Supporting Information

Spectroscopic Fingerprints of Cavity Formation and Solute Insertion as a Measure of Hydration Entropic Loss and Enthalpic Gain

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1 Materials and Methods

Alcohols with a nominal purity higher than 99% were purchased from VWR International (Germany), and dissolved in HPLC water. Temperature-dependent, low frequency spectra of EtOH, PrOH, BuOH, isoPrOH and tPeOH aqueous solutions were measured in the frequency range from 50 to 600 cm\(^{-1}\) for concentrations between 0.5 M and 1.5 M. Temperature-dependent low frequency spectra of tBuOH aqueous solutions were reported in Ref. 1.

We used a Bruker Vertex 80v FTIR spectrometer equipped with a liquid helium cooled silicon bolometer from Infrared Laboratories as a detector. The sample solutions were placed in a temperature controlled liquid transmission cell from Harrick Scientific Products (USA) with two 0.5 mm-thick polycrystalline diamond windows supplied by Diamond Materials (Germany) and 13 and 25 μm-thick Kapton spacers for the temperature- and concentration-dependent measurements, respectively. The exact sample layer thickness was determined by recording etalons of the empty cell before each series of measurements. For each single spectrum, 128 scans were averaged with a resolution of 2 cm\(^{-1}\). The spectra were smoothed with a 2 cm\(^{-1}\)-wide (5 points) moving average. During the measurements, the sample compartment was continuously purged with technical grade dry nitrogen to minimize air humidity.

![Figure S1. Absorption coefficient of 0.5 and 1 M isoPrOH and tPeOH solutions at different temperatures.](image)

2 Data Analysis

Using Lambert-Beer’s Law, the frequency-, concentration- and temperature-dependent absorption coefficient of the solution \(\alpha_{\text{solution}}(\nu, c_s, T)\) is expressed as: 2

\[
\alpha_{\text{solution}}(\nu, c_s, T) = \frac{1}{d} \ln \left( \frac{I_{\text{water}}(\nu, T)}{I_{\text{solution}}(\nu, c_s, T)} \right) + \alpha_{\text{water}}(\nu, T)
\]  

(1)

where \(d\) is the sample thickness, \(I_{\text{water}}(\nu, T)\) and \(I_{\text{solution}}(\nu, c_s, T)\) are the transmitted intensities of bulk water and of the solution at temperature \(T\) and concentration \(c_s\), respectively,
with \( \alpha_{\text{water}}(\nu, T) \) being the absorption coefficient of pure bulk water. Using bulk water as a reference helped to eliminate spectral features due to reflections at the cell windows of the sample cell. The residual absorption due to residual air in the absorption path was corrected by taking into account an intensity-scaled spectrum of water vapor.

Since the solute replaces a fraction of water molecules in solution, the effective molar extinction coefficient of the solvated solute at a specific concentration and temperature can be deduced from the effective absorption coefficient by:

\[
\epsilon^{\text{eff}}_{\text{solute}}(\nu, T) = \frac{\alpha_{\text{solute}}(\nu, c_s, T)}{c_s} = \frac{\alpha_{\text{solution}}(\nu, c_s, T) - \frac{c_w}{c_{w,b}} \alpha_{\text{water}}(\nu, T)}{c_s}
\]

where \( c_w \) and \( c_{w,b} \) are the water concentrations in the solution and in bulk water at the same temperature, respectively. This analysis was applied to all the samples considered in this work (the raw \( \alpha_{\text{solute}} \) data are presented in Fig.S1 for the newly measured samples, while the other spectra were previously measured), as shown in figure S2 below for four alcohols at different temperatures (the raw \( \alpha_{\text{solute}} \) data are presented in Fig.S1 for the newly measured samples).

Figure S2. Experimental hydration-shell resolved THz spectra of four hydrated alcohols at various temperatures, showing a band in the 100-300 cm\(^{-1}\) HB-stretching region and a characteristic intensity increase in the 450-600 cm\(^{-1}\) region. The black solid lines are linear fit of the THz intensity in the 450-600 cm\(^{-1}\) region, from which the slope plotted in figure 3-C of the main text is obtained.

As routinely done in THz-Far Infrared absorption data analysis for water systems (see for example Refs.4,5), the experimental molar extinction spectra from 50 to 300 cm\(^{-1}\) were fitted using a model with the following general functional form:

\[
\epsilon^{\text{eff}}_{\text{solute}}(\nu) = -n_{\text{hydr}} \epsilon_{\text{water}}(\nu) + \sum_{n=1}^{N} \epsilon_{\text{DHO},n}(\nu)
\]

where \( \epsilon_{\text{water}}(\nu) \) denotes the molar extinction coefficient of bulk water. The scaling factor \( (n_{\text{hydr}}) \) accounts for the replacement of bulk water by hydration water and describes the number of water molecules per solute molecule, which show a different absorption than in the bulk.
Additional positive contributions arise from resonances due to hydration water and to the low frequency intramolecular modes of the hydrated solute. As mentioned above, these contributions can be described by a sum of damped harmonic oscillator functions:

$$\epsilon_{\text{DHO},n}(\nu) = \frac{a^2 w^2 \nu^2}{4\pi^3 (\nu_d^2 + \frac{w^2}{4\pi^2} - \nu^2)^2 + \frac{w^2}{\pi^2 \nu^2})}$$

with $a$, $w$, and $\nu_d$ describing the amplitude, the width and the perturbed center frequency of the mode, respectively. The unperturbed center frequency can then be deduced accordingly:

$$\nu_0 = \sqrt{\nu_d^2 + \frac{w^2}{4\pi^2}}$$

As we have shown in our previous works, the main contribution of hydration water for a number of solvated alcohols (MeOH, EtOH, PrOH, BuOH, PeOH, tBuOH) in the low frequency spectra in a wide temperature and concentration range can be decomposed into two bands with unperturbed center frequencies of 164 cm$^{-1}$ and 195 cm$^{-1}$, respectively. While the amplitude of each of these two bands is temperature-, concentration- and solute-dependent, the center frequencies and the linewidths were found to be constant independently on the solute, concentration and temperature. The number of water molecules contributing to the hydration bands at 164 cm$^{-1}$ and 195 cm$^{-1}$ is proportional to the amplitudes ($a$) at their peak center, respectively, with the boundary condition that the sum of $n_{164}$ and $n_{195}$ must be equal to the total number of affected water molecules per solute ($n_{\text{hydr}}$), i.e.

$$n_\nu = \frac{a_\nu n_{\text{hydr}}}{a_{164} + a_{195}}$$

with $\nu = 164$ or 195 cm$^{-1}$. These partial amplitude values, that were measured and derived in our previous studies, were used as inputs for the group specific analysis discussed in the next section.

## 3 Number of hydration water molecules vs group

We decomposed the THz absorption spectra of solvated alcohols (MeOH, EtOH, PrOH, BuOH, PeOH, tBuOH) at fixed concentration and temperature into a sum of molecular building blocks contributions, i.e. from methyl (-CH$_3$), methylene (-CH$_2$), and hydroxyl (-OH) groups. Assuming that the central carbon atom of tBuOH does not contribute due to a lack of contact with water, all the other groups were weighted equally as:

$$
\begin{align*}
    a_{i,CH_2} &= \frac{a_{i,PeOH} - a_{i,MeOH}}{4} \\
    a_{i,CH_3} &= \frac{4a_{i,tBuOH} - (a_{i,BuOH} + a_{i,PrOH} + a_{i,EtOH} + a_{i,MeOH} + 6a_{i,CH_2})}{8} \\
    a_{i,OH} &= \frac{a_{i,tBuOH} + a_{i,PeOH} + a_{i,BuOH} + a_{i,PrOH} + a_{i,EtOH} + a_{i,MeOH} + 8a_{i,CH_3} - 10a_{i,CH_2}}{6}
\end{align*}
$$
where $a_t = a_{164} + a_{195}$.

We then estimate the partial group-specific number of water molecules contributing to the total hydration number by combining Eqs. (6) and (7) for $n_{\text{hydr}}$ and averaging over the whole set of alcohol solutions. The results for $n_{\text{hydr}}$ are shown in figure 2-B of the main text.

4 Group specific THz calorimetry

The working principle of THz calorimetry are briefly outlined below. In Ref. 3, we found that the temperature dependence of $n_{\text{hydr}}$ for the investigated set of alcohol aqueous solutions can be well approximated by a two-state model:

$$n_{\text{hydr}}(T) = \frac{n_{\text{hydr}}(0)}{1 + \exp \left( \frac{\Delta H_{\text{hydr}}}{R} \left( \frac{1}{T} - \frac{1}{T_{\text{hydr,melt}}} \right) \right)}$$

with $\Delta H_{\nu}$ being the enthalpic energy difference between the involved states, $R$ as universal gas constant, and $T_{\nu,melt}$, the melting temperature, i.e. the temperature where both states are equally populated. To correlate spectroscopic changes to thermodynamic quantities, we made the following ansatz for the mixing heat capacity with respect to a reference temperature ($T_{\text{ref}} = 400$ K, which is well beyond the melting temperature of bulk and hydration water):

$$\Delta C_p(T, T_{\text{ref}}) = n_{164}(T)(C_{164}^{p} - C_{\text{w,bulk}}^{p}) + n_{195}(T)(C_{195}^{p} - C_{\text{w,bulk}}^{p}) + \Delta C_{\text{solute}}^{p}(T_{\text{ref}})$$

where $C_p$ refers to heat capacity.

The temperature dependence of $\Delta C_p(T)$ is attributed exclusively to changes in $n_{164}(T)$ and $n_{195}(T)$, while $(C_{164}^{p} - C_{\text{w,bulk}}^{p}) = \Delta C_{164}^{p}$ and $(C_{195}^{p} - C_{\text{w,bulk}}^{p}) = \Delta C_{195}^{p}$ are temperature independent and obtained with respect to bulk water $C_{\text{w,bulk}}^{p}$. $\Delta C_{\text{solute}}^{p}(T_{\text{ref}})$ is a solute-specific parameter, which summarizes all solute-specific changes of the heat capacity at a given reference temperature with respect to bulk water.

From a global fit of the full set of alcohol aqueous solutions, we attributed a certain mixing heat capacity contribution to both hydration water and the cavity formation process (at a reference temperature of 400 K). The separation into two terms corresponds to imagining that first the solute cavity is formed in the liquid at 400 K (where hydration and bulk water are spectroscopically indistinguishable), then, at the temperature of interest, we consider that hydration water has a different structure and dynamics, and hence a different spectroscopic response with respect to the bulk. This is in principle due to both the HB-wrap formation (typically observed around hydrophobic solutes, as discussed in the main text) and the possible further hydration layer perturbations due to solute-water interactions. As discussed in the main text, hydration layer perturbations due to solute-water interactions are found to give a negligible contribution to entropy for hydrated alcohols. The results are in agreement with the well-documented macroscopic calorimetric observables and summarized in Ref. 3. We report in table 1 below the $\Delta C_{164}^{p}$, $\Delta C_{195}^{p}$ and $\Delta C_{\text{solute}}^{p}(400K)$ values as deduced in ref. 3:

Based upon $\Delta C_p(T)$ the temperature dependence of the mixing entropy S (as well as the
|    | hydration | MeOH | EtOH | PrOH | BuOH | PeOH | tBuOH |
|----|-----------|------|------|------|------|------|-------|
| $\Delta C^p_{164}$ | 35.5(2.3) |      |      |      |      |      |       |
| $\Delta C^p_{195}$ | 8.2(8)    |      |      |      |      |      |       |
| $\Delta C^solute(400K)$ | 19(3)   | 93(3) | 145(3) | 184(4) | 223(5) | 111(6) |       |

Table 1: $\Delta C^p_{164}$, $\Delta C^p_{195}$ and $\Delta C^solute(400K)$ values (in units of J/mol/K) as deduced in ref.\textsuperscript{3} for all alcohols from MeOH to PeOH.

The enthalpy, H, was determined:

$$
\Delta S(T) = \int_{T_{ref}}^{T} \frac{\Delta C^p(T)}{T} dT = \\
= \Delta C^solute(T_{ref}) \log \left( \frac{T}{T_{ref}} \right) + \Delta S_{164}(T) + \Delta S_{195}(T). 
$$

To dissect the entropy (as well as the enthalpy) into the partial contributions of each molecular group (-CH\textsubscript{3}, -CH\textsubscript{2} and -OH), the following equation, analogous to Eq.(7), has been used:

$$
\Delta S_{CH_2} = \frac{\Delta S_{PrOH} - \Delta S_{MeOH}}{4} \\
\Delta S_{CH_3} = \frac{4\Delta S_{tBuOH} - (\Delta S_{BuOH} + \Delta S_{PrOH} + \Delta S_{EtOH} + \Delta S_{MeOH} +}{8} \\
+ 6\Delta S_{CH_2}) \frac{8}{8} \\
\Delta S_{OH} = \frac{\Delta S_{tBuOH} + \Delta S_{PrOH} + \Delta S_{BuOH} + \Delta S_{PrOH} + \Delta S_{EtOH} +}{6} \\
+ \Delta S_{MeOH} - 8\Delta S_{CH_3} - 10\Delta S_{CH_2} \frac{6}{6}
$$

Figure S3. Group specific enthalpy contributions (at room temperature) to alcohols hydration from THz-calorimetry. Left: individual contributions of CH\textsubscript{3}, CH\textsubscript{2} and OH groups to hydration enthalpy, $\Delta H_{hyd}$. Middle: effective hydration numbers ($n_{hyd}$) derived from THz experiments, same as in figure 2-B of the main text. Right: $\Delta H_{hyd}$ values divided by $n_{hyd}$ and averaged separately over apolar (CH\textsubscript{2} and CH\textsubscript{3}) and polar (only OH) groups.
The results for the group-specific entropy and enthalpy at three selected temperatures are reported in figure 2 of the main text and in figure S3, respectively.

As concerns $\Delta H(T)$, the negative contribution of the hydroxyl group is the largest, followed by that of the methyl group. The value of the methylene group is slightly endothermic. When averaging over polar and apolar groups separately, we find that apolar CH$_2$ and CH$_3$ groups provide a negligible contribution to enthalpy, as opposite to the entropic contribution discussed in the main text.

5 THz fingerprint of bound water molecules

In the main text, we assign the absorption increase in the 450-600 cm$^{-1}$ region to a fingerprint of bound water molecules around the alcohol OH-group. This assignment implies that water contribution dominates over alcohol specific modes in that frequency region. This is demonstrated in figure S4, where alcohol and water spectra are compared.

![Figure S4](image)

Figure S4. Comparison between the molar extinction coefficients of four pure alcohols as obtained from the NIST Web-book and the molar extinction coefficient of water.

For all alcohols, we observe that their molar extinction coefficients are about three times smaller than the molar extinction of water. Furthermore, the investigated mixtures contain 1 M alcohol compared to 55 M of water, therefore the alcohols contribution to the changes as plotted in Figure 3 and S2 are negligible. As a consequence, the sharp maxima in the alcohol spectra, e.g. centered at 420 cm$^{-1}$ and 490 cm$^{-1}$ for isopropanol, are barely visible in the difference spectra of Fig.3 and S2. Thus, the contribution of the alcohol is negligible in the investigated frequency region, and we attribute all the changes to hydration water.
6 Molecular dynamics simulations

Classical molecular dynamics simulations of three systems, MeOH, BuOH and tBuOH solvated in water were carried out with the Gromacs 4.6.1 software package.\textsuperscript{6} The OPLS all-atom force field\textsuperscript{7} and the TIP4P-2005 model\textsuperscript{8} were adopted to describe the solute molecule and water, respectively. The trajectories of tBuOH were taken from our previous investigation\textsuperscript{1} and the trajectories of MeOH and BuOH were produced following the same protocol used for tBuOH. In summary, for each system the coordinates of the solute were optimized with respect to the internal energy and then placed in the center of a cubic box with an initial edge length of 40 Å. In the following simulations, the coordinates of the solute atoms were kept fixed (we checked in our previous work\textsuperscript{1} that releasing the constraint on solute atomic coordinates do not affect the structural and dynamical properties we are interested in): this allows a spatially resolved analysis of water properties in the hydration shell of the solute (more details below). Long range electrostatics were treated with the particle mesh Ewald algorithm on a 1.2 Å spatial grid with a fourth order interpolation.\textsuperscript{9,10} Short-range electrostatic and Lennard-Jones forces were shifted to zero between 9.0 and 10.0 Å. Long-range dispersion corrections were applied for the energy and pressure. Neighbor lists were updated every 10 femtoseconds (fs) during equilibration and 8 fs during production, with a 13.0 Å distance cutoff. The time step for integration was set to 1 fs. The SETTLE algorithm\textsuperscript{11} was used to constrain the intramolecular degrees of freedom of water molecules. The system was equilibrated for 1 nanosecond (ns) in the isobaric-isothermal (NPT) ensemble at a pressure of 1 bar and the temperature of 303 K using temperature coupling via a stochastic velocity rescaling thermostat and a Berendsen weak-coupling barostat\textsuperscript{12} with a time constant of 1.0 picosecond (ps). This was followed by a 100 ns production run in the canonical (NVT) ensemble at the same temperature as the equilibration using a Nose-Hoover thermostat\textsuperscript{13} with a time constant of 5.0 ps. During production coordinates and velocities were saved every 8 fs for subsequent analysis.

The Density Functional Theory based DFT-MD simulation, from which the theoretical THz spectrum of hydrated tert-butanol shown in figure 3 of the main text is obtained, was taken from our previous investigation.\textsuperscript{1} In a nutshell, a born-Oppenheimer DFT-MD simulation was carried out in the nve ensemble (with average $T=290\pm 4$ K) with the CP2K package\textsuperscript{14,15} on a 0.2 M aqueous solution of tBuOH (one solute in the simulation box). The electronic representation consisted in the BLYP functional,\textsuperscript{16,17} including Grimme D2 correction for dispersion,\textsuperscript{18} GTH pseudopotentials\textsuperscript{19} for all atoms, and a combined Plane-Wave (400 Ry density cutoff) and TZV2P gaussian basis sets. The theoretical THz spectrum was calculated using our previously developed strategy, based on the Fourier transform of the correlation function of velocities modulated by Atomic Polar Tensors (APT). See refs.\textsuperscript{1,20} for all details.

7 Theoretical group-specific hydration entropy

In order to spatially resolve properties of water molecules in the solute (MeOH, BuOH, tBuOH) hydration shell, we defined a three-dimensional cubic grid centered on the immobilized solute
molecule. The grid contains 32 x 32 x 32 volume elements (voxels) with a grid constant of 0.5 Å. At each time frame of the trajectory, water molecules were assigned to a voxel based on their center of mass position. The solvation shell of each CH₂, CH₃, OH group was defined by voxels within 3.5 Å from the vdW-surface of the respective group (see more details in ref.¹). We adopted the 3D-2PT method by Persson et al.²¹, which is an extension of the two-phase thermodynamics (2PT) method²² that allows for a spatially resolved analysis of hydration entropies on a grid, like the one described above. Directly starting from molecular dynamics trajectories, we have computed the local velocity autocorrelation functions for delay times up to 1.6 picoseconds (ps). We have treated translational and rotational degrees of freedom of the rigid water molecules separately. The Fourier transform of the local velocity autocorrelation functions defines the local vibrational DOS (density of states). The local DOS is then used to calculate the local entropy per molecule by means of the 2PT expressions for rigid molecules [Lin]. The bulk water entropy per molecule is obtained as an average for voxels far (< 9 Å) from the solute. For each voxel, local deviations of the molecular entropy from the bulk value are calculated as \( \Delta S_{\text{hyd}}(r) = S(r) - S_{\text{bulk}} \). The group-specific hydration entropy per molecule, \( \Delta S_{\text{hyd}}^{\text{group}} \), is calculated by integrating over the voxels in the solvation environment of each chemical group.

As regards the orientation dynamics results presented in the main text, we have calculated the orientational correlation function of the dipole vector of the water molecules from the classical MD simulations as:

\[
C^{(2)}(\mu) = \frac{P_2(e^{(t)}(t)e^{(0)}(0))}{P_2(e^{(0)}(0)e^{(0)}(0))}
\]

where \( P_2 \) is the 2-th rank Legendre polynomial and \( e^\mu(t) \) is the water dipole moment (unit vector) at time \( t \).²³ The orientation relaxation time, \( \tau^{(2)}_\mu \), is given by the time integral of \( C^{(2)}_\mu \).
8 Comparison between THz-calorimetry and standard calorimetry approaches

Figure S5. Displayed are the tabulated temperature and solute-dependent changes in entropy and enthalpy taken from previous calorimetric references (blue line) and the values deduced by THz-calorimetry (red dots, used as inputs for the building-block decomposition discussed in the main text). All values are reproduced from ref.3.

Figure S6. Comparison between hydration entropy and enthalpy values for all alcohols at 293K as obtained from standard calorimetry (top) and THz calorimetry (bottom) by means of the building-block decomposition introduced in the present work. Panel D is the same as figure 2A of the main text.
9 THz fingerprint of bound waters: dependence of the slope on the fitted frequency range.

Figure S7. Comparison of the fitted slope of the THz intensity taking into account two different frequency ranges for hydrated alcohols at 293K: upper in the 400-500 cm\(^{-1}\); lower 450-600 cm\(^{-1}\). The vertical lines separate primary (left), secondary (center) and tertiary (right) alcohols. The comparison shows that the trend of the slope is independent on the fitted frequency range.

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