Supporting information for Quantifying how step-wise fluorination tunes local solute hydrophobicity, hydration shell thermodynamics and the quantum mechanical contributions of solute-water interactions

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1 Dangling OH bands after Gaussian background subtraction



Fig. 1 Temperature dependence of the dangling OH peaks in the hydration shell of MFE, DFE and TFE. These peaks were obtained from the respective minimum area non-negative SC spectra (transparent solid lines), after subtracting the background (dashed lines) using a Gaussian fit. Analogous to figure 4 in the main text.

2 Hydration thermodynamics

The experimental hydration free energy varies as MFE<DFE<EtOH<TFE (SI tables 1 and 2). A similar trend is visible in our calculated hydration free energies (SI figure 2 and table 3), lending confidence to our models. The most noticeable deviation between both sets of values is that the free energy difference between DFE and EtOH is much smaller in simulation than in experiment.

The differences in hydration free energy between the 4 alcohols suggests that mono- and (to a lower extent) difluorinated groups are hydrophilic whereas trifluorinated groups are hydrophobic. However, the differences in hydration free energy between the alcohols might also reflect the fact that the electron-withdrawing effect of fluorine extends as far as the alcohol group. To assess the extent to which changes in the electronic density of the alcohol group may impact hydration free energies, we looked at the partial

charges on the fluorine and alcohol oxygen atoms that were used in the MD simulations (SI Figure 3). Both atoms have negative charges (as expected), and for both atoms they vary as MFE<DFE<TFE. The change in the partial charges of the alcohol oxygen between the fluorinated alcohols is of the same magnitude as that observed for fluorine itself. This result plainly suggests that the varying influence of the alcohol group on the hydration free energy of increasingly fluorinated ethanol derivatives is not negligible. Moreover, changes in oil-water partition coefficients resulting from the fluorination of small molecules are known to be heavily dependent on adjacent functional groups.¹⁻⁷ Nonetheless, our prior results suggest that the dominant contribution to the change in hydration free energy with fluorination comes from the tail of the alcohol.⁸ We estimated the contribution of each of the fluorinated groups on the change in hydration free energy due to the fluorination of methyl groups in apolar amino acid side chains.⁹ By decomposing the hydration free energy into contributions from the amino acid backbone and the side chain, we found that -CFH₂ and -CF₂H groups are more hydrophilic than -CH₃, while -CF₃ groups are more hydrophobic. Moreover, sequential fluorination steps, from -CFH₂ to -CF₃, have only a minor impact on the repulsive interactions, due to increasing surface area, between the fluoromethyl group and water. This implies that the changes in hydrophobicity are largely due to changes in the attractive interactions between -CFH₂, -CF₂H or -CF₃ and water.

Table 1 Henry's law coefficients for EtOH, MFE, DFE, and TFE.

Solute	K _H	Units	T (K)	Reference DOI
EtOH	20 ± 3	kPa	293.2	10.1021/je900711h
EtOH	184 ± 35	M atm ⁻¹	298.2	10.5194/acp-15-4399-2015
MFE	120 ± 20	kPa	293.2	10.1021/je900711h
DFE	60 ± 20	kPa	293.2	10.1021/je900711h
TFE	59 ± 6	${ m M}~{ m atm^{-1}}$	298.2	10.5194/acp-15-4399-2015

Table 2 Experimental hydration free energy of EtOH, MFE, DFE, and TFE.

Solute	$K_{\rm H}$ ratio (f)	$-RT\ln(f)$ (kJ mol ⁻¹)	$\Delta G_{\rm hyd}$ (kJ mol ⁻¹)
EtOH	-	-	$\textbf{-21.0}\pm0.8$
MFE	6.0	-4.4	$\textbf{-25.3}\pm0.9$
DFE	3.0	-2.7	$\textbf{-23.6}\pm0.9$
TFE	0.3	2.8	$\textbf{-18.2}\pm0.9$

Table 3 Hydration free energy ($\Delta G_{Hyd,Total}$) and its Coulombic ($\Delta G_{Hyd,Coul}$) and Lennard-Jones ($\Delta G_{Hyd,LJ}$) components for MFE, DFE and TFE at 298 K. Hydration free energies are presented in kJ mol⁻¹ as the mean and the standard error of the mean of five independent FEP simulations. Data for TFE is taken from ref. 8. Related with SI figure 2.

	$\Delta G_{Hyd,Total}$	$\Delta G_{Hyd,Coul}$	$\Delta G_{Hyd,LJ}$
MFE	$\textbf{-22.472} \pm 0.032$	-28.592 ± 0.027	6.120 ± 0.008
DFE	$\textbf{-20.382}\pm0.019$	$\textbf{-28.978} \pm 0.029$	8.596 ± 0.020
TFE	$\textbf{-13.953} \pm 0.018$	$\text{-24.925} \pm 0.013$	10.972 ± 0.014

3 Non-water-bonded hydroxy groups in the hydration shell of MFE, DFE and TFE



Fig. 2 Hydration free energy (ΔG_{Hyd}) of MFE, DFE and TFE and difference in hydration free energy ($\Delta \Delta G_{Hyd}$) between MFE/DFE/TFE and ethanol at 298 K from simulation. The dashed line corresponds to $\Delta \Delta G_{Hyd} = 0$. Hydration free energies are presented as the mean of five independent FEP simulations. Data for TFE and EtOH are taken from ref. 8. Related with SI table 3.



Fig. 3 Correlation between the partial atomic charges of fluorine (q_F) and oxygen (q_O) in MFE, DFE and TFE. The dashed line is a linear fit to the data, for which the fit equation and the regression coefficient are presented. TFE charges were retrieved from ref. 8. Presented in tabular form in SI table 4.



Fig. 4 Probability of having exactly one (panel A) or two (panel B) hydrogen bond-like structures forming in a hydration shell, calculated with MD simulations at different temperatures, for MFE, DFE and TFE. Note the different scales on each panel. Data for TFE are extracted from ref. 8. Tabulated in SI table 7.

Table 4 Partial atomic charges (in elementary charge units, rounded to the third decimal place) on the oxygen and fluorine atoms of MFE, DFE and TFE. Charges for TFE are retrieved from ref. 8. For MFE and DFE, charges are presented as the mean and standard error of the mean of individual RESP fits for 252 conformations of the alcohol. Shown in graphical form in SI figure 3.

	q _O	$q_{\rm F}$
MFE	$\textbf{-0.660} \pm 0.002$	$\textbf{-0.243}\pm0.001$
DFE	$\textbf{-0.630} \pm 0.002$	$\textbf{-0.224} \pm 0.001$
TFE	-0.594	-0.181

Table 5 Average number, $\langle k \rangle$, of non-water-bonded and hydrogen bond-like hydroxy structures, in the [278, 358] K range. Data for TFE retrieved from ref. 8. Data is presented as mean and standard error of the mean of five measurements and is depicted in graphical form in figure 7.

	$\langle k \rangle$: Non-water-bonded OH				
T (K)	MFE	DFE	TFE		
278	0.121 ± 0.004	0.205 ± 0.009	0.155 ± 0.006		
298	0.128 ± 0.005	0.228 ± 0.009	0.246 ± 0.012		
318	0.121 ± 0.007	0.269 ± 0.010	0.297 ± 0.002		
338	0.143 ± 0.016	0.321 ± 0.016	0.409 ± 0.007		
358	0.187 ± 0.013	0.351 ± 0.013	0.473 ± 0.014		
	$\langle k \rangle$: Hydrogen bond-like OH				
T (K)	MFE	DFE	TFE		
278	0.210 ± 0.001	0.175 ± 0.003	0.082 ± 0.001		
298	0.214 ± 0.002	0.193 ± 0.002	0.101 ± 0.001		
318	0.218 ± 0.001	0.205 ± 0.001	0.121 ± 0.001		
338	0.220 ± 0.001	0.214 ± 0.000	0.136 ± 0.000		
250		0.000 + 0.000	0.140 + 0.001		

Table 6 Free energies of formation (kJ mol⁻¹) of non-water-bonded and hydrogen bond-like hydroxy structures, calculated using equation 4, in the [278,358] K range. Errors for the free energies are obtained by propagation of the standard error of the mean value of $\langle k \rangle$. Data for TFE are extracted from ref. 8. Related with figures 8 and 10.

	$\Delta G = -RT \ln \langle k \rangle$: Non-water-bonded OH					
T (K)	MFE	DFE	TFE			
278	4.883 ± 0.075	3.662 ± 0.102	4.313 ± 0.087			
298	5.095 ± 0.091	3.665 ± 0.101	3.474 ± 0.121			
318	5.575 ± 0.148	3.471 ± 0.103	3.208 ± 0.019			
338	5.474 ± 0.325	3.197 ± 0.142	2.512 ± 0.047			
358	$\textbf{4.995} \pm \textbf{0.203}$	3.112 ± 0.111	2.228 ± 0.089			
	$\Delta G = -RT \ln\langle k \rangle$: Hydrogen bond-like OH					
T (K)	MFE	DFE	TFE			
278	3.609 ± 0.008	4.025 ± 0.033	5.786 ± 0.017			
298	3.824 ± 0.023	4.080 ± 0.025	5.689 ± 0.025			
318	4.033 ± 0.008	4.189 ± 0.010	5.584 ± 0.015			
338	4.256 ± 0.012	$\textbf{4.334} \pm \textbf{0.004}$	5.610 ± 0.009			
358	4.506 ± 0.007	4.474 ± 0.003	5.667 ± 0.028			

Table 7 Probability of having exactly one or two hydrogen bond-like structures in the hydration shell of MFE, DFE or TFE. Data for TFE extracted from ref 8. Results are presented as the mean and standard error of the mean of five measurements. See SI figure 4.

		$P(\#OH \cdot \cdot F/H = 1)$		
T (K)	MFE	DFE	TFE	
278	0.204 ± 0.0007	0.161 ± 0.0018	0.078 ± 0.0006	
298	0.206 ± 0.0018	0.176 ± 0.0015	0.095 ± 0.0009	
318	0.207 ± 0.0003	0.184 ± 0.0010	0.113 ± 0.0007	
338	0.208 ± 0.0006	0.191 ± 0.0005	0.125 ± 0.0008	
358	0.206 ± 0.0004	0.198 ± 0.0005	0.136 ± 0.0009	
		$P(\#OH \cdots F/H = 2)$		
T (K)	MFE	DFE	TFE	
278	0.003 ± 0.0001	0.007 ± 0.0004	0.002 ± 0.0001	
298	0.004 ± 0.0001	0.008 ± 0.0002	0.003 ± 0.0001	
318	0.005 ± 0.0002	0.010 ± 0.0002	0.004 ± 0.0000	
338	0.006 ± 0.0002	0.011 ± 0.0003	0.005 ± 0.0002	
358	0.007 ± 0.0002	0.012 ± 0.0002	0.006 ± 0.0003	

4 Intermolecular interactions of water-solute dimers in the vacuum from SAPT

As described in the main text, we used SAPT to calculate the interaction energy of solute-water dimers in the vacuum. The dimer configurations were extracted from molecular dynamics calculations of the solute in a water box at 298 K and are therefore representative of a fully hydrated solute. Two types of configurations were considered: those where one of the water hydroxy groups points to one of the fluorine atoms of the solute (referred to as hydrogen bond-like OH structures) and those where none of the water hydroxy groups points to the fluorine (referred to as water-bonded OH structures). The later name highlights that in the MD simulations the water molecule in the dimer very frequently donates two hydrogen bonds to nearby water molecules (not present in the SAPT calculation).



Fig. 5 A) Total interaction energy *v.s.* distance for water-solute dimers in water-bonded OH configuration (water-MFE as red circles, water-DFE as blue squares, water-TFE as green triangles), calculated at the DF-SAPT2+(CCD) δ MP2/aug-cc-pVTZ level of theory. The distance corresponds to the closest water oxygen-fluorine pair. Configurations are extracted from MD simulations at 298 K. The inset molecules represent a conformation of a water-TFE dimer corresponding to one of the plotted data points. The number of points in each data set is: MFE: 1000; DFE: 999; TFE: 1000.

B) Ratio of average energy components $\langle E \rangle_{Elec,Disp,Disp}$; $\langle E \rangle_{Ind,Ind,Elec}$ of the water-alcohol interaction in hydrogen bond-like structures; the subscripts indicate the energy component (electrostatics, induction or dispersion). Data for TFE are extracted from ref. 8. The number of points in each data set is MFE: 2890; DF: 1537; TFE: 1314; related to figure 11 in the main text, SI figure 6 and SI table 8.

Table 8 Average components and total intermolecular interaction energy $(kJ mol^{-1})$ in a water-alcohol dimer. Results are reported as the mean and standard error of the mean for multiple configurations of hydrogen bond-like or water-bonded hydroxy groups. The number of configurations used in calculating the mean and error is reported after each compound. Data for TFE are extracted from ref. 8. Presented in graphical form in figure 11, related with SI figures 5 and 6.

		Hydrogen bond-like OH				
	# confs.	Induction	Electrostatics	Exchange	Dispersion	Total
MFE	1933	$\textbf{-12.520} \pm 0.134$	$\textbf{-27.192} \pm 0.231$	49.287 ± 0.561	-13.344 ± 0.095	$\textbf{-3.769} \pm 0.131$
DFE	1032	$\textbf{-7.194} \pm \textbf{0.119}$	$\textbf{-16.558} \pm 0.213$	30.989 ± 0.551	$\textbf{-10.694} \pm \textbf{0.116}$	$\textbf{-3.457} \pm 0.149$
TFE	784	$\textbf{-3.226} \pm 0.063$	$\textbf{-7.954} \pm 0.137$	15.594 ± 0.392	$\textbf{-7.646} \pm 0.114$	$\textbf{-3.232}\pm0.138$
		Water-bonded OH				
	# confs.	Induction	Electrostatics	Exchange	Dispersion	Total
MFE	997	$\textbf{-0.983} \pm 0.054$	-2.377 ± 0.185	6.024 ± 0.268	$\textbf{-4.473} \pm 0.078$	$\textbf{-1.809}\pm0.131$
DFE	959	$\textbf{-0.899} \pm 0.039$	$\textbf{-2.273} \pm 0.156$	6.399 ± 0.226	$\textbf{-4.505} \pm \textbf{0.074}$	$\textbf{-1.278} \pm 0.121$
TFE	878	$\textbf{-0.437} \pm \textbf{0.014}$	$\textbf{-1.131}\pm0.092$	4.172 ± 0.125	$\textbf{-3.767} \pm \textbf{0.056}$	$\textbf{-1.162}\pm0.074$



Fig. 6 Interaction energy of solute-water dimers *vs.* distance for MFE (red circles), DFE (blue squares) and TFE (green triangles), decomposed into individual contributions: induction (panels A,B), electrostatics (panels C,D), exchange (panels E,F) and dispersion (panels G,H). The number of points in each data set is MFE, hydrogen bond-like: 2890; DFE, hydrogen bond-like: 1537; TFE, hydrogen bond-like: 1314; MFE, water-bonded: 1000; DFE, water-bonded: 999; TFE, water-bonded: 1000. Data for TFE are extracted from ref. 8. Related with figure 11 of the main text, SI figure 5 and SI table 8.

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