesized to be a rotation about the H(of acid)–O(of water) intermolecular H-bond, with an estimated barrier of approximately 12 kJ mol^{-1} for the trifluoroacetic acid–water complex (cf. mode II in Ref. [10]). In the present cases, similar motions would connect two inequivalent minima, such as i-I and i-III or i-II and i-IV. Because of the noticeable energy difference between the two minima, the more stable one is significantly favored while the less stable one is not observed in the jet expansion.

In the aforementioned acid–water complexes, the H-wagging motion, where the non-bonded H-atom of water flaps from above to below the H-bonded ring plane, was predicted to have a very small barrier and connects two *equivalent* geometries (Figure 3 and 4 of Ref. [10]). This mode is best viewed as associated with a large-amplitude motion in these complexes, as suggested by Leopold et al., to account for the absence of the *c*-type transitions.[7] A similar wagging motion in ML–water, on the other hand, connects two inequivalent minima, that is, conformers i-I and i-II, with a very low barrier from i-II to i-I and a more substantial barrier of 3.8 kJ mol^{-1} from i-I to i-II (Figure S2). This complex potential-energy surface results in the unique and well-defined orientation conformations of free OH which are detected in the current study.

We further note that while the ab initio calculation correctly predicted the most stable monohydrate conformer identified experimentally, it failed in the case of the dihydrate. Clearly, extensive experimental spectroscopic data are crucial for the unambiguous identification of the specific conformations in the gas phase, as demonstrated in the present study.

The experimental internal rotation barrier height of the ester methyl group is around 5.1 and 5.2 kJ mol^{-1} for the mono- and dihydrate of ML, respectively, higher than that of the ML monomer at 4.76 kJ mol^{-1}.[16] This difference is attributed to a decrease in the C=O–H(of the ester methyl group) van der Waals distance(s) when the intramolecular H-bond in ML is replaced with the intermolecular H-bonded ring upon hydration. In ML-water, the van der Waals distances O4–H11 and O4–H12 become slightly shorter, by 0.016 and 0.013 Å, respectively, compared to the monomer distances. In the dihydrate, the corresponding distances are even shorter by 0.019 and 0.029 Å, respectively. The insertion of one or two water molecules offers greater flexibility to optimize both intermolecular H-bonding and the van der Waals interaction between the carbonyl O atom and the H atoms of the ester methyl group, resulting in an increasing

internal rotation barrier in going from ML to ML–water to ML–$(water)_2$.

In summary, ML-$(water)_{1,2}$ strongly favors the compact *insertion* topology over the *addition* one in the delicate competition between intra- and intermolecular H-bonding interactions. The monohydrate conformer identified herein is also the dominant one responsible for the induced solvent VCD signatures in water. This result suggests that such a tightly bound structure is quite robust, although it must be kept in mind that the bulk water environment may strongly affect the relative stabilities of the conformers. The unique dihydrate conformer identified is not the most stable one predicted. This finding highlights the significance of high-resolution spectroscopic work in providing quantitative data to test theories for identifying specific water binding topologies, thus helping to build a solid foundation for interpreting solution measurements.

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