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Setting up the HyDRA blind challenge for the microhydration of organic molecules†

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The procedure leading to the first HyDRA blind challenge for the prediction of water donor stretching vibrations in monohydrates of organic molecules is described. A training set of 10 monohydrates with experimentally known and published water donor vibrations is presented and a test set of 10 monohydrates with unknown or unpublished water donor vibrational wavenumbers is described together with relevant background literature. The rules for data submissions from computational chemistry groups are outlined and the planned publication procedure after the end of the blind challenge is discussed.

1 Introduction

The microhydration of organic matter[1–3] deserves a systematic, unbiased comparison between theory and experiment.[4] The primary and most fundamental quantities to be benchmarked are probably structure and energy of cold, neutral 1 : 1 hydrate complexes prepared in supersonic jet expansions.[5] Any isomerism in the docking of individual water molecules to multifunctional organic molecules[6] is of particular interest in this context, because theoretical input is most valuable and reliable for trends and comparisons.[7] This is where systematic model errors often tend to cancel,[8] paving the way for helpful approximations. The properties of monoisomeric systems are valuable for a first calibration of absolute quantities, which are typically more challenging because they require highly accurate treatments of electronic structure and nuclear dynamics effects. It is rewarding that there are numerous rotational spectroscopy studies of monohydrates with more or less direct structural and sometimes relative energy information available in the literature.[5,9–11] These provide a lot of detail on the shallow potential energy landscapes of solvation phenomena.

A currently underexplored proxy to the hydrogen bond structure and energy of microhydrates is the wavenumber of the hydrogen-bonded OH stretching vibration $\tilde{\nu}_{OH_b}$ of any docking water serving as a hydrogen bond donor.[12] As a single number for a given monohydrate complex which can be derived from vibrational spectroscopy in a straightforward way, it offers a set of advantages over more demanding structural studies. For multifunctional substrates, linear IR and Raman spectroscopy can provide an immediate survey over competing hydrogen bond docking sites due to the simplicity and intensity of the vibrational fingerprint of the OH group.[13,14] To compensate for the low spectral resolution, double resonance techniques allow for rigorous size and conformational distinction,[15] relaxation experiments can identify the most stable conformation,[16] and ^{18}O labelling of water can unambiguously discriminate from other hydride stretching modes in the vicinity.[17] The spectral position of the OH stretching vibration is very sensitive to the strength of the hydrogen bond, spanning about two orders of magnitude in relation to the typical spectral width of an isolated vibrational transition.

A theoretical model which successfully predicts only a single observable quantity such as $\tilde{\nu}_{OH_b}$ is likely to initially get the right answer for the wrong reason, as multidimensional anharmonicity is not easy to model rigorously. This is particularly true if the experimental answer is known beforehand, due to a multitude of available and conceivable model variants and parameters. Therefore, large training sets, blind test components and iterative refinements are essential ingredients on the path towards systematic success for the modeling of OH stretching wavenumbers of monohydrates. Even a largely empirical model with a high success rate for a selected observable can be useful for the experimental gas phase cluster community. This is still close to the current status, where each observable and sometimes even each research group has its favourite recipes (functionals, basis sets, scaling factors) to assist experiment. There may be more or less systematic

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correlations between the observed wavenumber shifts and experimental or computed proton affinities and gas phase basicities[18–20] or calculated hydrogen bond lengths,[21] to name just a few possible links to be exploited. Ultimately, one must hope for a number of systematically successful models which connect theory and experiment on multiple observables, not only the vibrational wavenumber. Meaningful approximations such as elaborate scaling techniques,[22,23] local mode models,[24,25] parameterised harmonic DFT predictions,[26] *ab initio* molecular dynamics,[27] polarisable force fields[28] or hierarchical models building on high level treatments of the smallest systems or subgroups[29] may be identified or we may even witness the victory of machine-learning approaches[30] towards such challenges.

While blind challenges have become popular in different chemical subcommunities such as protein[31] and crystal structure prediction[32] or physicochemical data for drug molecules in solution,[33–36] we are not aware of a blind challenge explicitly addressing vibrational spectroscopy data as a rigorous connecting point between theory and experiment. This may also be due to the fact that this connection relies on challenging electronic structure and vibrational anharmonicity issues at the same time. However, this is also subtly true for observables like molecular structure[37] and energy differences,[38] and therefore it appears timely to investigate a bolder case.

The HyDRA challenge is meant to kick off such a systematic approach to microhydration, with numerous conceivable follow-up options. HyDRA stands for *Hy*drate *D*onor *R*edshift *A*nticipation, where redshift refers to the wavenumber downshift of the donor OH vibration relative to the symmetric stretching fundamental of the water molecule[39,40] at 3657 cm^{-1}. The switch between absolute values and relative trends is thus trivial in this case, because it only involves adding or subtracting this experimental monomer value. In the present work, we use the sign convention that a positive downshift describes a lower wavenumber in the complex than in monomeric water. Here, we outline the construction of an initial training and test set for neutral organic monohydrates which was recently offered to theory groups,[41] connected with the invitation to participate in a blind challenge.

2 Molecular systems

2.1 Experimental training set

The first goal in this challenge was to identify a number of vibrationally well-characterised, diverse monohydrate complexes of small organic molecules in the existing experimental literature, for which the lowest energy structure involves water as the hydrogen bond donor and thus generates a characteristic donor OH stretching vibrational fundamental ν_{OH_b}. For this purpose, a call among vibrational spectroscopists was initiated early in 2021 and the suggestions were collected on a website,[41] summarising the observed wavenumber $\tilde{\nu}_{OH_b}$, the organic species (with CAS number), the DOI of the relevant publication and the contact email of the submitter.

Further mandatory entries of every submission included the proposing researcher and institution (not necessarily from the group publishing the experimental data) as well as the spectroscopic detection, wavenumber calibration, and cooling techniques used. Concerning the observed wavenumber, the submitter had to estimate its accuracy, to predict the relevant docking site for the observed water molecule and to assess whether the monohydrate was the global minimum arrangement of the two complex partners.

Optional entries for further assessment and use of the submissions beyond the initial training included supporting researchers like coworkers and endorsing colleagues as well as spectroscopic data on the free (or otherwise engaged) OH stretching vibration of the hydrate water ($\tilde{\nu}_{OHf}$), the wavenumber and relative intensity of a potential resonance partner to ν_{OHb} (possibly stealing intensity and shifting its band centre), and any isotope substitution information or information on observed docking isomers.

Because it is essential for the challenge that the training set data are well secured, it was possible to list additional assignment measures concerning the organic molecule conformation, the docking site, and the size assignment to a monohydrate, as well as to comment on any other relevant issue.

Based on more than a dozen submissions from half a dozen countries over half a year, a small committee consisting of a PhD student, an undergraduate research student and two experimental spectroscopy group leaders made a selection of 10 systems to be recommended to the theory community for the training of their models. Among others, methanol[14] was not included into the core training set because of its very large amplitude internal motion and a capped phenylalanine[42] was not included because the global minimum hydrate structure presumably does not involve water as a hydrogen bond donor, although a higher-energy conformer does. Several ketones (cycloheptanone, cyclohexanone, 4,4-dimethylcyclohexanone, (−)-fenchone, 2-fluoroacetophenone, pinacolone, 3,3,5,5-tetramethylcyclohexanone)[43,44] were not included to keep the balance between represented functional groups. The growing set of non-selected submissions is still made available, with the goal of a comprehensive curated database on OH stretching wavenumbers of hydrate complexes in mind. Numerous interesting monohydrates are still missing in the database, such as systems where the water induces a strong restructuring of the solute[42] or floppy ring systems.[45]

The 10 systems selected for the HyDRA training set are shown in Fig. 1 together with the three-letter acronym used in this work and with their CAS registry number. Each of them fulfills a number of desirable properties for this initial training process (Table 1). All are believed to have water acting as a hydrogen bond donor in the global minimum structure, all contain less than 100 electrons to facilitate accurate quantum-chemical modeling. All except APH (where IR spectroscopy was required to detect the second isomer[43,46]) have only one experimentally observed monohydrate conformation in the jet-cooled vibrational spectrum. For all except IMZ, the free OH stretching wavenumber of the solvating water is also known experimentally. All except for the methyl ketones ACE and APH with their low barrier methyl torsions are fairly stiff, with no monomer

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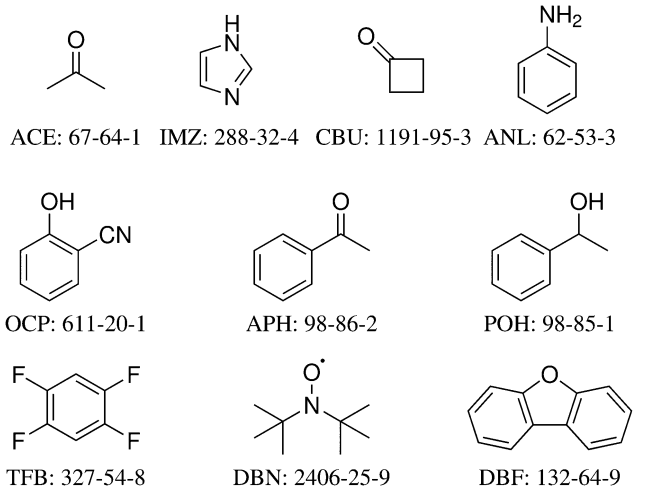

Fig. 1 The structural formulas, abbreviations, and CAS registry numbers of the 10 systems selected for the HyDRA training set, sorted according to their electron number.

fundamental wavenumber significantly below 30 cm^{-1}. For most monohydrates of the training set, there is more than one spectroscopic study in the literature, and in a few cases (ACE, IMZ) there are also isotope substitution experiments. In particular, many monohydrates (APH, ANL, CBU, DBF, IMZ) have been characterised structurally by rotational spectroscopy.[46–50] In two cases (ACE, APH), there is a well-established vibrational b2lib resonance[43] (a resonance of the water OH stretch with the bending overtone (b2) and a hydrogen bond librational (lib) mode) which makes these systems particularly interesting for advanced anharmonic models, but models not including such a resonance can also be applied, because we provide the deperturbed OH stretching wavenumber as well. The rationale behind offering this choice shall be explained briefly for the case of acetone, where it is particularly pronounced. Experimentally, one finds a dominant transition at 3538 cm^{-1} and a secondary transition with about half the intensity at 3516 cm^{-1}. The latter is believed to be a three-quantum state involving the water bending overtone and a librational motion of the water molecule against the acetone. It would normally be too weak to be observed, but its vicinity to the OH_b stretching state leads to intensity borrowing from the OH_b state. A perfect vibrational model would thus predict both states at 3538 and 3516 cm^{-1} and it would predict the 3538 cm^{-1} signal to carry more intensity, because it has more OH_b character. However, such a vibrational model would have to include higher order anharmonic couplings which shift around the levels and redistribute their IR transition strength. More approximate theoretical models and in particular (scaled) harmonic models are unable to describe this resonance and therefore they are better compared to the hypothetical OH_b stretching band centre which would be observed if this resonance were absent (*e.g.* due to a softening of the water bending vibration). In a two-state analysis, this hypothetical or deperturbed band centre can be estimated from the experimental band positions and intensities.[43] It is 3531 cm^{-1} and corresponds to the intensity centre of the experimental doublet. To properly train a harmonic or simplified anharmonic model, one should therefore try to match 3531 cm^{-1} instead of 3538 or 3516 cm^{-1} for ACE, and 3530 cm^{-1} instead of 3536 or 3514 cm^{-1} for APH. In two other cases (ANL, DBN), there may be an analogous resonance, but this remains experimentally open and therefore the deperturbed value for OH_b spans the experimentally observed main transition. To analyse such resonances, it is essential to avoid embedding of the monohydrates in matrices, because matrices may also induce site splittings which are difficult to distinguish from a resonance.[51]

In terms of experimental techniques, 5 monohydrates were characterised by UV/IR double resonance techniques (in different laboratories in France, Germany, Japan and Spain) and 6 by FTIR spectroscopy (in Germany), all in supersonic jet expansions. 6 compounds are aromatic, 1 is a radical, 3 are ketones, 2 are alcohols/phenols. The hydrogen bond acceptor atoms include O, F, N and π-systems.

The target benchmark observables are summarised in Table 2. Either the absolute OH_b-wavenumbers $\tilde{\nu}_{exp}(OH_b)$ of the hydrogen-bonding water or equivalently their downshifts Δ_{OH} from the isolated water symmetric stretching fundamental can be targeted. For models including full anharmonicity and thus the postulated Darling–Dennison-like fourth-rank 1–3 resonance for four systems, the most intense OH_b transition can be addressed directly. For models which do not include such resonances, it may be better to address the values in square brackets, which attempt to correct for this anharmonic perturbation with a coupling matrix element on the order of 10 cm^{-1} and involve a larger error bar due to the correction uncertainty. For imidazole it is worth mentioning that most techniques detect both the NH- and OH-bonded isomers,[50,57] whereas theory and a slit jet expansion study[17] indicate a clear energetical preference for the OH-bonded isomer which is of interest in the context of this challenge.

Table 1 Desirable properties for the training set members together with individual assessments whether they and their monohydrates fulfill them (+) or not (–)

	ACE	APH	ANL	CBU	DBF	DBN	IMZ	OCP	POH	TFB
Unique observed 1 : 1 conformer?	+	–	+	+	+	+	+	+	+	+
Global minimum?	+	+	+	+	+	+	+	+	+	+
Isotope data?	+	–	–	–	–	–	+	–	–	–
Further experimental references?	+	+	+	+	+	+	+	–	+	–
OH_f known?	+	+	+	+	+	+	–	+	+	+
Potential b2lib-resonance?	+	+	+	–	–	+	–	–	–	–
Less than 100 e^-?	+	+	+	+	+	+	+	+	+	+
Lowest monomer-vibration >30 cm^{-1}?	–	–	+	+	+	+	+	+	+	+

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Table 2 Training set of 10 acceptor molecules – abbreviations, CAS registry numbers (CAS RN) and published experimental OH_b-wavenumbers $\tilde{\nu}_{exp}(OH_b)$ (with estimated uncertainty in parentheses) of the acceptor molecules in the monohydrates selected for the training set. In square brackets, estimated deperturbed OH_b-wavenumbers after removal of a three-quantum resonance (see text) are provided. These wavenumbers in brackets should be targeted by vibrational models which do not include such an anharmonic resonance. Where the resonance remains hypothetical, the deperturbed wavenumber uncertainty (in parentheses) spans the experimentally observed main transition wavenumber. Also provided are downshifts Δ_{OH}/cm^{-1} (positive, if the complex has a lower wavenumber) from the water monomer fundamental at 3657 cm^{-1}

Acceptor molecule	Abbreviation	CAS RN	$\tilde{\nu}_{exp}$ $(OH_b)/cm^{-1}$	Δ_{OH}/cm^{-1}
Acetone[43]	ACE	67-64-1	3538(1) [3531(2)]	119(1) [126(2)]
Acetophenone[43]	APH	98-86-2	3536(1) [3530(2)]	121(1) [127(2)]
Aniline[52]	ANL	62-53-3	3524(1) [3526(3)]	133(1) [131(3)]
Cyclobutanone[43]	CBU	1191-95-3	3548(1)	109(1)
Dibenzofuran[49]	DBF	132-64-9	3623(1)	34(1)
Di-*tert*-butyl nitroxide[53]	DBN	2406-25-9	3484(2) [3487(4)]	173(2) [170(4)]
Imidazole[17]	IMZ	288-32-4	3458(2)	199(2)
o-Cyanophenol[54]	OCP	611-20-1	3595(2)	62(2)
1-Phenylethanol[55]	POH	98-85-1	3620(2)	37(2)
1,2,4,5-Tetrafluorobenzene[56]	TFB	327-54-8	3647(1)	10(1)

2.2 Experimental test set

For the experimental test set of vibrationally uncharacterised monohydrates, a multifaceted approach was chosen. Because their experimental data had to be secured and kept secret until the end of the blind challenge, some of the considered systems were already experimentally characterised in the research groups forming the selection committee, but not yet published. Others were at least pre-explored to increase the likelihood of a successful assignment during the runtime of the blind challenge. Furthermore, an informal call to microwave spectroscopy groups was made to collect suggestions for systems which had already been characterised structurally, to minimise the risk that a subsequent vibrational characterisation meets unexpected difficulties. This approach led to a preselection of 15 monohydrate proposals, for which there is no gas phase vibrational spectroscopy record in the literature. From those, the final selection of 10 official test systems was made one month after the publication of the training set, by the same selection committee. These 10 target systems for the blind challenge are summarised in Fig. 2 (ordered by number of electrons) and Table 3 (in alphabetical sequence). Note that if the model to be submitted by a participant involves a three-quantum b2lib resonance (*vide supra*), a short discussion of the consequences for the deperturbed water OH_b wavenumber is recommended.

Table 3 Test set of 10 acceptor molecules – abbreviations, CAS registry numbers (CAS RN) and expected minimum number of OH stretching signals in the most stable monohydrate *n*(OH), among which the hydrogen-bonded water OH_b wavenumber $\tilde{\nu}_{exp}(OH_b)$ (or its downshift Δ_{OH}/cm^{-1} from the water monomer fundamental at 3657 cm^{-1}) should be predicted. If a three-quantum resonance is predicted (see text), estimated deperturbed water OH_b wavenumbers after removal of this resonance[43] may also be provided. For *n*(OH) > 2 (hydroxy compounds), we recommend that the theory groups report all OH stretching fundamentals, because there may be mode mixing between the hydrogen-bonded alcoholic and water OH bonds. Alternatively, we recommend to report the mode which shows the strongest downshift when $H_2{}^{16}O$ is replaced by $H_2{}^{18}O$, because it carries the strongest water stretching character

Acceptor molecule	Abbreviation	CAS RN	*n*(OH)
Cyclooctanone[58,59]	CON	502-49-8	2
1,3-Dimethyl-2-imidazolidinone[60,61]	DMI	80-73-9	2
Formaldehyde[62,63]	FAH	50-00-0	2
Methyl lactate[64,65]	MLA	547-64-8	3
1-Phenylcyclohexane-*cis*-1,2-diol[66]	PCD	125132-75-4	4
Pyridine[67,68]	PYR	110-86-1	2
Tetrahydrofuran[69,70]	THF	109-99-9	2
Tetrahydrothiophene[71]	THT	110-01-0	2
2,2,2-Trifluoroacetophenone[72]	TPH	434-45-7	2
2,2,2-Trifluoroethan-1-ol[73,74]	TFE	75-89-8	3

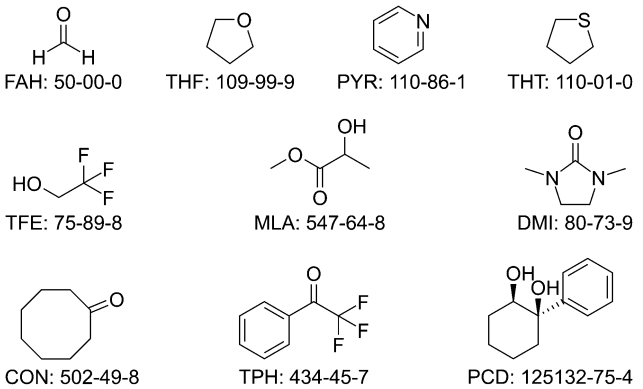

Fig. 2 The structural formulas, abbreviations, and CAS registry numbers of the 10 systems selected for the HyDRA test set.

Each target system, ordered by increasing number of electrons and thus computational complexity, will be briefly discussed in the following to introduce the most relevant literature sources for structural and other information.

For FAH as the simplest molecule in the test set, it is long established by theory[75–77] and experiment[63] that water coordinates asymmetrically. The OH stretching vibration which is of interest in this challenge has been determined in matrix isolation,[62,78] but to the best of our knowledge not in the gas phase without environmental influence. In cryogenic matrices, split signals were found (3580, 3585 cm^{-1} in neon and argon, 3573, 3578 cm^{-1} in a nitrogen matrix). These can give a first orientation, but the vacuum-isolated transition may be located above, below or in this range and the splitting may be lifted if it is caused by matrix interaction. Whether the complex is planar

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or quasiplanar is difficult to determine with the available experimental data[63], but we expected to provide a single experimental vacuum-isolated water OH_b stretching wavenumber to be predicted by the different models.

Because of its relevance for clathrate formation, the OH stretching spectrum of the THF monohydrate has been obtained in CCl_4 solution[79] at 268 K. A broad (about 80 cm^{-1} FWHM) hydrogen-bonded OH stretching fundamental was located near 3450 cm^{-1} at high dilution. Due to thermal and solvent effects, this absolute value is not suitable for the direct comparison to environment-free ground state calculations. In a theoretical study from 2005, it was concluded that the complex has never been observed in spectroscopic experiments.[70] With respect to gas phase investigations, we found no evidence to revise this statement. In particular, there appears to be no rotational spectroscopy characterisation of the monohydrate, but one can expect one or two isomers, due to the complex pseudorotational dynamics of the monomer.[69,80]

The PYR monohydrate is a model system for photoinduced homolytic water splitting.[81] Its structure is quite flexible, as evidenced by rotational spectroscopy.[68] It includes a tunneling motion with an inverted H/D isotope effect, but this is not directly relevant for the vibrational transition at low resolution. There is a room temperature gas phase value for the hydrogen-bonded OH stretching mode in PYR monohydrate,[82] at 3480 cm^{-1}. However, for such a soft and flexible hydrogen bond, it is likely that the cold transition obtainable in a jet expansion occurs at significantly lower wavenumber. While ultracold helium droplets should exhibit much smaller, but still significant[17,83] environmental shifts than a room temperature gas phase measurement, a corresponding recent study[67] does not address the relevant spectral range and isotope composition.

In contrast to the THF situation, the monohydrate of THT has been structurally characterised in much detail,[71] also with respect to the water orientation relative to the ring. We are not aware of a complementary vibrational gas phase study and thus considered this to be a valuable diversification of the test set, also in preparation for more challenging thio compounds.[84]

In TFE, as in many fluorinated alcohols,[73] the first solvating water acts primarily as a hydrogen bond acceptor, but the symmetric stretching mode is only subtly shifted from the water monomer value by this interaction and by an additional donor contact to the CF_3 group. This provides valuable benchmark information for small complexation shifts, but the IR activity of such weakly perturbed symmetric OH stretching motions in water molecules is low. Therefore, Raman spectroscopy[14] was expected to provide key vibrational information in this case. Structurally, the preference of the monohydrate for an insertion complex is well established[74] and the related, structurally more diverse case of hexafluoroisopropanol is also well studied.[85,86] By including the simplest model of a peptide co-solvent[87] monohydrate into the vibrational target systems, the characterisation of their unusual biochemical properties can be supported.[88]

For MLA with its weak internal hydrogen bond between the hydroxy group and (preferentially) the carbonyl group, a solvent water has different options to coordinate. It can insert into the internal hydrogen bond, or add to either end, or even to the ester oxygen. Due to the activation barrier for the first process, jet experiments have to make sure that insertion is not kinetically hindered.[89] This is important, because theory predicts insertion to be most stable. In this context, it is essential that there is experimental microwave evidence for the inserted structure,[64] in which the solute also directs the dangling water hydrogen to one side. The competition from lactate conformations with the carbonyl group pointing away from the hydroxy group is intense in aqueous solution,[65] but not yet in the monohydrate. In contrast to jet studies of the methanol complex[89] and matrix studies of the ammonia complex,[90] we are not aware of matrix isolation or jet studies of the OH stretching vibration of the monohydrate.

For the urea derivative DMI, a solution study[60] has revealed broad absorption maxima of the monohydrate in 1,2-dichloroethane (3431 cm^{-1}) and CCl_4 (3460 cm^{-1}) solution, downshifted by 162 and 155 cm^{-1}, respectively, from the monomer symmetric OH stretch of water in the same solution. We are not aware of structural data for the monohydrate in the gas phase, but there is evidence for involvement of the C═O group in the hydrogen bond[60] and the DMI monomer has been characterised by rotational spectroscopy.[61]

Monomeric CON has been structurally characterised by microwave jet spectroscopy and shown to exist in a dominant boat-chair conformation with non-equivalent lone pairs of the oxygen.[58] The energy difference to the next conformation is so large that monohydration is unlikely to switch the energy sequence. Therefore up to two isomers of the monohydrate are expected[59] and the more stable one is of interest in the present challenge. As the energy balance between the two docking isomers could be subtle, we recommend to calculate both and to provide at least the donor OH stretching wavenumber of the more stable one. Note that there is isotopic exchange evidence for transient formation of the geminal diol from the ketone monohydrate,[59] but such a competing structural isomer should be easily distinguishable from the monohydrate complex also in the vibrational spectrum and is not the target for the present investigation. We are not aware of any vibrational study of the monohydrate of CON.

TPH is an unsymmetric ketone, in which the water molecule is strongly directed to one of the C═O lone electron pairs. Its monohydrate was recently accurately characterised by rotational spectroscopy and theory[72] but we are not aware of a published gas phase vibrational study. Comparison to the well-studied non-fluorinated parent compound APH from the training set will reveal the influence of fluorination through space and through several bonds.

PCD as the most complex member of the test set is of stereochemical and hydrogen bond topological interest. Note that the two OH groups are *cis*-configured, whereas the absolute chirality is not relevant for the monohydrate. The diol forms two weak, but cooperative hydrogen bonds (OH–OH and OH–π) which give rise to separate OH stretching transitions in CCl_4 solution.[66] The water in the monohydrate has several options to

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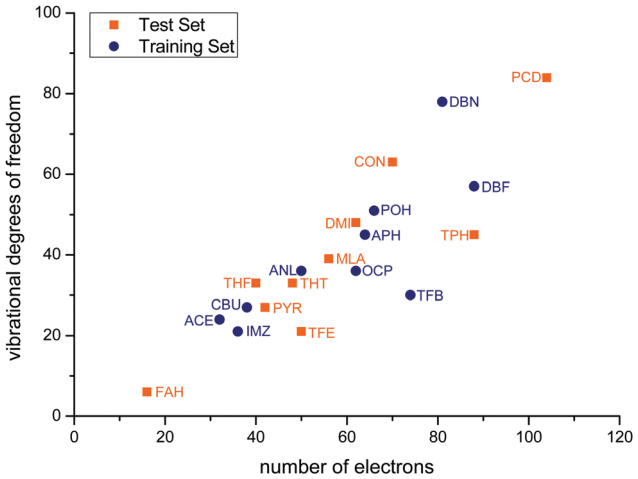

Fig. 3 Vibrational degrees of freedom $3N_n - 6$ of the training (blue) and test (orange) solute molecules with N_n nuclei for which monohydrates are investigated as a function of their number of electrons n_e.

attach or insert into this hydrogen bond chain and the most stable conformation is sought. In this particular case, we recommend an extensive search among the possible conformations to identify the global minimum conformation. It is going to be characterised by IR/UV spectroscopy and isotope labelling. We are not aware of previous gas phase work on this system.

Fig. 3 correlates the number of vibrational degrees of freedom $3N_n - 6$ for N_n nuclei with the number of electrons n_e of the solutes for the training and test sets. The sets span an order of magnitude in each quantity and deviate significantly from a linear relationship, with some systems being more challenging for the nuclear dynamics treatment and others for the electronic structure treatment. Two of the test set members (FAH, PCD) represent an extrapolation relative to the training set, whereas the others tend to fill gaps in terms of electron and nuclear degrees of freedom.

Acceptors which were considered as suitable candidates for the test set, but are postponed for later investigation to maximise its diversity and to reduce its conformational complexity, include acetaldehyde (AAH: 75-07-0), 4′-fluoroacetophenone (FPH: 403-42-9), hexafluoroisopropanol (HFP: 920-66-1),[85,86] *N*,*N*-dimethylformamide (DMF: 68-12-2) and 2,2,4,4-tetramethylpentan-3-one (TPO: 815-24-7). Other candidates which require further testing or turned out to be less suitable at this stage include benzaldehyde, 4-fluorobenzaldehyde, furan, thiophene,[91] propylene oxide, and 4-methoxy-2,2,6,6-tetramethyl-1-piperidinyloxy. Further interesting candidates which were suggested by microwave groups and will have to be further analysed in terms of suitability include propargyl alcohol,[92] furfuryl alcohol, and furfuryl mercaptane[93] as well as thenyl alcohol and thenyl mercaptane.[84]

3 Experimental methods

3.1 Description of experimental procedures

All experimental data of this blind challenge refer to translationally and rotationally cold molecules ($T < 20$ K) without contact to other molecules or carrier gas atoms, but with some residual vibrational excitation in soft modes from the initial thermal population. There is the possibility of conformational trapping behind barriers, which may partially avoid relaxation to the global minimum structure. This is the typical situation in adiabatic carrier gas expansion experiments into vacuum, either free[94] or skimmed to form a molecular beam,[95] with a starting temperature of 300 K or somewhat higher for low-volatility compounds. The specific monohydrates were chosen to minimise the risk of significant conformational trapping in most cases. The trapping can be intermolecular, if two or more hydrogen bond formation sites are available in the solute molecule. In such a case, cold monohydrates with water docking on the less favourable site cannot quantitatively interconvert into the most favourable site on the timescale of the experiment in all cases. This is particularly relevant for the three alcohols in the test set, where water can attach to any lone pair or insert into a pre-existing hydrogen bond of the solute.[89] The insertion is typically an activated process and if the activation energy significantly exceeds 5 kJ mol^{-1}, it may not happen sufficiently fast under the low collision rates of the supersonic expansion. The trapping can also be of intramolecular nature, if the solute exists in different conformations with higher barriers. For ring puckering modes, the barriers are not always sufficiently low for efficient funneling into the vibrational ground state. For intramolecular hydrogen bonds, the solutes are chosen such that relaxation into the global minimum structure was typically proven experimentally, or is at least likely. Constitutional relaxation is evidently not considered. Thus, the decomposition of formaldehyde into CO and H_2 is disregarded for the global minimum criterion, although it is exothermic by about 9 kJ mol^{-1} at low temperature.[96] Also, the exothermic diol formation from the reaction of a formaldehyde molecule with a water molecule[97,98] is not considered. The solutes always remain in the constitution given in Fig. 2.

The spectroscopic methods used to probe the monohydrates may be distinguished into action and linear techniques. In action techniques, the effect of the photons on the monohydrates is probed, *e.g.* ionisation, dissociation or fluorescence. In linear techniques, the effect of the monohydrates on the photons is probed, *e.g.* direct infrared absorption[13] or inelastic (Raman) scattering.[87] Action techniques often offer much higher sensitivity, they can be size-selective and conformationally selective.[15,99–101]

3.2 Challenges and experimental difficulties

Linear techniques probe all the molecular systems present in the expansion, based on their photon absorption or scattering cross sections. They can usually identify size (*e.g.* hydration number) by variation of the expansion conditions and by following the signal evolution, at least for 1:1 complexes if those do not spectrally overlap with other cluster compositions. Conformations can only be distinguished if they differ in their spectral fingerprint, sometimes with the help of isotope substitution. There is a less liberal molecular size limit for linear techniques due to the decreasing vapour pressure and the limited sensitivity. Action techniques may in turn suffer from

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unwanted competing processes such as fragmentation and may still be problematic for many non-aromatic systems and even some aromatic systems with fast processes in the electronically excited state.[102,103] The best is always a combination of both techniques, such as in the case of POH from the training set. This is, however, unrealistic on the time scale of this challenge and for the choice of molecules. It was anticipated that one member of the test set (PCD) would only be characterised by an action technique (IR/UV double resonance), whereas the others would be mostly accessed by direct infrared absorption. For the latter, a recent instrumental development[104] is very helpful for monohydrates, because its gas recycling allows for the use of expensive isotopologues, solutes and carrier gases. In some cases, where the water vibration of interest has a low infrared intensity or may be distributed over several OH stretching modes in the complex, linear Raman spectroscopy[14,87] could provide the required information.

Aggravated by the partial double-blind character of the challenge, it could not be strictly ruled out that a training or test set member has to be removed completely from the challenge, because experiments or their interpretations reveal a major problem. Such problems may include the discovery of new monohydrate or even monomer conformations which complicate an unambiguous assignment,[38] issues with the cluster size assignment, experimental downtimes due to instrument failure, commercial availability bottlenecks, *etc.* However, we expected that such problems would not exceed a 10% threshold and thus do not significantly narrow the significance of the challenge. Indeed, at the time of writing, only one of the test systems contains a non-critical degree of experimental uncertainty, whereas the others appear to be unambiguous in their interpretation.

4 Challenge procedure

4.1 Theory group involvement

Theory groups and other researchers interested in the systematic prediction of OH stretching wavenumbers for monohydrates were alerted about this blind challenge *via* news groups, conferences, and direct contact. The training set list of 10 organic solvates was provided at this time. Interested groups were given the possibility to register for the challenge before the test set was published. They could then be alerted immediately upon the start of the actual competition. Registrations up to the submission deadline 6 months later were accepted. A unique entry code was provided to each participant in order to allow them later to review their own submitted data.

Although it did not stand as a strict rule, the calculations for all molecules in both sets (test and training) had to be carried out as consistently as possible. This meant that the level of theory at all different stages (conformer search, optimisation, calculation of frequencies, *etc.*) were expected to be the same. The same also applied to methods not based on molecular structure. For example, if a regression was used, the same model was expected to be applied to all systems, while some parameters of the protocol were allowed to change. For example, in some systems conformational searches might be redundant, or carry different parameters due to the range of molecular sizes. It is also possible that some geometry optimisation criteria call for adaptation. These computational details were expected to be provided at the end of the challenge. Assistance to all the participating groups was provided throughout the challenge duration, strictly avoiding any direct contact between the theory and the experimental groups, in the true spirit of a double-blind challenge.

One cannot rule out that we have overlooked published cold gas phase vibrational work on a system in the test set, or that such work appeared on the scientific record before the experimental HyDRA data are released after the end of the challenge. This could have been due to activities of other experimental groups not involved in the challenge, or due to data leakage from our experimental groups despite substantial effort to keep the results confidential among the contributing experimentalists. In such a case, the affected test set member would be shifted to training set status, because one cannot rule out that some model-proposing participants had a knowledge advantage over others. However, at the time of writing, we are not aware of such an incidence. The goal was clearly to keep the blind character as unquestionable as possible.[33]

4.2 Mandatory data submission

The mandatory part of the submissions for this blind challenge was compact. For each of the training and test set members, a single predicted wavenumber for the hydrogen-bonded water OH stretching mode in the most stable monohydrate in cm^{-1} had to be provided in a standardised online form. We strongly recommended to provide together with this number an error estimate. This could be based on an actual statistical analysis (*e.g.*, from the errors observed in the training systems) or even from personal convictions. Each participant group had the freedom to select which systems to compute (and ultimately submit data). In other words, all submissions were eligible to acceptance even if incomplete.

This compact table of up to 20 numbers (plus uncertainties) had to be accompanied by a detailed description of the rational prediction method employed, to be included as a separate, autonomous file in the supplementary information of the planned publication. The description had to contain all the details required for the reproduction of the results, such as the employed methods and program packages, with suitable references. Scaling parameters, employed atomic masses and any other parameters and computational keywords required for reproduction had to be provided. Any additional computed data deemed of interest for the monohydrates (see next section) could be included into the supplement. This document will remain in the full responsibility of the submitting authors and should include all the names and affiliations of the contributing co-authors as well as the role of each co-author in the submission. The use of ORCID IDs is strongly recommended.

4.3 Optional data submission

Optional parts of the submission could be, in the sequence of decreasing importance for the goals of this blind challenge,

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and in free format to be included in the supplementary information:

(a) A compact table of possible resonance partners of the hydrogen-bonded OH stretching mode of water, where predicted. This should include the wavenumber of the perturber and its fractional share of the intensity (square of the zero order OH stretching wavefunction), and for control purposes also the fractional share of the OH intensity and the stretching wavenumber of the perturbed OH stretching state. From this and the mandatory submission of the predicted OH stretching wavenumber, a coupling matrix element can be obtained in the 2-level dark perturber approximation, see ref. 43. Such information will only be possible if anharmonic calculations or coupling models are included. For other submissions, the submitted OH stretching wavenumber will be taken as the deperturbed zero order OH stretch which is obtained from experiment in such a 2-level deperturbation, in the few cases where such a resonance is observed.

(b) A table of any other OH stretching wavenumbers of the monohydrate, in particular the free OH stretch of the water and any other OH stretching mode in the acceptor molecule. If strong mixing of the OH oscillators is predicted, the mode with the strongest hydrogen-bonded water character should be submitted in the mandatory part and all the others in this part. One way to identify the mode with dominant water vibration character is to calculate the spectrum for $H_2{}^{18}O$. The OH stretching mode with the strongest isotope downshift is the one of interest.

(c) IR intensities and Raman scattering activities for all the OH stretching modes of the monohydrate, where available, preferably in km mol^{-1} and in Å^4 u^{-1}, including the depolarisation ratio for polarised light.

(d) Any spectral information on isotopologues which may be useful for the experimental analysis and for follow-up work (D, ^{18}O), always specifying the exact employed atomic masses. We recommend to always use the explicit isotopic masses for best method comparison.[105] Some programs use masses averaged over natural isotopic composition by default. This may have relatively small consequences for the current low resolution vibrational spectra and systems (still up to 5 cm^{-1} for vibrations involving sulfur due to a ratio of 1.003 between the natural atomic mass and the main isotope mass), but is clearly detrimental when comparing to high resolution (rotational) spectroscopy in the future.

(e) Relative energy (in kJ mol^{-1}, excluding and including zero-point vibrational energy corrections) and spectral properties of any higher-lying conformations of the monohydrates which were investigated, within a range of 3–5 kJ mol^{-1} of the global minimum structure. Here, global is defined under the restriction that the chemical bond connectivity remains the same, so rearranged bonding patterns like geminal diols[59,97,98] as structural isomers of noncovalent ketone monohydrates[96] are not considered. Geometries, when available, may be provided.

After the official submission deadline for model contributions, there was a limited time window for the correction of submissions. After this window was closed, the raw experimental data were made publicly available on a data repository, such that the challenge was closed on both ends.

4.4 Evaluation of the blind challenge

The submitted OH stretching data will be carefully evaluated and compared with the experimental values in different ways. Correlation plots for training, test and combined sets will be produced and analysed for all complete submissions, with a possible focus on which set is predicted better. Where several incomplete submissions focus on the most simple systems, which is to be expected for high-level theoretical treatments, analysis of such subsets with benchmark character will be attempted.

4.5 Publication of the results

The results will be published in a relatively compact many-author manuscript with extensive supplementary information in the responsibility of separate experimental and computational author subgroups, planned to be part of the present PCCP themed collection on benchmarking in 2022. The final selection of the methods and results included will be subject to different criteria including diversity of methods, sophistication of the approach and total number of 'coincident' submissions. Our expectation is, however, that all submissions will be considered. The submission of the data does not change the ownership of the data, the latter remains exclusive to the participating group. Any participants whose results are not included are still welcome to submit their work independently. Participants selected to participate in the joint paper are expected to respond to two rounds of manuscript reviews and to remove inconsistencies and gaps. Failure to reply within a two-week period effectively confirming co-authoring could result in exclusion from the joint publication. The publication should be viewed as the starting point for numerous follow-up activities by the individual groups, such as completing or improving their predictions in a non-blind fashion. Groups which did not meet the submission deadline are invited to present their results independently as well. Some experimental assignments may have to be revisited in the light of systematically conflicting predictions. Optional data provided by the computational approaches may help to better understand the spectra. The double-sided theory-experiment interplay will continue, as usual in the field. All these activities profit from a fast publication of the primary blind challenge results.

4.6 Post-publication activities

After publication of the results of the HyDRA blind challenge, the training and test sets can be extended to more strongly and even more weakly bound monohydrates, to charged systems (where more powerful experimental techniques are available[106–108]), to dihydrates, to isotope effects, to other vibrations, or to further observables such as structures and relative energies. These extensions may be targeted by different groups and will hopefully lead to a continuous refinement of the theoretical modelling of the microhydration of organic matter, identifying the most powerful and universal models in the field.

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There are indeed many interesting monohydrates which were not considered for the present challenge for various reasons. This includes systems where the global minimum structure is hidden behind a large monomer isomerisation barrier,[109] and some systems which are closely related to members of the training or test set.[43,110] It also includes the numerous systems where the global minimum structure involves water as a pure acceptor. In terms of acceptor elements beyond O and N, there are many extension possibilities towards S[84,111,112] which remain to be explored. For the structurally well characterised acid hydrates,[113,114] one may expect complex vibrational dynamics whenever the OH stretching excitation comes close to degenerate proton transfer barriers.

5 Conclusions

We have described a first systematic blind challenge initiative in the field of hydrogen bond-induced shifts in solvating water molecules. It consists of a training set of 10 literature-known 1 : 1 hydrate complexes spanning a downshift window of nearly 200 cm^{-1}. 10 vibrationally unassigned monohydrates were proposed for the actual blind test and promised to be experimentally characterised during the runtime of the challenge. The combined experimental results and predictions will be jointly published to identify the most promising empirical, semiempirical and *ab initio* models in the field. Several options for the extension of this initial challenge in chemical and spectral space are proposed, in the spirit of continuous benchmarking.[115]

We see this direct match between electronic structure theory and vibrational spectroscopy as an important complement to more traditional and well-established blind challenges in the field of protein[116] or crystal structure[117] prediction, where subtle energy differences also relate to zero point or thermal vibrational energy and thus anharmonicity treatments, besides getting the potential energy hypersurfaces right. This is even more obvious for the field of room temperature hydration,[118] where an atomistic method which systematically predicts correct free energy differences for a good reason is likely to predict reliable vibrational shifts of monohydrates as well. However, there is a long path of convergence between rigorously atomistic and other, more empirical or approximate or machine-learning models which are more easily extendable to macroscopic samples. Clearly, there is plenty of room in between. Blind challenges may be among the most objective procedures to find out where we stand.

Author contributions

T. L. F.: data curation, formal analysis, investigation, visualization, writing – review and editing; M. B.: data curation, investigation, visualization, writing – review and editing; A. Z.: investigation, methodology, validation, writing – review and editing; R. A. M.: conceptualization, funding acquisition, methodology, project administration, resources, software, writing – review and editing; M. A. S.: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing – original draft, writing – review and editing.

Conflicts of interest

There are no conflicts of interest to declare.

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