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Ander Camiruaga, Gildas Goldsztejn, Pierre Çarçabal. Isotopic dependence of intramolecular and intermolecular vibrational couplings in cooperative hydrogen bond networks: singly hydrated  $\alpha$ -O-Phenyl-Mannopyranoside as a case study.. *Physical Chemistry Chemical Physics*, 2023, 10.1039/D3CP00908D . hal-04055623

**HAL Id: hal-04055623**

**<https://hal.science/hal-04055623>**

Submitted on 3 Apr 2023

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# PCCP

Physical Chemistry Chemical Physics

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. Camiruaga, G. Goldsztejn and P. Çarçabal, *Phys. Chem. Chem. Phys.*, 2023, DOI: 10.1039/D3CP00908D.



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# Isotopic dependence of intramolecular and intermolecular vibrational couplings in cooperative hydrogen bond networks: singly hydrated $\alpha$ -O-Phenyl-Mannopyranoside as a case study.

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**Abstract.** Hydrogen bonding (HB) is associated to frequency shifts, spectral broadening and intensity variation of the vibrational bands of the donor stretching modes. This is true in all systems, from the most basic molecular models, to more complex ones, and biological molecules. In the gas phase, the latter can be either fully isolated, with only intramolecular HB, or micro-solvated. The conformation of such systems are stabilized by networks of intramolecular and intermolecular HB where the donor groups can be coupled. This has been well identified in the case of singly hydrated monosaccharides and in particular for  $\alpha$ -O-Phenyl-Mannopyranoside where the addition of a single water molecule reduces the number of observed conformations to a unique one, stabilized by such a cooperative network of intra- and intermolecular HB. In the present study we have revisited this prototypical system to scrutinize subtle effects of isotopic substitution in the solvent molecule. Besides the obvious isotopic shift, they evidence coupling between intramolecular modes of the sugar and the water, promoted by the intermolecular HB. The systematic substitution of water by heavy water, or methanol, also allowed to decompose the relation between HB strength and frequency shift.



## Introduction

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DOI: 10.1039/D3CP00908D

Ever since they have been discovered around the 1920's-1930's hydrogen bond (HB) interactions, either *intermolecular*, that is between different molecular entities, or *intramolecular* between different functional groups within a single molecule, have been at the centre of interest of scientists seeking at understanding countless processes of molecular origin. Vibrational spectroscopy has always been considered as a very powerful probe of these forces.<sup>1</sup> It has been quickly recognized that spectral signatures of the stretching modes of the donor groups encode information on the non-covalent interactions in which they are engaged. When a polar group is engaged in an HB, the frequency, intensity and width of its donating stretching band are modified with respect to the “free” vibration. Although this has been observed and modelled over decades, there are still debates on the relation between these experimental spectral signatures of covalent bond vibrations and the nature and strength of the non-covalent HB perturbation. For instance, the Badger-Bauer rule, holding since the late 30's,<sup>2</sup> states that the stronger the interaction, the larger the stretching frequency red-shift of the donor group must be. However, there are several occurrences of counter-examples, and spectroscopists keep on designing model systems challenging this rule.<sup>3</sup> This illustrates that the spectroscopic manifestations of HB are in fact very complex to apprehend. Nevertheless, the governing HB networks of more complicated molecular assemblies have been characterized by gas phase vibrational spectroscopy. As complexity increases, so does the vibrational picture. In particular, vibrational couplings and resonances come into play. For instance, vibrational resonances between modes from two interacting molecules can be “universally” promoted by HB, as demonstrated by systematic chemical or isotopic substitution.<sup>4</sup>

In the case of flexible biomolecules, HB plays a role as important as the chemical bonding. It rigidifies specific conformations within the molecules and dictates the influence of the solvent. This has been studied by vibrational spectroscopy in the gas phase for peptides.<sup>5-8</sup> Systematic approaches on several model systems allowed identifying spectral signatures of biological motifs such as  $\beta$ -strands,  $\gamma$ - and  $\beta$ -turns. In the cases of hydrates, perturbation theory based models established relations between the intramolecular coupling of the O-H stretching modes of water and the strength of the intermolecular bonding.<sup>9</sup> Vibrational spectroscopy was also used to explore the role of HBs in DNA nucleobases and analogues. Their biological activity and aggregation properties relies on strong intermolecular hydrogen bonding with neighbouring molecules.<sup>10,11</sup>



Sugars represent another important group of biomolecules, with numerous OH groups that can orient themselves to create complex cooperative networks of HB.<sup>12</sup> Pioneered by the group of John Simons in Oxford,<sup>13</sup> their conformational preferences have been investigated by gas phase spectroscopy, starting from monosaccharides,<sup>14,15</sup> their hydrates<sup>12,16</sup> and growing rapidly to larger oligomers,<sup>17–19</sup> to complexes with peptides,<sup>20,21</sup> or to glycoconjugated systems, beyond the biological context.<sup>22</sup> Their high conformational flexibility makes their study by vibrational spectroscopy a difficult task. The large number of O-H stretching bands all gather in a relatively small spectral window and are often coupled. In the case of hydrated complexes, where the water stretching bands overlap the sugar contributions, isotopic substitution with heavy water has been used to decipher the contributions from the sugar to the ones from the solvent molecules,<sup>23,24</sup> by shifting down the water bands by about 1000 cm<sup>-1</sup>, in the O-D stretching region, which enabled determining the conformational choices of the scrutinized systems, from multi-hydrated monosaccharides, to mono-hydrates of disaccharides.<sup>25</sup>

In the present work, we have revisited the system that has been first studied as a monosaccharide-heavy water complex in the gas phase:  $\alpha$ -O-Phenyl-Mannopyranoside (apMan). The unique populated structure and conformation of the singly hydrated complex apMan-water (apMan-W), as determined by the early work of Simons *et co.*,<sup>12</sup> are shown in Figure 1, which also illustrates the normal mode motions and nomenclature which will be used thereafter. We pushed further the principle of isotopic substitution by studying the most abundant isotope of the apMan (apManH4) complexed with H<sub>2</sub>O, HOD, D<sub>2</sub>O, CH<sub>3</sub>OH and CH<sub>3</sub>OD, as well as the substituted apManD4, where all the hydroxyl groups are deuterated, isolated and in interaction with D<sub>2</sub>O. We focused our attention on subtle spectroscopic manifestations of isotopic substitution, aiming at probing in a more intimate way the intermolecular forces *via* the spectroscopy of intramolecular donor groups.

## Methods

### Experimental

We employed a well-established experimental approach that has been extensively used to obtain conformer selective and mass-resolved vibrational spectra of non-volatile compounds and clusters in the gas phase, including biomolecules<sup>26</sup> and in particular sugars.<sup>27</sup>

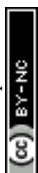


The solid compounds were vaporized by laser desorption coupled to a supersonic jet of rare gas at 5 bars of backing pressure and expanded through a 500  $\mu\text{m}$  cylindrical pulsed valve (Jordan PSV) into the source vacuum chamber ( $P=10^{-4}$  mbar during valve operation). Experiments were conducted with either Neon or Argon as a carrier gas without any effect on the observed spectra presented thereafter. The desorption laser beam (Minilite Continuum, 10 Hz, 500  $\mu\text{J}/\text{pulse}$ , 1064 nm) was focused down to a size similar to the nozzle diameter onto the surface of the desorption sample.

For complex formation, the supersonic jet carrier gas was seeded with room temperature vapour pressure of pure  $\text{H}_2\text{O}$ , pure  $\text{D}_2\text{O}$ , a blend of  $\text{H}_2\text{O}:\text{HOD}:\text{D}_2\text{O}$  obtained by mixing  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  in a 1:1 ratio. Such mixtures which led to intensity ratios close to the expected 1:2:1  $\text{H}_2\text{O}:\text{HOD}:\text{D}_2\text{O}$  (as shown in Figure 2c) allowed considering that  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  densities were identical and stable for both isotopic species. It also allowed recording simultaneously the data for the different isotopic forms under the exact same experimental conditions. Then, we can consider that cluster size distributions were similar for both  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  hydrates. The same precautions were taken for methanol spectra which were recorded with a 1:1 mixture of  $\text{CH}_3\text{OH}:\text{CH}_3\text{OD}$ . In both cases, we observed slight excess of the natural isotopomers (Figure 2c and Figure 2f).

The many collisions occurring at the early stage of the expansion cooled down the desorbed molecules and stabilize the complexes. They were then entrained with the molecular beam towards the differentially pumped ionization region of a linear Time-Of-Flight (TOF) mass spectrometer, where they interacted with the spectroscopy lasers, separated from the source chamber by a 2 mm skimmer.

The molecules and complexes are detected by measuring their 2 Color Resonantly Enhanced MultiPhoton Ionization (2c-REMPI) spectra. The excitation photons are obtained from a frequency doubled, dye laser (Lambda Physics PDL3002, 10 Hz, Coumarin 540a, 500  $\mu\text{J}/\text{pulse}$ ) scanned over the UV range of the  $\pi-\pi^*$  electronic transition of the phenyl ring of apMan (36000-37000  $\text{cm}^{-1}$ ). The ionization photons are obtained from a Nd:YAG pumped UV OPO (Horizon Continuum, 10 Hz, 32258  $\text{cm}^{-1}$ , 2 mJ/pulse). Both UV beams were propagated in the same direction in the vacuum chamber and overlapped spatially and in time at the centre of the TOF ionization zone. The excitation laser was collimated to form a 2 mm parallel beam while the ionization beam is focused in the overlap zone, by a 1 m lens. The produced ions were then mass-separated by the Willey-Mac Laren LTOF with a resolution allowing for clear



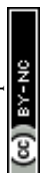
identification of the various isotopic substances observed here (see Figure 2). For all systems under study, Resonant 2-Photons Ionization (R2PI) spectroscopy (the one color version of REMPI) can provide very satisfactory results both in terms of ionization yields and spectroscopy. The lower energy of the ionization photons of the 2C-REMPI scheme allowed minimizing the

amount of excess energy in the complex ions and then prevent misleading signals issued from fragmenting larger clusters.

To record conformer specific, mass-resolved vibrational spectra of the systems under study, we used the double resonance InfraRed Ion Depletion (IRID) spectroscopy scheme.<sup>26</sup> The tunable infrared source was a Nd:YAG pumped OPO/OPA (LaserVision) covering the range of the O-D and O-H stretching modes, between 2300-3800  $\text{cm}^{-1}$ . The intensity of the spectra were corrected for the laser power gradual increase from 2400  $\text{cm}^{-1}$  to 3800  $\text{cm}^{-1}$ . Finally, the spectral calibration of the OPO/OPA system was achieved by measuring atmospheric water absorption lines by means of a photoacoustic detector located inside the laser casing, close to its output.

### Desorption samples preparation

Our desorption samples preparation used to consist in rubbing a solid graphite substrate bar against a mixture of the analyte powder and graphite. In the present work, we used a new method, inspired from the process of Matrix Assisted Laser Desorption Ionization (MALDI) imaging sample preparation robots,<sup>28</sup> and from the method experimented by Küpper *et al.*,<sup>29</sup> but at a much lower cost and level of sophistication, which comes with the advantage of simplicity and versatility. We used a simple action aerograph (Iwata Aerograph Revolution Mini Line-M2 HP) to spray a 5mg/ml solution of apMan in ethanol on the surface of the graphite bar, using 1.5 bar of nitrogen at room temperature as a spray carrier. The spray opening and distance to the graphite bar (typically 2 cm) were set so that its plume covers the 2 mm width of the bar. The ethanol solvent evaporates readily when it reaches the surface of the bar, leaving a thin, uniform layer of the analyte on the surface. The details of this sample preparation method is beyond the scope of the present paper but we can briefly review its advantages. First, it is much more reproducible and scalable. Second, it can apply to any sample texture (dry, moist or flaky powders, oily liquids, and greasy solids) provided that they can be dissolved and that they stick to the graphite surface while the solvent evaporates. It leads to a much-improved stability of the source, which is key for pump-probe experiments such as our double resonance spectroscopy scheme. Most importantly, it is much more conservative in analyte consumption



as it reduces the used amounts by about one order of magnitude. In the present work, this “spraying” method required no more than few milligrams of apMan for the complete experimental work, while it would have needed several tens of mg (up to 100 mg) with the “rubbing” method.

## Deuteration

All compounds were commercially available and used without any further purification (apMan from Carbosynth Ltd., water and methanol isotopes from Sigma-Aldrich).

For the deuteration of apMan, we repeated two to three cycles of H/D exchange with an excess of deuterated methanol and freeze drying. This led to a distribution of deuteration on the hydroxyl groups of apMan (Figure 2d).

## Computational

The conformational landscape of apMan-W has been thoroughly investigated by Simons et al.<sup>12,24</sup> and did not need further exploration. In the present study, we focused on the uniquely observed, most stable conformer of apMan-W identified from the initial study.<sup>12</sup> This complex adopts a fully cooperative conformation where the water molecules inserts between OH4 and OH6, in an all clockwise conformation, noted “c\_ins4”, to follow the nomenclature of the initial paper,<sup>12</sup> represented in Figure 1.

All calculation were done at the B3LYP(D3)/cc-pVTZ level of theory. We have recalculated the energies and vibrational spectra for all isotopic forms of the complexes at this level. For the sake of verification, we have also recalculated the relative energies of about 20 conformations of apMan-W, which confirmed that the new level of theory does not call the results from the initial study into question.

When binding energies have been calculated, they have been corrected for the Basis Set Superposition Error (BSSE), using the routine counterpoise method.

All quantum chemistry calculations were performed using the Gaussian 16, Rev. B 0.1.<sup>30</sup>





## Results

### Experimental vs. computational spectra comparison

The agreement between the calculated and experimental spectra of non-hydrated apMan and apManD4, and of the heavy water singly hydrated complex, apMan-D<sub>2</sub>O is illustrated in Figure 3.

For comparison with the observed IRID spectra, we produced synthetic spectra by applying interaction and isotope specific scaling factors to the calculated harmonic frequencies. Uniform scaling factors of 0.96 applied to all calculated O-H/O-D stretching frequencies lead to satisfactory qualitative agreement with the experimental data and lead to the same conclusions of the present work. However, we have decided to apply different scaling factors depending on the isotopomer and on the nature of the interactions in which the hydroxyl groups are engaged, which provide and much improved quantitative correspondence between the experimental and calculated spectra.

The O-H stretching frequencies of groups either free or involved in *intramolecular* non-covalent interactions were multiplied by a factor of 0.96. The stretching frequencies of the O-H groups involved as donor in *intermolecular* HB were scaled by 0.98. These scaling factors were determined from the same calibration procedure, based on frequency calculations for benchmark systems (mono and disaccharides, either isolated or singly hydrated), already applied in the past.<sup>22</sup> For deuterated species, using the scaling factors determined for the O-Hs stretching modes led to systematic underestimation of the vibrational frequencies of the O-D groups. Much-improved agreement were obtained for scaling factors of 0.97 for the free or *intra*-molecularly bound O-D stretching frequencies, and 0.99 for the frequencies of the O-D groups involved as donor in *inter*-molecular bonding. These four scaling factor have been applied to all calculated frequencies reported thereafter.

The interaction and isotope specific scaling factors used here illustrate that these scaling factor do not only take anharmonicity into account, as too often considered. They also correct for the overall approximations and errors of the method and level of theory.

Higher scaling factors for O-D stretches than for O-H's can be considered as an anharmonicity effect. Indeed, the D isotope being heavier, the associated vibrational reduced mass is higher and their vibrational states lie lower than the H isotope states in the same vibrational potential.



This also implies that the vibrational motion of O-D explores a smaller range of interatomic distance than the O-H motion. The harmonic approximation being more valid at the bottom of the potential and for small vibrational motions, we may then consider that the O-D motions are closer to the harmonic approximation than O-H's and the O-D's scaling factor are closer to 1 (0.97 vs. 0.96 and 0.99 vs. 0.98).

The difference between the scaling factors of the *intra*- and the *intermolecular* donor groups cannot be interpreted similarly. Although Hydrogen bonding increases the anharmonicity and the span of the donor stretching vibrational motions, the scaling factors we determine are higher (closer to 1) for strongly hydrogen bonded donor groups (0.98 vs. 0.96 and 0.99 vs. 0.97). We can then only conclude that the level of theory used here overestimates the effect of intermolecular interactions on the donor bands frequencies but certainly not that the motions are less anharmonic.

## 2c-REMPI spectra

2c-REMPI spectra of apMan-H<sub>2</sub>O, apMan-HOD, and apMan-D<sub>2</sub>O are essentially identical, as shown in Figure . The 2c-REMPI spectroscopy reflects the populations of the structures adopted in our experimental conditions. In the present case, there is no doubt that isotopic substitution has no influence on the conformational distribution of apMan-W and we observe only the most stable conformation of the complex, shown in Figure 4.

Figure also features the 2c-REMPI spectrum of the methanol complex apMan-CH<sub>3</sub>OH. It is strikingly similar to the apMan-W spectra. We can then conclude that under our experimental conditions the methanol complex adopts the same unique *c\_ins4* conformation as the hydrated complex, with the methyl group replacing the free hydroxyl group of water. As for the hydrates isotopes, the 2c-REMPI spectrum of the methanol complex is insensitive to the deuteration state of the methanol moiety and the apMan-CH<sub>3</sub>OD spectrum is identical.

## IRID spectra

Figure displays the IRID spectra of apMan, its complexes apMan-H<sub>2</sub>O, apMan-HOD and apMan-D<sub>2</sub>O, and the corresponding calculated scaled harmonic spectra. In the case of apMan-HOD, two isomers coexist: (i) apMan-H\*OD (light blue in Figure b) where the water molecule is bound to apMan *via* its O-H group, (ii) apMan-HOD\* (dark blue in Figure b), bound *via* the O-D group of water. Figure 1 illustrates the normal mode analysis, which enables identifying the vibrational motions associated to the observed bands.



In spite of the weak intensity of its mass peak, we could observe the IRID spectrum of apManD4-D<sub>2</sub>O, shown in Figure, together with the IRID spectra of apMan-CH<sub>3</sub>OH, apMan-CH<sub>3</sub>OD, and compared to the IRID spectra of the three isotopomers of apMan-W. View Article Online  
DOI: 10.1039/D3CP00908D

For all complexes studied here, table 1, summarizes the calculated and experimental frequencies, frequency shifts and the splitting between the coupled vibrations.

### *Intramolecular bound hydroxyl stretching modes*

The partly unresolved bands located between 3600 and 3650 cm<sup>-1</sup> are assigned to the  $\sigma_2$ ,  $\sigma_3$  and  $\sigma_6$  stretching motions of the groups OH<sub>2</sub>, OH<sub>3</sub> and OH<sub>6</sub> of apMan, respectively. These groups are involved in relatively weak *intramolecular* interactions, constrained by the rigid <sup>4</sup>C<sub>1</sub> pyranose ring of apMan. OH<sub>2</sub> and OH<sub>3</sub> do not interact with the water molecule. OH<sub>6</sub> does, but only on the O<sub>6</sub> oxygen side, as an acceptor. It is then normal that the stretching frequencies of these three groups are unaffected by the water isotopic substitution.

### Free water band $\sigma_{fw}$

The band located at 3727 cm<sup>-1</sup> in the spectrum of apMan-H<sub>2</sub>O (Figure a) and 3717 cm<sup>-1</sup> for apMan-HOD (Figure b) is assigned to the  $\sigma_{fw_H}$  stretching mode of the free OH group of water in the apMan-HOD\* isomer. This slight difference between these observed frequencies (3726 7cm<sup>-1</sup> vs. 3718 cm<sup>-1</sup>) is properly reproduced by the scaled harmonic calculated frequencies (3718 cm<sup>-1</sup> vs. 3712 cm<sup>-1</sup>). It reflects the *intramolecular* coupling between  $\sigma_{fw_H}$  and  $\sigma_{bw_H}$  in apMan-H<sub>2</sub>O, inherited from the coupling between the symmetric and asymmetric stretching modes of both O-H vibrators of H<sub>2</sub>O. In apMan-HOD\*, the increased energy gap between  $\sigma_{bw_D}$  and  $\sigma_{fw_H}$  breaks down the *intramolecular* coupling. Since one effect of this coupling is to increase the energy gap between the coupled modes, it increases the  $\sigma_{fw_H}$  frequency in apMan-H<sub>2</sub>O. In apMan-HOD\*, the coupling is off and the  $\sigma_{fw_H}$  frequency is lowered.

For apMan-H\*OD (Figure 5b) and apMan-D<sub>2</sub>O (Figure 5c),  $\sigma_{fw_D}$  is observed at 2735 cm<sup>-1</sup> and 2753 cm<sup>-1</sup>, respectively. We can note a striking difference with  $\sigma_{fw_H}$  of apMan-H<sub>2</sub>O and apMan-HOD\* (Figure 5a and Figure 5b, respectively): a doublet structure is observed in the O-Ds region, while a single line is found for the free O-H stretches.

When unexpected differences between H and D containing molecular assemblies are observed, one often invokes H/D exchange as a possible cause. However, in the present case, it is very unlikely that this can explain the rising of the doublet associated to  $\sigma_{fw_D}$ . Indeed, the sugar



molecules are evaporated downstream the supersonic expansion and the water molecules seed the carrier gas upstream. Although the molecules meet in the collision rich region of the jet, it is unlikely that there is enough many body encounters between evaporated sugars and water molecules to generate significant amounts of H/D exchange products. Moreover, we perform double resonance spectroscopy targeting a specific conformation of the system. The correspondence between the 2c-REMPI spectra of the various isotopomers of apMan-W complexes (Figure 4) indicate that there is no other conformation formed upon deuteration of the water molecules. Since the conformational relaxation and cooling occur simultaneously in the collision rich zone of the supersonic jet, it is unlikely that H/D exchange between heavy water and the mannoside can be relaxed into the exact same unique cooperative conformation of the complex (Figure 1).

Broadened or splitted  $\sigma_{fw_D}$  could also be due to contamination from larger hydrated clusters fragmenting in the singly hydrated mass channel. However, several experimental precautions have been taken to prevent such large distributions of hydrated clusters: the same  $\sigma_{fw_D}$  doublets have been observed independently of the carrier gas, the backing pressure and whether the experiments were conducted with the carrier gas being seeded by pure D<sub>2</sub>O or with the H<sub>2</sub>O:HOD:D<sub>2</sub>O mix. In the latter case, the densities of H<sub>2</sub>O and D<sub>2</sub>O are similar and there is no reason for significantly different size distributions. Finally, the R2PI spectra of multiply hydrated apMan (up to three water molecules)<sup>24</sup> are well resolved and do not overlap the apMan-W REMPI band probed for measuring the IRID spectra reported here.

To interpret the doublet structure near the  $\sigma_{fw_D}$  band of apMan-D<sub>2</sub>O and apMan-H\*OD we propose it is due to a resonance between the fundamental  $\sigma_{fw_D}$  and an overtone or combination band of lower energy vibrational bands. For such coupling to be so efficient, it is likely that it involves vibrational motion kinetically linked or involving the free O-D group. In the calculated spectra of apMan-D<sub>2</sub>O and apMan-H\*OD, there is a large number of normal modes involving the bending or rocking motions of OH<sub>4</sub>, as well as the bending of the water molecule, in the range between 1200 and 1500 and cm<sup>-1</sup>. It is difficult to identify which modes contribute to this coupling. We believe that the water bending modes, which directly involve the motion of the free D atom and which may be highly kinetically coupled to the free O-D motion, is central to this coupling.

The IRID spectrum of apManD4-D<sub>2</sub>O (Figure 6) also features a doublet structure in the region of  $\sigma_{fw_D}$ . The similarity with the doublet of apMan-D<sub>2</sub>O confirms the proposed important role

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DOI: 10.1039/D3CP00908D



of the water bending modes in the coupling at the origin of the doublet. Indeed, the other possible modes involving the bending and rocking of the sugar hydroxyl groups in the vicinity of the water molecules will be shifted upon deuteration of the sugar moiety, which should affect the coupling.

### *Intermolecularly bound hydroxyl stretching modes*

Between 3400 and 3550  $\text{cm}^{-1}$ , a strong doublet dominates the spectra of apMan-H<sub>2</sub>O (Figure 5a) and apMan-H\*OD (Figure 5b). It corresponds to the symmetric (noted *s*) and asymmetric (noted *as*) coupled stretching motions of  $\sigma_4$ , the sugar OH<sub>4</sub> donor group, and  $\sigma_{\text{bw}_H}$ , the water donor group  $\text{bw}_H$ . Although the complexes are not symmetric the “*s*” and “*as*” notation is used to reflect the motions of the vibrators in these modes, in analogy to the symmetric and asymmetric stretching modes in symmetric molecules such as water or carbon dioxide. In the *s* mode, the sugar H<sub>4</sub> and the water bound H both move in phase, while they are out-of-phase in the *as* mode, as pictured in Figure 1. The splitting between the corresponding calculated frequencies is smaller for apMan-H\*OD than for apMan-H<sub>2</sub>O (51  $\text{cm}^{-1}$  vs. 55  $\text{cm}^{-1}$ ). It is difficult to evaluate experimentally this splitting as the symmetric mode of apMan-H\*OD and the  $\sigma_4$  mode of apMan-HOD\* overlap. It seems however confirmed by the well resolved *as* band observed at 3465  $\text{cm}^{-1}$  for apMan-H<sub>2</sub>O, and at 3474  $\text{cm}^{-1}$  for apMan-H\*OD. As a qualitative interpretation, this difference of splitting is likely to be due to the absence of  $\sigma_{\text{fw}_H}$  in apMan-H\*OD and, consequently, the absence of the *intramolecular* coupling between  $\sigma_{\text{fw}_H}$  and  $\sigma_{\text{bw}_H}$ .

For the deuterium bound complexes apMan-HOD\* and apMan-D<sub>2</sub>O,  $\sigma_{\text{bw}_D}$  is found around 2550  $\text{cm}^{-1}$ . We can note a manifestation of the *intramolecular* coupling between the water O-D symmetric and asymmetric vibrators in the difference between the frequencies of  $\sigma_{\text{b}_D}$  measured for apMan-HOD\* (2559  $\text{cm}^{-1}$ ) and for apMan-D<sub>2</sub>O (2547  $\text{cm}^{-1}$ ). In the latter, the *intramolecular* coupling between both *s* and *as* water O-D stretching modes increases the splitting between the corresponding vibrational bands, while there is no such coupling in HOD. As above, this effect is well reproduced by the scaled anharmonic frequency calculations.

Another point can be noted by the examination of the bands of the donor bound bands of the isotopomers of apMan-W and of apMan-CH<sub>3</sub>O<sub>H/D</sub> complexes (Figure 6). The symmetric band of the  $\sigma_{\text{bw}_H}/\sigma_4$  mode in the spectrum of apMan-H<sub>2</sub>O is accompanied of a shoulder on its blue side, while the corresponding band in the apManD<sub>4</sub>-D<sub>2</sub>O spectra is not. Similarly, there are



several bands next to the H donor bound bands of apMan-CH<sub>3</sub>OH and they are not observed for the corresponding bound OD of apMan-CH<sub>3</sub>OD. This indicates that these bands are also due to resonances with overtones or combination bands of lower energy vibrational modes. They do not originate from contamination either from spectra of larger fragmenting clusters, or from other 1:1 complexes with virtually the same conformation, differing only by slight variation in the relative orientation of both subunits of the complexes. For apMan-H<sub>2</sub>O and apMan-CH<sub>3</sub>OH such quasi-degenerate conformations exist, their calculated energy differences being of the order of 0.2 kJ/mol, well below the precision of the level of theory. They differ only by the orientation of the free hydroxyl group of water, or of the methyl group of methanol, as shown in **Error! Reference source not found.** The very small differences between the calculated spectra of these variations is below the bandwidth of the IR laser and do not allow deciphering whether only one or both conformers are observed. Moreover, if they were responsible for the bands forming shoulders on the side of the main observed bands they should be as easily observed in the spectra of apMan-D<sub>2</sub>O and apMan-CH<sub>3</sub>OD.

### Complexation induced frequency shifts and binding energies

When the H donors stretching frequencies of complexes reflects the effects of hydrogen bonding as well as the competing effects of *intra*- and *intermolecular* vibrational coupling, as in apMan-H<sub>2</sub>O and apMan-H\*OD spectra, it is difficult to extract the pure H bonding frequency shift, which can inform on the relative *intermolecular* strength, according to the Badger Bauer rule.<sup>2</sup> In apMan-HOD\* and in apMan-D<sub>2</sub>O, a single strong band associated to the sugar bound  $\sigma_4$  mode is observed at 3499 cm<sup>-1</sup> and 3500 cm<sup>-1</sup>. In these cases, the *intermolecular* coupling is absent and the uncoupled band frequency falls in between the bands of the coupled modes observed for apMan-H<sub>2</sub>O/H\*OD, in agreement with calculation. This allows determining a frequency shift of *ca.* 170 cm<sup>-1</sup> (3672 cm<sup>-1</sup> for  $\sigma_4$  in the spectrum of the isolated molecule – Figure 3a – vs. 3499 cm<sup>-1</sup> in the HOD\* complex or 3500 cm<sup>-1</sup> in the D<sub>2</sub>O complex – Figure 5b and Figure 5c), purely induced by the *intermolecular* HB with water, without the vibrational *intermolecular* coupling perturbation. It can be compared to the 238 cm<sup>-1</sup> redshift of  $\sigma_4$  in apMan-CH<sub>3</sub>OD, also perturbed only by the *intermolecular* H bonding.

Comparing the spectrum of apMan-H<sub>2</sub>O and of apMan-CH<sub>3</sub>OH (Figure 6), one can appreciate that the  $\sigma_{\text{wH}}/\sigma_4$  doublet is found at a significantly lower energy for the methanol complex. The central frequency of the doublet of apMan-CH<sub>3</sub>OH is 3457 cm<sup>-1</sup>, 29 cm<sup>-1</sup> below the central frequency of the apMan-H<sub>2</sub>O doublet (3486 cm<sup>-1</sup>). Likewise, the  $\sigma_4$  band of apMan-CH<sub>3</sub>OD is



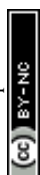
found at  $3434\text{ cm}^{-1}$  (Figure 6, bottom),  $65\text{ cm}^{-1}$  below the  $\sigma_4$  band of apMan-D<sub>2</sub>O ( $3499\text{ cm}^{-1}$ , Figure 5c). The  $\sigma_{\text{bw}_D}$  band in apMan-CH<sub>3</sub>OD, at  $2574\text{ cm}^{-1}$ , indicates a redshift of  $144\text{ cm}^{-1}$  in comparison to isolated CH<sub>3</sub>OD frequency ( $2718\text{ cm}^{-1}$ )<sup>31</sup>. apMan-HOD\* is the most readily comparable complex with apMan-CH<sub>3</sub>OD. We measured its  $\sigma_{\text{bw}_D}$  frequency at  $2559\text{ cm}^{-1}$ , leading to a  $168\text{ cm}^{-1}$  shift with respect to the free OD stretching frequency of HOD in the gas phase ( $2727\text{ cm}^{-1}$ )<sup>32</sup>. The calculated binding energy of apMan-CH<sub>3</sub>OH is  $60\text{ kJ/mol}$ , compared to  $57\text{ kJ/mol}$  for apMan-H<sub>2</sub>O. The difference between these computed values is close the accuracy of the computational method. Moreover they reflect the global binding energy while the frequency shifts we measure are witnesses of the local, mode specific interactions in which the groups are engaged as donors. The larger  $\sigma_4$  shift on apMan-CH<sub>3</sub>OD indicates that the interaction of OH4 as donor with the hydroxyl group of methanol is stronger than with water. On the contrary, the larger  $\sigma_{\text{bw}_D}$  shift in apMan-HOD\* than in apMan-CH<sub>3</sub>OD indicates that the interaction of water as a donor to O6 is stronger than the one of methanol. Once again, this is well reproduced in the calculated intermolecular distances provided by the calculations. The H4-O<sub>methanol</sub> distance ( $1.83\text{ \AA}$ ) is shorter than the H4-O<sub>water</sub> distance ( $1.85\text{ \AA}$ ), and the O<sub>methanol</sub>-O6 distance ( $1.85\text{ \AA}$ ) is longer than the O<sub>water</sub>-O6 distance ( $1.83\text{ \AA}$ ).

## Conclusions

In this study, subtle spectroscopic manifestations of isotopic substitution have been scrutinized, beyond the mere isotopic shifts, and analysed in synergy with quantum chemistry calculation, in a prototypical cooperative hydrated complex formed by an important monosaccharide, apMan, and water. This system has already been thoroughly studied by Simons *et al.* to identify its conformational preferences.<sup>12,24</sup> Expectedly, isotopic substitution does not affect the conformational landscape of this system.

For all spectral signatures considered here, the B3LYP-D3/cc-pVTZ computational results are in excellent qualitative and quantitative agreement with the experimental observation. We have identified vibrational scaling factors for hydroxyl stretching modes that depend on the strength of the non-covalent interaction the modes are involved in, and of the isotopic substitution. These refined scaling factors improve the quantitative agreement between experimental and computed spectra.

The exploitation of spectroscopic signatures of the isotopic substitution allows interrogating the influence of intermolecular HB on vibrational couplings, either *intramolecular* between the



symmetric and asymmetric stretching modes of water, or *intermolecular* between the stretching modes of the donor OH of apMan and water. Since it exists only because of the intermolecular HB between both molecules, this latter coupling must encode information on the interaction, still to be unveiled.

Water deuteration (or methylation, with apMan-CH<sub>3</sub>OH) can be considered as a switch to “turn on or off” the *intermolecular* coupling between the symmetric and asymmetric stretching modes involving the motion of the donor hydroxyl groups of the mannoside and of the water, in competition with the similar, but *intramolecular*, coupling between the symmetric and asymmetric stretching modes of water. By “turning off” the *intermolecular* coupling, we have evidenced the relative strength of the *intermolecular* interaction of apMan with water and methanol and proved that, if the overall interaction is stronger with methanol, the donor interaction OH $\cdots$ O<sub>6</sub> is stronger for water than for methanol, while the OH<sub>4</sub> $\cdots$ O one is stronger for methanol. Moreover, the measured frequency of the uncoupled  $\sigma_4$  vibration of donor hydroxyl of apMan in apMan-D<sub>2</sub>O, apMan-HOD\* and apMan-CH<sub>3</sub>OD, allows appreciating the complexation induced frequency shift free of the perturbation from the coupling with the donor stretching of the other moiety of the complex. In these cases, and in these cases only, we can relate the frequency shifts to the Badger-Bauer rule,<sup>2</sup> which is verified here. The calculated binding energies of the water and methanol complexes are the same but these values relate to the overall strength of both HB involved. The  $\sigma_4$  frequency redshifts are larger in the methanol complexes and the local OH<sub>4</sub>-O<sub>methanol</sub> interaction appears stronger than the OH<sub>4</sub>-O<sub>water</sub> interaction, as indicated by calculated *intermolecular* distances. On the contrary, the OH<sub>water</sub>-O<sub>6</sub> interaction is stronger than the OH<sub>methanol</sub>-O<sub>6</sub> one, which is why the calculated bonding energies are similar for both systems. Such consideration may help calibrating more sophisticated computational approaches than the one used here, aiming at describing in detail vibrational couplings, anharmonic effects, and more generally non-covalent interactions.

We have also observed signatures of resonances with the donor O-H stretching, that are absent for donor O-D bands. Similarly, we have also shown resonances with the free O-D stretches that are not observed for free O-H stretching modes. The complex spectroscopy of these systems in the mid-IR, so called “fingerprint region”, prevented identifying unambiguously the modes involved in these resonances.

The simulation of coupled hydroxyl stretching modes is considered as a difficult challenge for the spectroscopy of large and flexible molecular assemblies, in particular those of biological





interest containing sugar components. The system under study has been chosen for its relative simplicity. The fact that only one conformation is populated under the molecular beam conditions, and its simple and well resolved spectroscopy makes this investigation a case study of how substitutions, either isotopic or methylated, can reveal properties on non-covalent interactions from the spectroscopy of hydroxyl stretches and provides useful benchmarks for studying more difficult similar systems.

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## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgements

AC post-doctoral fellowship was funded by LabEx PALM (ANR-10-LABX-0039-PALM).

This work was performed using HPC resources from the “Mésocentre” computing center of Centrale Supélec and École Normale Supérieure Paris-Saclay supported by CNRS and Région Île-de-France (<http://mesocentre.centralesupelec.fr/>).

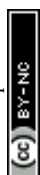
The authors want to acknowledge the help of Nicolas Elie and Dr. David Touboul for the first tries for the spraying methods for sample preparation.

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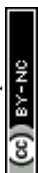
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## Table caption

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Table 1. Experimental and calculated frequencies (in  $\text{cm}^{-1}$ ), splitting and HB induced frequency shifts of isolated apMan, and the complexes with water, heavy water, methanol and heavy methanol. For each system, the experimental frequencies are given above the calculated ones that are in italics. The calculated frequencies are scaled by the isotope and interaction dependant scaling factors defined in the text.



## Figure captions

Figure 1. The most stable, uniquely observed, clockwise conformation “*c\_ins4*” of apMan-W and the notation of the OH groups. This *c* conformation correspond to the most stable and most abundant conformation of the isolated molecule.<sup>12</sup> The apMan-Methanol complex adopts the same *c\_ins4* conformation with the methyl group replacing the free hydroxyl of water (fw). The notation and normal mode analysis of the vibrational modes discussed thereafter are also given.

Figure 2. TOF mass spectra of the various isotopic species studied here, recorded at the most intense peak of their respective 2c-REMPI spectrum. (a) apMan-H<sub>2</sub>O with pure H<sub>2</sub>O seeding the carrier gas, (b) apMan-D<sub>2</sub>O, with the carrier gas seeded by pure D<sub>2</sub>O, (c) apMan-H<sub>2</sub>O, apMan-HOD and apMan-D<sub>2</sub>O, with a 1:1 H<sub>2</sub>O:D<sub>2</sub>O mixture ( $\omega_{\text{exc}}=36713 \text{ cm}^{-1}$ ); (d) apMan-D<sub>n=1,4</sub> ( $\omega_{\text{exc}}=36728 \text{ cm}^{-1}$ ); (e) apMan-D<sub>n=1,4</sub>-D<sub>2</sub>O ( $\omega_{\text{exc}}=36713 \text{ cm}^{-1}$ ); (f) apMan-CH<sub>3</sub>OH/CH<sub>3</sub>OD ( $\omega_{\text{exc}}=36709 \text{ cm}^{-1}$ ). In all cases,  $\omega_{\text{ion}}=32258 \text{ cm}^{-1}$ .

Figure 3. Comparison between the IRID and the B3LYP(D3)/cc-pVTZ computational spectra of (top) apMan, (middle) apManD4 and (bottom) apMan-D<sub>2</sub>O. The assignment of the bands  $\sigma_{\text{n}}$  refers to the stretching mode of the OH<sub>n</sub> group of the mannoside,  $\sigma_{\text{fw}}$  and  $\sigma_{\text{bw}}$  refer to the stretching of the free and bound hydroxy groups of water, respectively. The free or intramolecularly bound O-H frequencies (blue zone) are scaled by 0.96, the intermolecular donor O-H frequencies (green zone) are scaled by 0.98, the free or intramolecularly bound O-D frequencies (orange zone) are scaled by 0.97 and the intermolecular donor O-D frequencies (red zone) are scaled by 0.99.

Figure 4. 2c-REMPI of the three isotopic species of apMan-W, recorded simultaneously for the three isotopes, and for apMan-CH<sub>3</sub>OH/D.

Figure 5. Experimental and calculated vibrational spectra of (a) apMan-H<sub>2</sub>O, (b) apMan-HOD and (c) apMan-D<sub>2</sub>O. For the apMan-HOD isotopomer, the scaled calculated spectra for both possible isomers apMan-H\*OD in light blue, and for apMan-HOD\* in dark blue, are shown. The weak free O-D observed and calculated intensities have been multiplied by 3 to be more easily visible.

Figure 6. IRID spectra of apMan-H<sub>2</sub>O/HDO/D<sub>2</sub>O, apManD4-D<sub>2</sub>O, apMan-CH<sub>3</sub>OH and apMan-CH<sub>3</sub>OD.



Figure 7. Variations of the most stable conformers of (top) apMan-H<sub>2</sub>O and (bottom) apMan-CH<sub>3</sub>OH. The calculated spectra of each conformer are compared to the experimental spectra of the right. The colors of the bars refer to the box color of each conformer.

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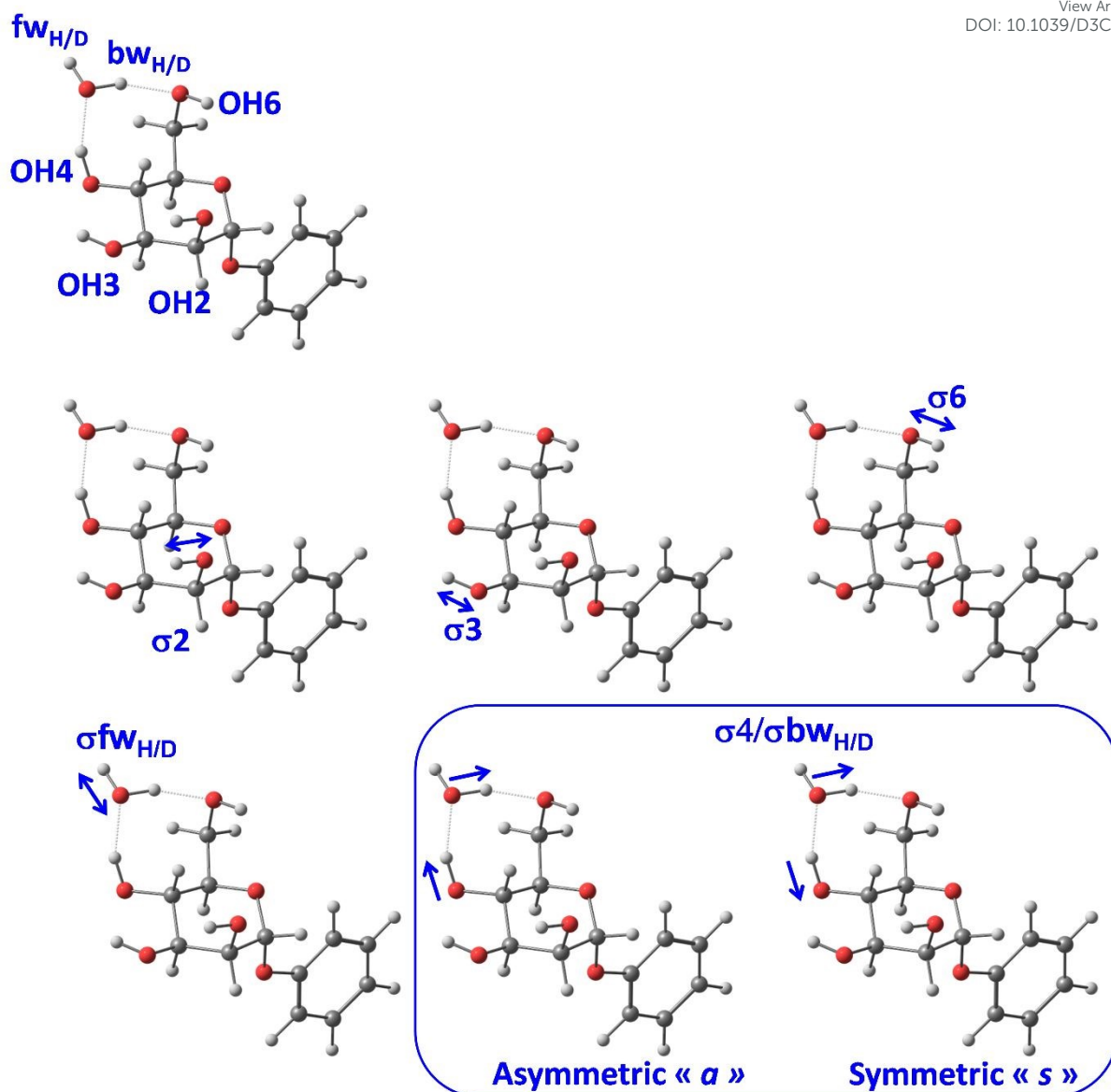


Table 1. Experimental and calculated frequencies (in  $\text{cm}^{-1}$ ), splitting and HB induced frequency shifts of isolated apMan, and the complexes with water, heavy water, methanol and heavy methanol. The HB induced frequency shifts are given only for systems where it can be measured without intermolecular coupling. For each system, the experimental frequencies are given above the calculated ones that are in italics. The calculated frequencies are scaled by the isotope and interaction dependant scaling factors defined in the text.

	$\sigma_{\text{fwh}}$	$\sigma_{\text{fwd}}$ central (splitting)	$\sigma_4$ - $\sigma_{\text{bwh/D}}$ sym. / asym. (splitting)	$\sigma_4$ (HB shift)	$\sigma_{\text{bwd}}$ (HB shift)
apMan	-	-	-	3672	-
	-	-	-	<i>3675</i>	-
apMan-H <sub>2</sub> O	3727	-	3507 / 3465 (42)	-	-
	<i>3718</i>	-	<i>3523 / 3468 (55)</i>	-	-
apMan-H*OD	-	2735 (4)	> 3500 <sup>a</sup> / 3474 (>34) <sup>a</sup>	-	-
	-	<i>2724</i>	<i>3524 / 3473 (51)</i>	-	-
apMan-HOD*	3717	-	-	3500 (-172)	2559 (-168)
	<i>3712</i>	-	-	<i>3506 (-169)</i>	<i>2563</i>
apMan-D <sub>2</sub> O	-	2753 (15)	-	3499 (-173)	2547
	-	<i>2739</i>	-	<i>3506 (-169)</i>	<i>2552</i>
apMan(D4)-D <sub>2</sub> O	-	2756 (18)	2595 / 2557 (38)	-	-
	-	<i>2739</i>	<i>2589 / 2542 (47)</i>	-	-
apMan-CH <sub>3</sub> OH	-	-	3485 / 3430 (55)	-	-
	-	-	<i>3512/3455 (67)</i>	-	-
apMan-CH <sub>3</sub> OD	-	-	-	3434 (-238)	2574 (-144)
	-	-	-	<i>3467 (-208)</i>	<i>2576</i>

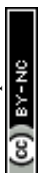
- a. The overlap with the  $\sigma_4$  apMan-HOD\* prevents a precise determination of the frequency of the  $\sigma_4$ - $\sigma_{\text{bwh/D}}$  symmetric mode.





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DOI: 10.1039/D3CP00908D

Figure 1. The most stable, uniquely observed, clockwise conformation “*c<sub>ins4</sub>*” of apMan-W and the notation of the OH groups. This *c* conformation correspond to the most stable and most abundant conformation of the isolated molecule.<sup>12</sup> The apMan-Methanol complex adopts the same *c<sub>ins4</sub>* conformation with the methyl group replacing the free hydroxyl of water (fw). The notation and normal mode analysis of the vibrational modes discussed thereafter are also given.



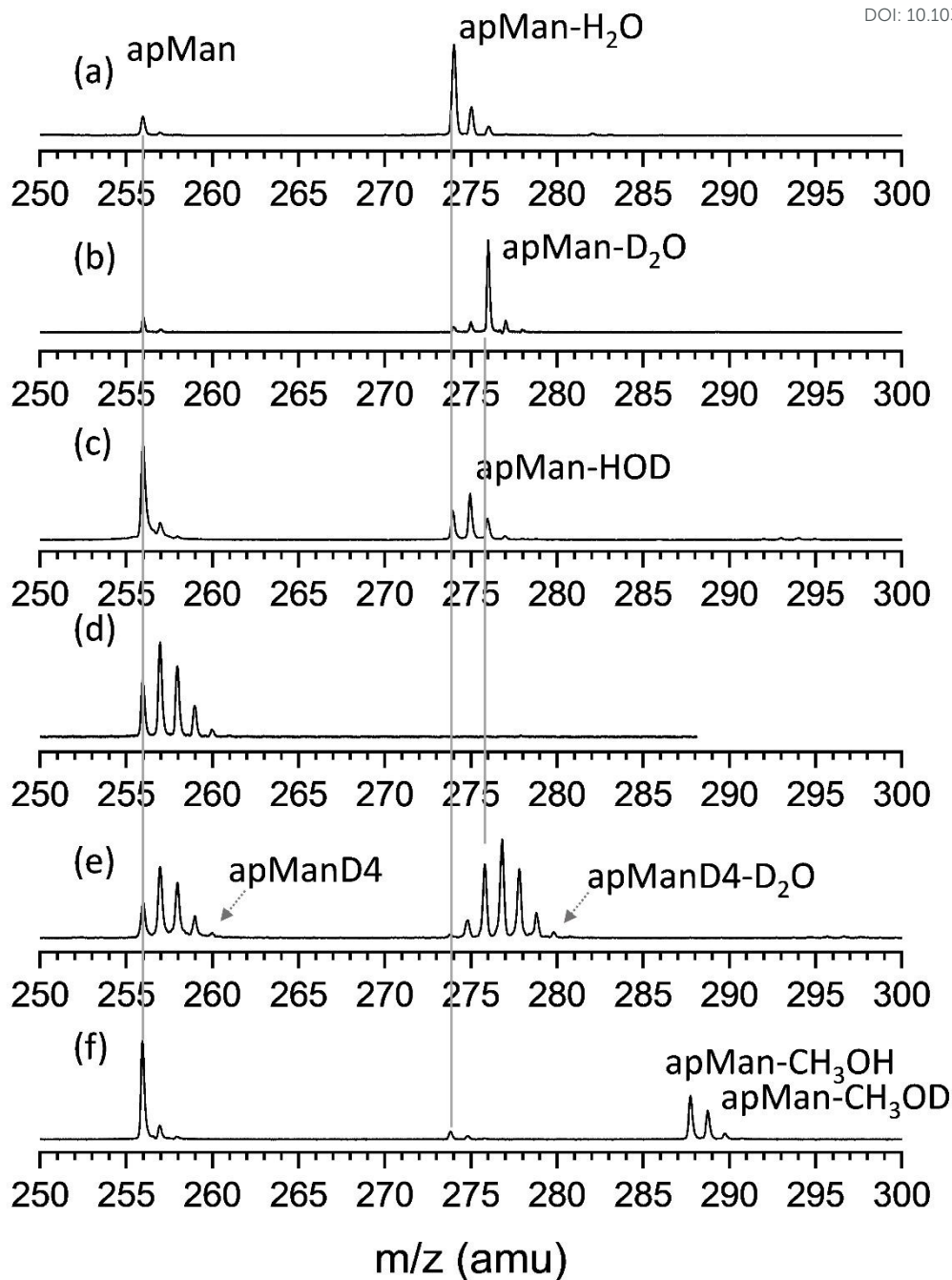


Figure 2. TOF mass spectra of the various isotopic species studied here, recorded at the most intense peak of their respective 2c-REMPI spectrum. (a) apMan-H<sub>2</sub>O with pure H<sub>2</sub>O seeding the carrier gas, (b) apMan-D<sub>2</sub>O, with the carrier gas seeded by pure D<sub>2</sub>O, (c) apMan-H<sub>2</sub>O, apMan-HOD and apMan-D<sub>2</sub>O, with a 1:1 H<sub>2</sub>O:D<sub>2</sub>O mixture ( $\omega_{\text{exc}}=36713 \text{ cm}^{-1}$ ); (d) apMan-D<sub>n=1,4</sub> ( $\omega_{\text{exc}}=36728 \text{ cm}^{-1}$ ); (e) apMan-D<sub>n=1,4</sub>-D<sub>2</sub>O ( $\omega_{\text{exc}}=36713 \text{ cm}^{-1}$ ); (f) apMan-CH<sub>3</sub>OH/CH<sub>3</sub>OD ( $\omega_{\text{exc}}=36709 \text{ cm}^{-1}$ ). In all cases,  $\omega_{\text{ion}}=32258 \text{ cm}^{-1}$ .



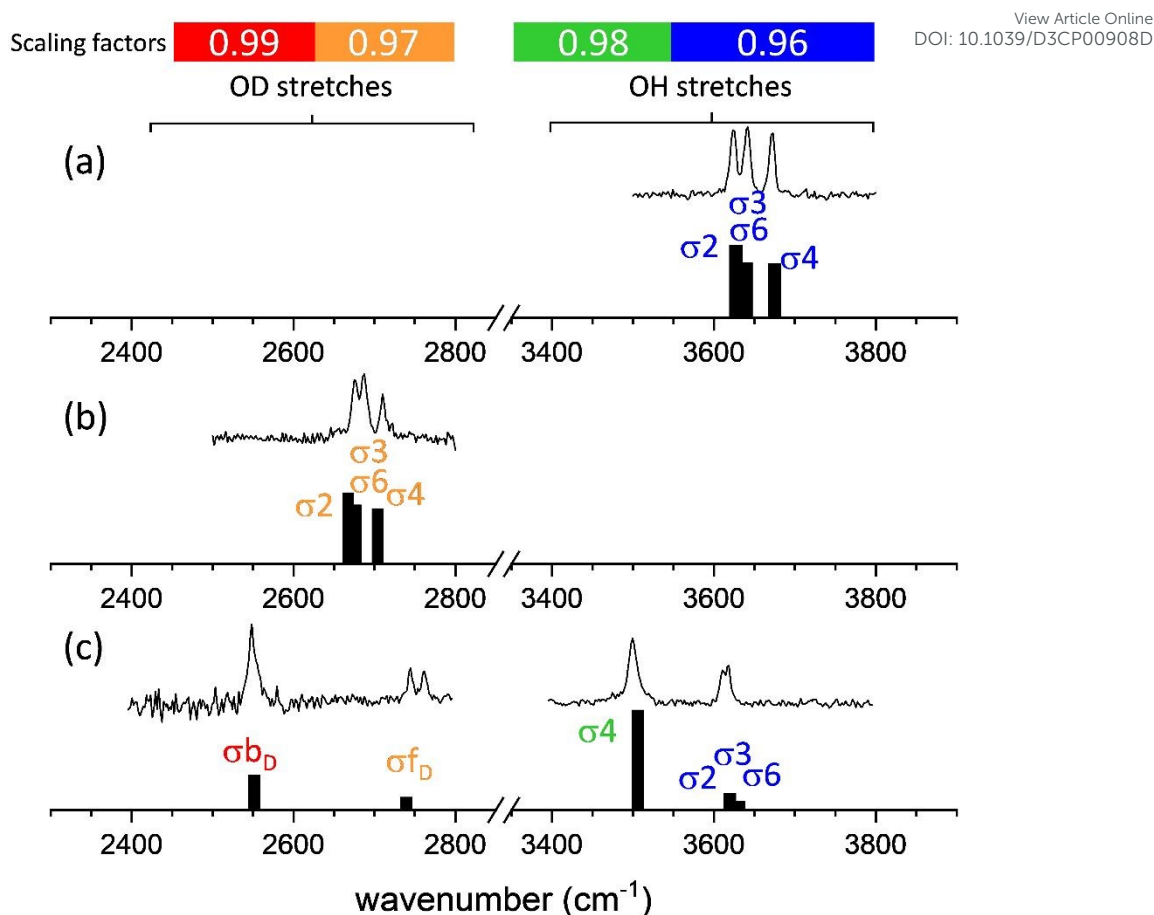


Figure 3. Comparison between the IRID and the B3LYP(D3)/cc-pVTZ computational spectra of (top) apMan, (middle) apManD4 and (bottom) apMan-D<sub>2</sub>O. The assignment of the bands  $\sigma_n$  refers to the stretching mode of the OH<sub>n</sub> group of the mannoside,  $\sigma_{fw}$  and  $\sigma_{bw}$  refer to the stretching of the free and bound hydroxy groups of water, respectively. The free or intramolecularly bound O-H frequencies (blue zone) are scaled by 0.96, the intermolecular donor O-H frequencies (green zone) are scaled by 0.98, the free or intramolecularly bound O-D frequencies (orange zone) are scaled by 0.97 and the intermolecular donor O-D frequencies (red zone) are scaled by 0.99.



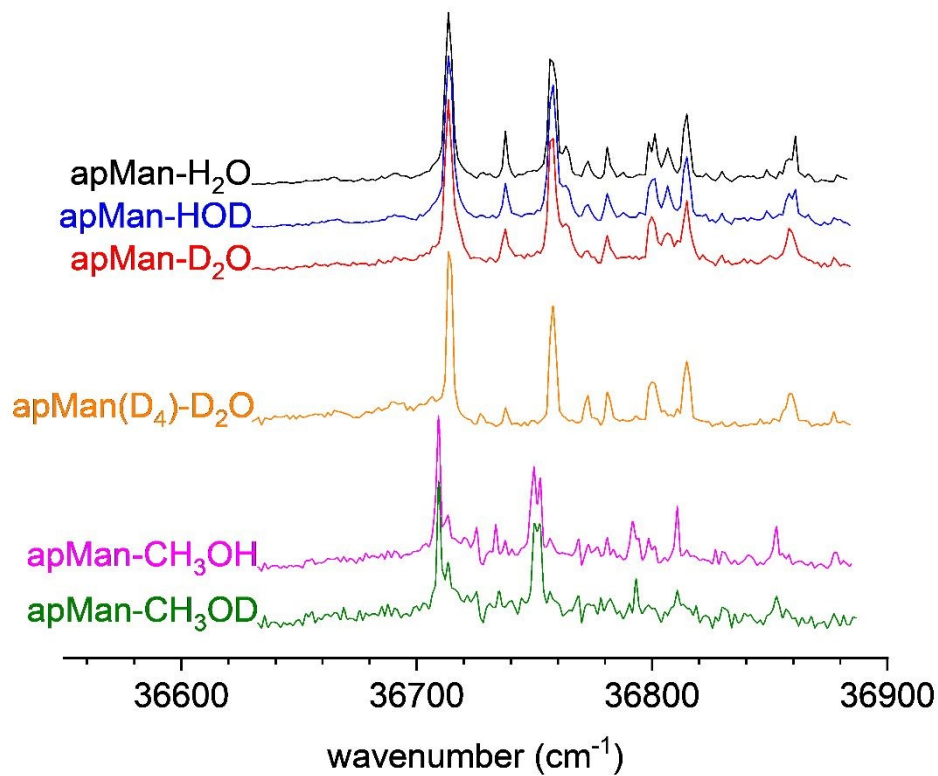


Figure 4. 2c-REMPI of the three isotopic species of apMan-W, recorded simultaneously for the three isotopes, and for apMan- $\text{CH}_3\text{OH}/\text{D}$ .



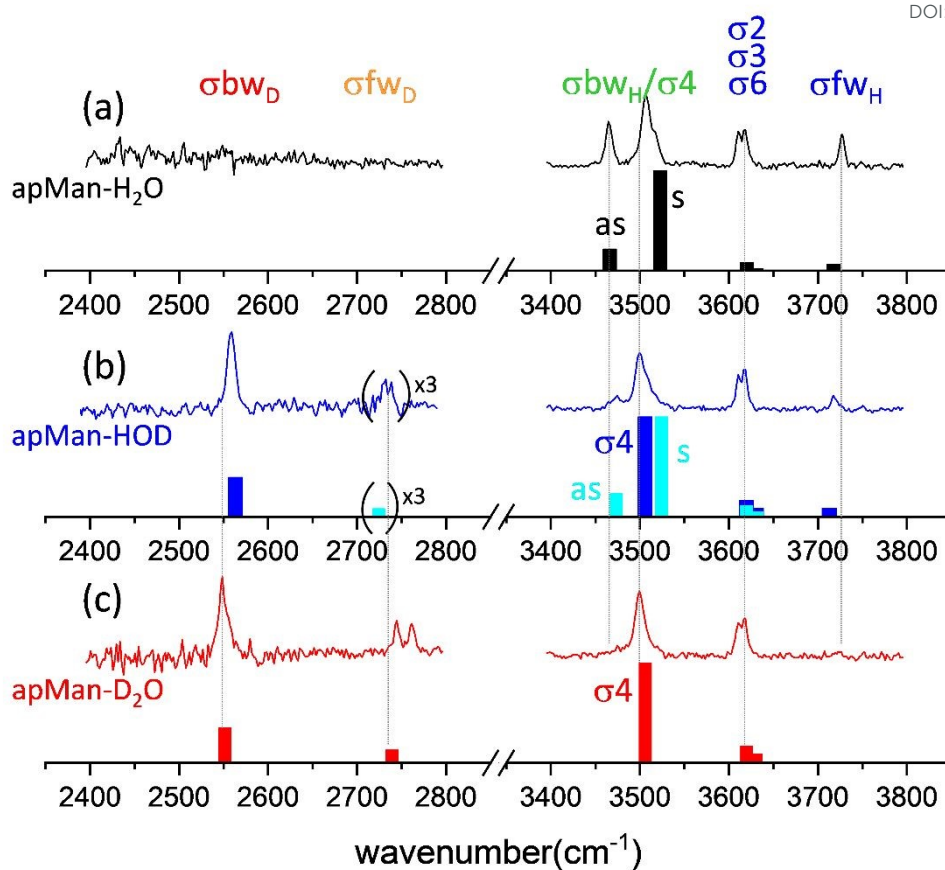


Figure 5. Experimental and calculated vibrational spectra of (a) apMan-H<sub>2</sub>O, (b) apMan-HOD and (c) apMan-D<sub>2</sub>O. For the apMan-HOD isotopomer, the scaled calculated spectra for both possible isomers apMan-H\*OD in light blue, and for apMan-HOD\* in dark blue, are shown. The weak free O-D observed and calculated intensities have been multiplied by 3 to be more easily visible.



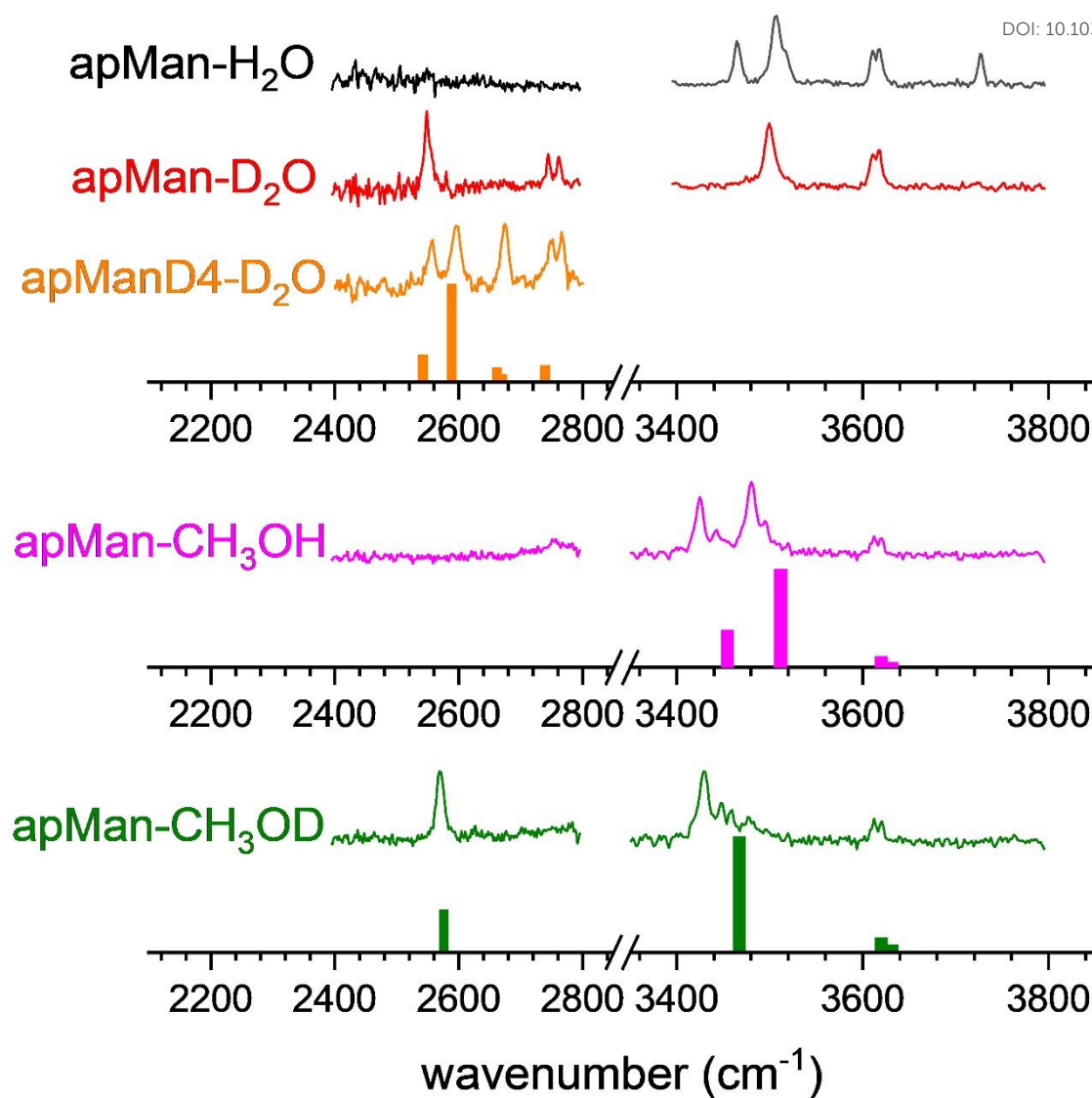


Figure 6. IRID spectra of apMan-H<sub>2</sub>O/HDO/D<sub>2</sub>O, apManD4-D<sub>2</sub>O, apMan-CH<sub>3</sub>OH and apMan-CH<sub>3</sub>OD.



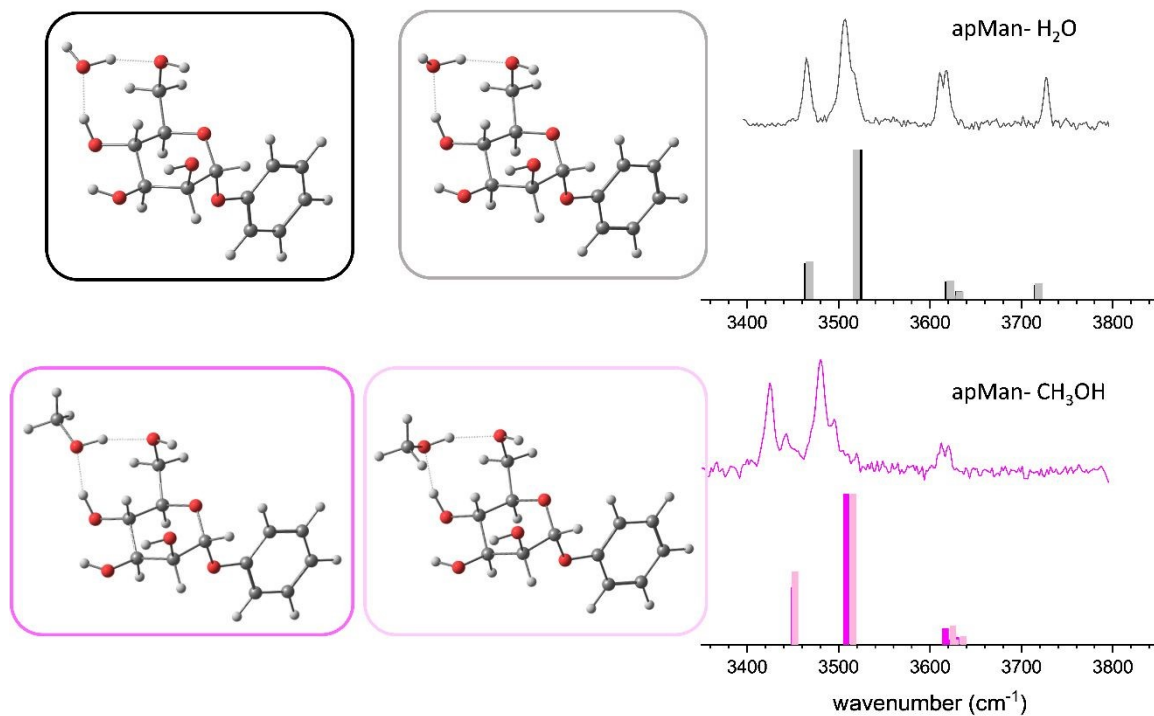


Figure 7. Variations of the most stable conformers of (top) apMan-H<sub>2</sub>O and (bottom) apMan-CH<sub>3</sub>OH. The calculated spectra of each conformer are compared to the experimental spectra of the right. The colors of the bars refer to the box color of each conformer.

