Dynamics of water of hydration near disaccharides strongly depends on solute topology

MAPPING DENSITY FLUCTUATIONS, ROTATIONAL ANISOTROPY AND H-BOND EXCHANGE MECHANISM AROUND DISACCHARIDES

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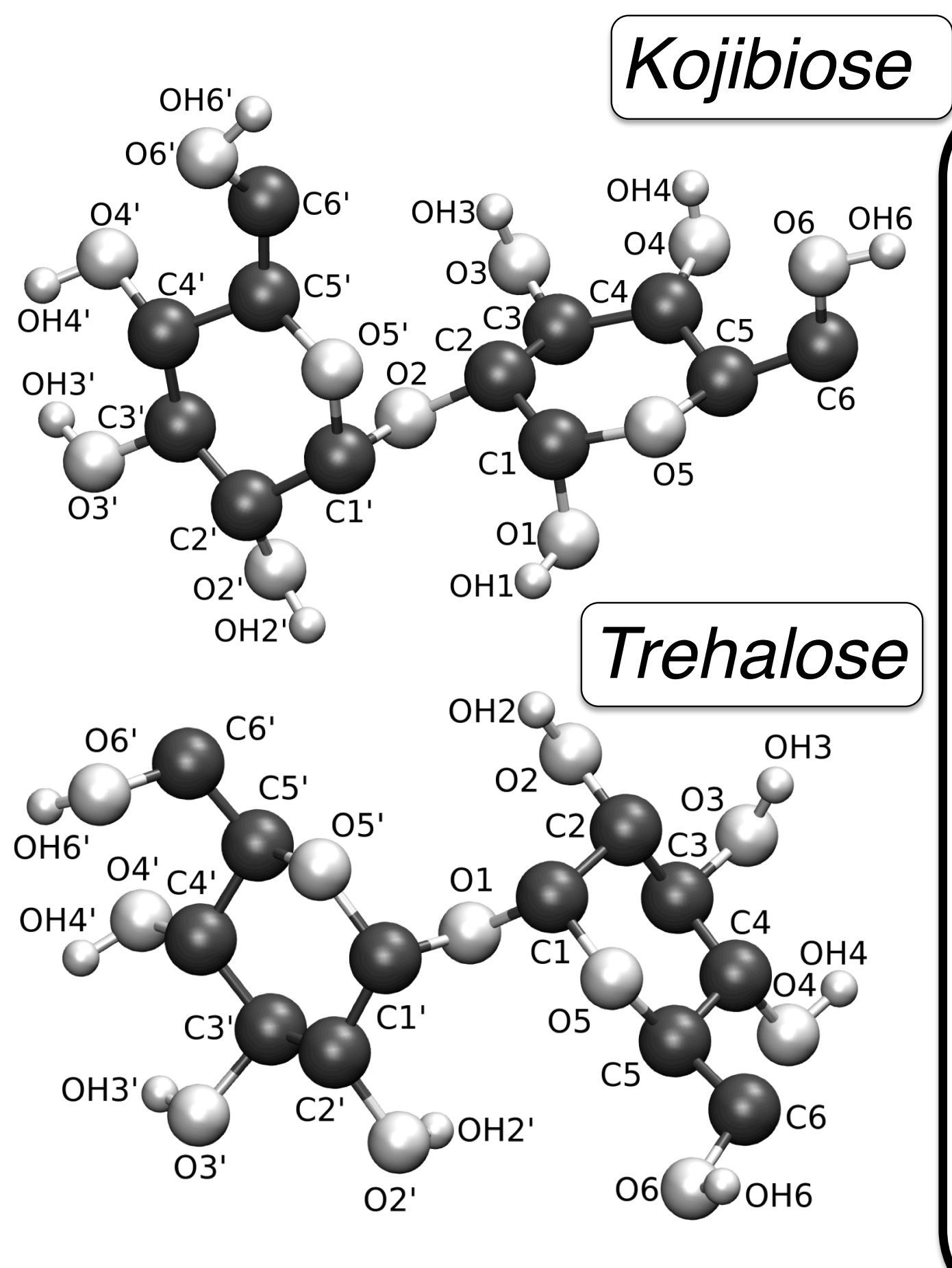
1. MOTIVATION AND METHOD

BIOMOLECULAR SOLVATION STRUCTURE/ DYNAMICS

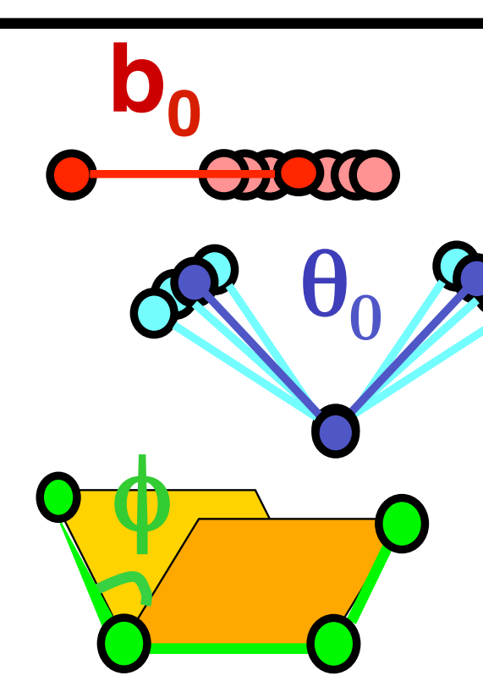
- Solvent structure and dynamics are important for biological function.
- Experimental and computational studies of water structure near biomolecules suggests solute amphiphilicity is key to controlling water structure through a combination of solute functional groups /water interaction energy and solute topology.
- Resolving these effects for large molecules is challenging. However, disaccharides (because of a number of energetically identical OH groups) potentially allow these effects to be disentangled.

MOLECULES AND METHODS



Classical Atomistic MD

- All-atom simulations (NVE) for water dynamics.
  - ① GLYCAM sugar parameters
  - ② SPC/E water
- Replica Exchange MD (in temperature) for slow degrees of freedom.



Bonded Interactions

$$U_{bond} = K_b\,(b - b_0)^2$$
$$U_{angle} = K_\theta\,(\theta - \theta_0)^2$$
$$U_{dihedral} = U\,(\phi, \phi_0, k_\phi)$$

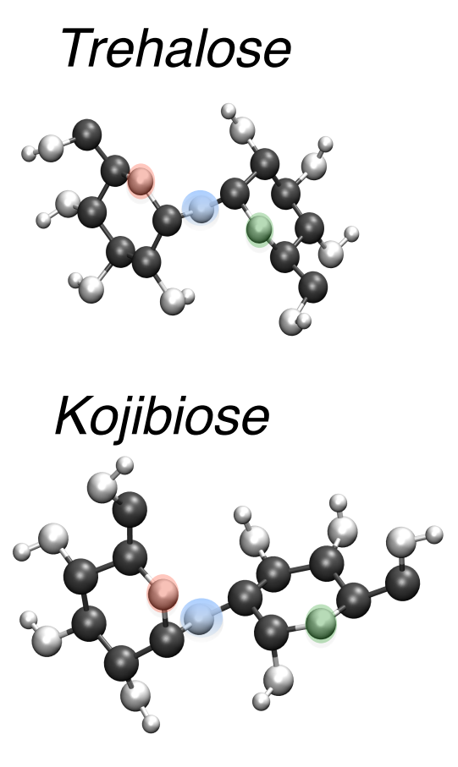
Non-bonded Interactions

$$U_{LJ} = \varepsilon\left[\left(\frac{\sigma_{i,j}}{r_{i,j}}\right)^{12} - 2\left(\frac{\sigma_{i,j}}{r_{i,j}}\right)^{6}\right]$$
$$U_c = K\frac{q_1 q_2}{r}$$

2. WATER STRUCTURE AND DYNAMICS

TIME AVERAGED STRUCTURE

- Both sugars are amphiphilic.
- Linking oxygen is hydrophobic.
- Trehalose linking oxygen is more hydrophobic.



Increasing Hydrophobicity

Hydration Number (fluctuations)

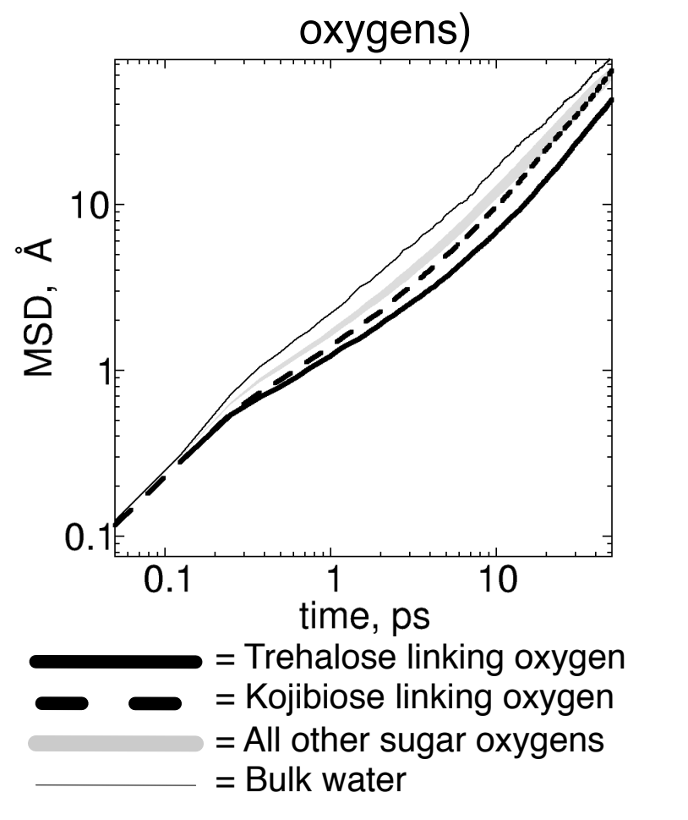
	Trehalose	Kojibiose
Linking Oxygen	0.6 (0.76)	1.04 (0.46)
O5	1.4 (0.37)	1.9 (0.38)
O5’	1.4 (0.37)	1.4 (0.38)
Hydroxyl groups	3.0 (0.26)	3.1 (0.27)
Bulk water	6.1 (0.19)	

STRUCTURAL DYNAMICS

MAPPING TRANSLATION

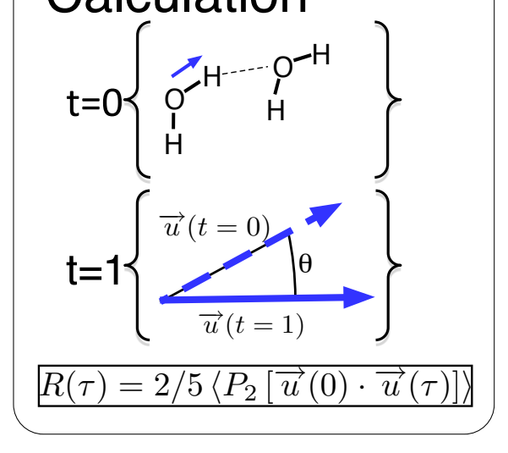
- Translation of water molecules is slowed around sugar oxygens.
- Translation is slowest around the linking oxygens and most slowed around Trehalose linking oxygen.

Mean Square Displacement of Water (< 3.5 Å of individual sugar oxygens)



MAPPING ROTATIONAL ANISOTROPY

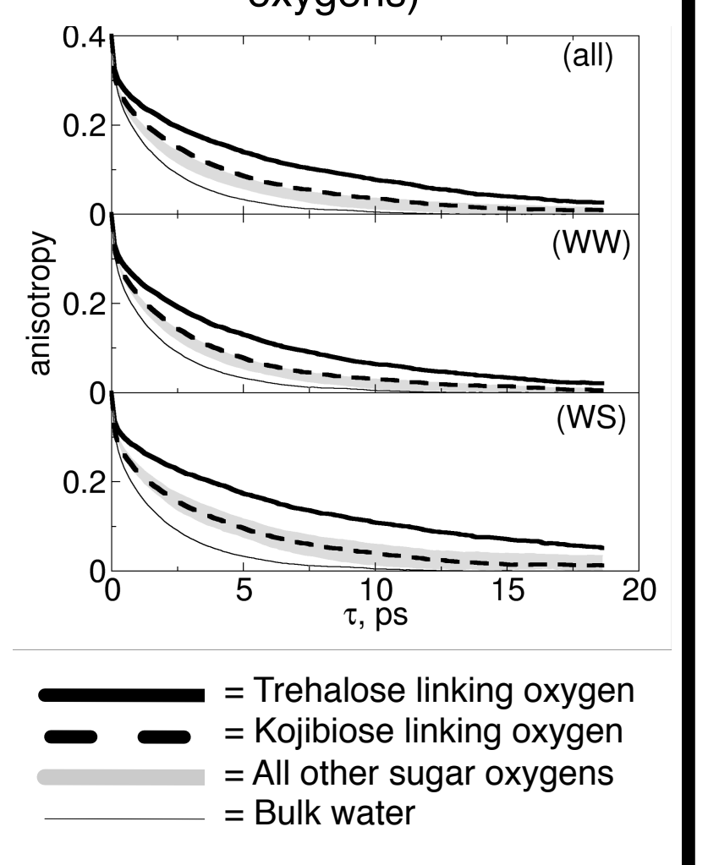
Calculation



$$R(\tau) = 2/5\,\langle P_2\,[\vec{u}(0)\cdot\vec{u}(\tau)]\rangle$$

- Hydration water reorients more slowly than water in bulk.
- Slowest reorienting water is near linking oxygen and bound to a sugar (Trehalose induces greater slow down than Kojibiose).

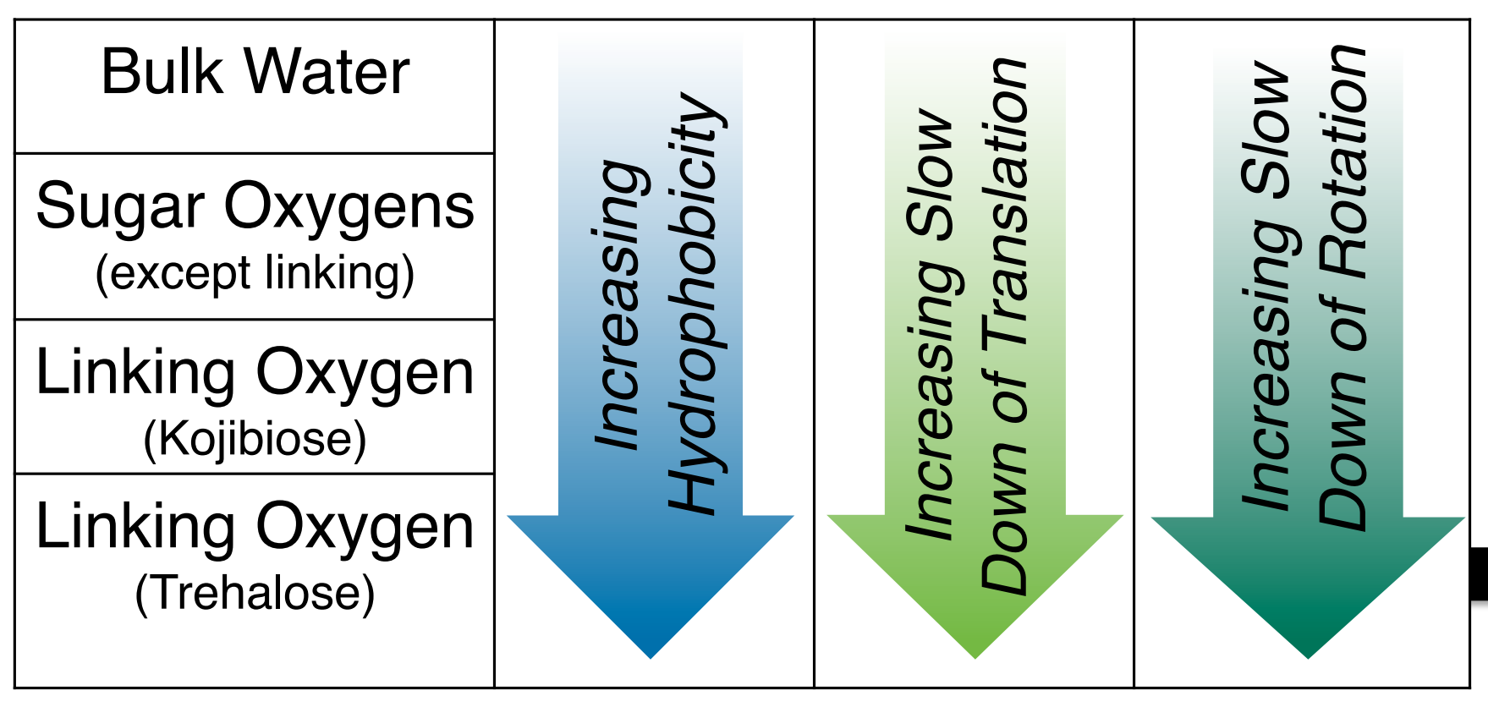
(< 3.5 Å from individual sugar oxygens)



	Population	Trehalose	Kojibiose
Linking Oxygens	WW	6.7	4.2
	WS	10.2	5.1
Other Oxygens	WW	3.5	3.4
	WS	5.3	4.6

Bulk water = 2.3 ps

SUMMARY OF TRENDS



Bulk Water	*Increasing Hydrophobicity*	*Increasing Slow Down of Translation*	*Increasing Slow Down of Rotation*
Sugar Oxygens (except linking)			
Linking Oxygen (Kojibiose)			
Linking Oxygen (Trehalose)			

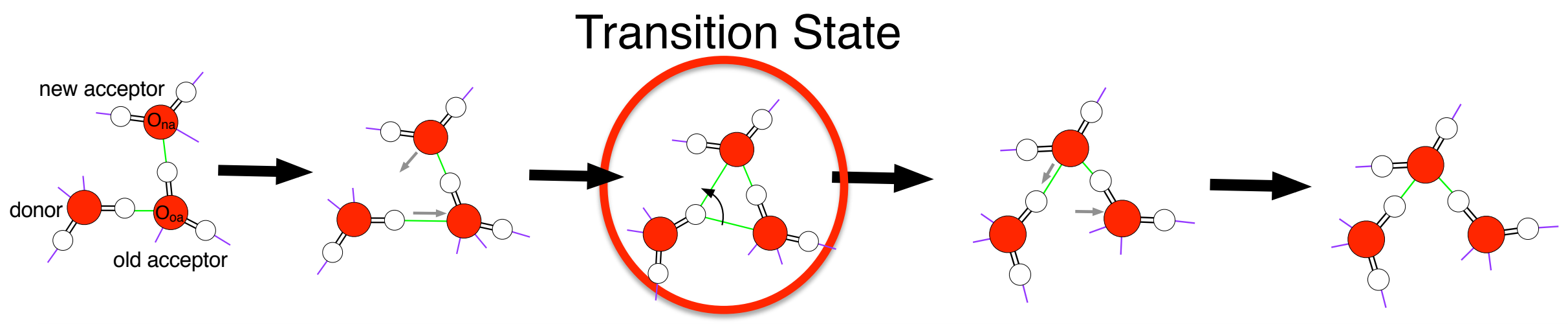
What is the molecular mechanism that underlies these trends?

3. RELATING DYNAMICS AND H-BOND EXCHANGE

CONCEPTUAL MODEL

JUMP MECHANISM: H-BOND EXCHANGE

after Laage, Hynes and coworkers



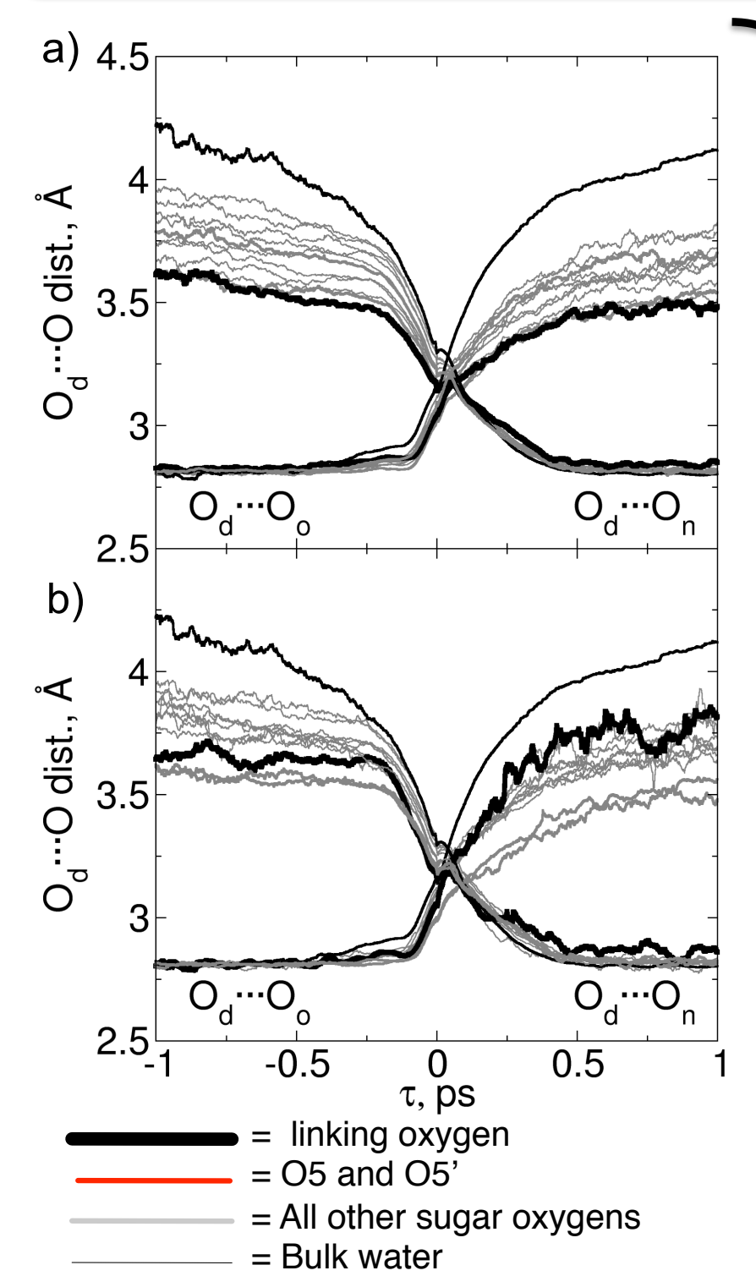
1.) Laage and Hynes (2006) Science, 311, 832-835
2.) Laage and Hynes (2006) Chemical Physics Letters, 433(1-3), 80-85
3.) Laage and Hynes (2008) Journal of Physical Chemistry B, 112(45), 14230-14242
4.) Laage, Stirnemann and Hynes (2009) Journal of Physical Chemistry B, 113 (8), 2428-2435
5.) Sterpone, Stirnemann, Hynes and Laage (2010) Journal of Physical Chemistry B, 114(5), 2083-2089
6.) Stirnemann, Hynes, and Laage (2010) Journal of Physical Chemistry B, 114 (8), 3052-30

FEATURES OF HYDROGEN BOND EXCHANGE IN BULK H_2O, NEAR AMINO ACIDS AND TRIMETHYLAMINE N-OXIDE (TMAO):

1. Occurs via a ***rapid, large amplitude angular jump***.
2. Jump occurs when fluctuations in the local H-bonding network lead to an over coordination of the old acceptor and under coordination of the new.
3. The transition state is transient and characterized by a bifurcated hydrogen bond with equal distances between the donating H and the Os of the old and new acceptors.

HYDROGEN BOND EXCHANGE NEAR DISACCHARIDES

IS H-BOND EXCHANGE HAPPENING NEAR LINKING OXYGENS VIA JUMPS? CAN DIFFERENCES BETWEEN TREHALOSE, KOJIBIOSE AND BULK WATER EXPLAIN ANISOTROPY?

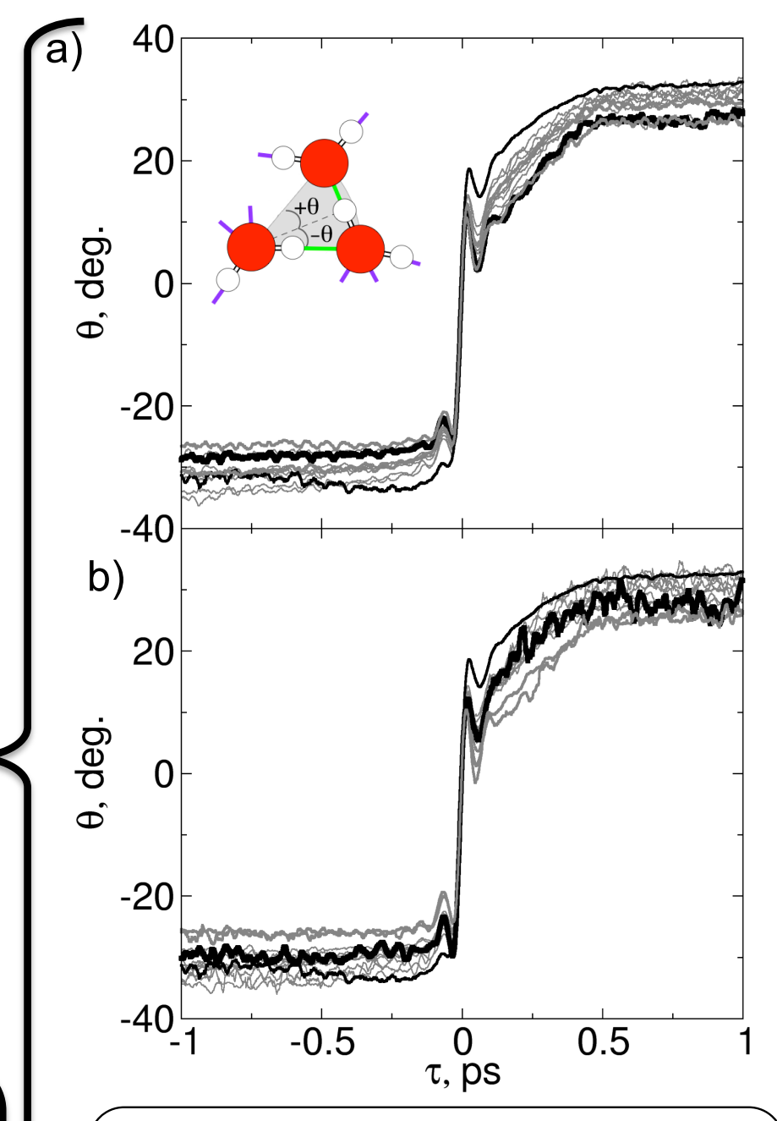


Distances between donating, old accepting and new accepting oxygens through an H-bond switching event for water➔sugar H-bonds within 3.5 Å of the linking oxygen of a) Kojibiose and b) Trehalose.

Changes in distance between donor oxygen, old acceptor and new acceptor oxygens are the same near the linking oxygens of Kojibiose and Trehalose for water➔sugar H-bonds.

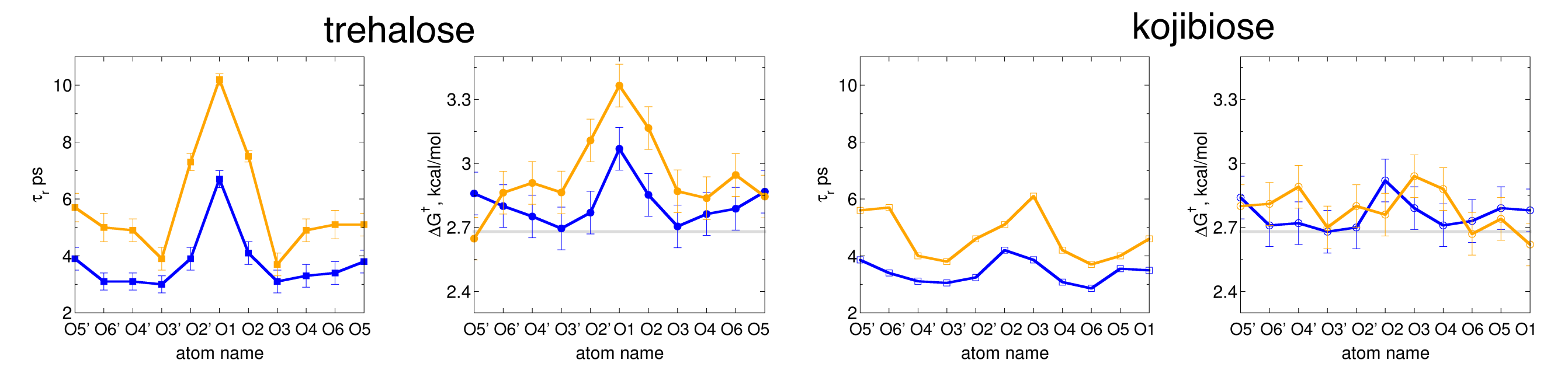
Changes in jump angles during H-bond exchange are quantitatively the same for water➔sugar H-bonds near Kojibiose and Trehalose.

TRENDS IN GEOMETRIC PARAMETERS AROUND HYDROGEN BOND EXCHANGE EVENTS DO NOT CORRELATE WITH ANISOTROPY TRENDS.



Angles between rotating OH and the bisector plane of the angle defined by the 3 oxygens involved in an H-bond switching event for water➔sugar H-bonds within 3.5 Å of the linking oxygen of a) Kojibiose and b) Trehalose.

CAN CHANGES IN THE FREE ENERGY OF THE TRANSITION STATE (ΔG) EXPLAIN CHANGES IN THE WATER ROTATIONAL DYNAMICS?*

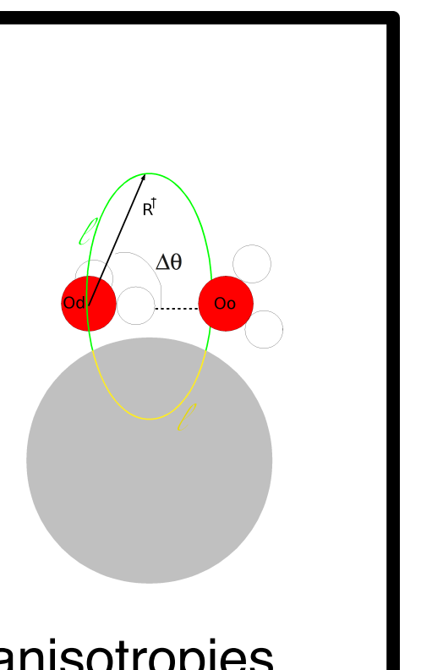


- Yes, the rate of H-bond exchange correlates well, **but not perfectly**, with ΔG*.

= water➔water H-bond
= water➔sugar H-bond

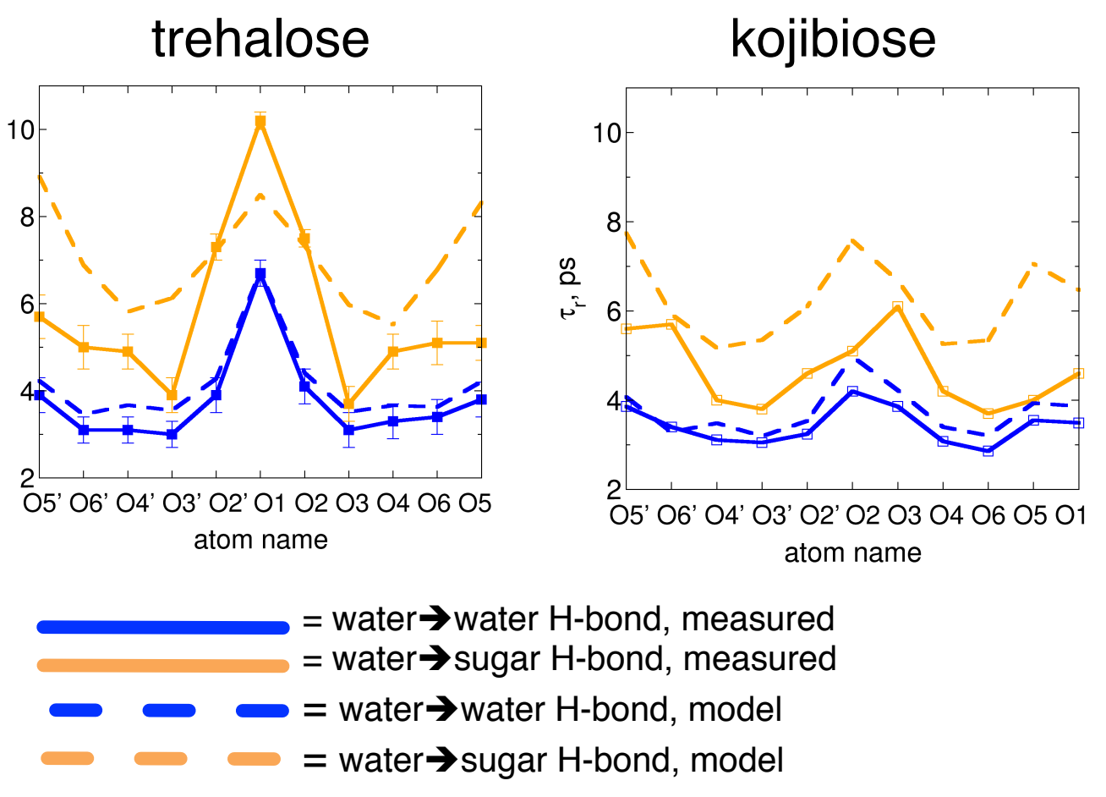
WHAT IS THE ORIGIN OF CHANGES IN ΔG FOR WATER NEAR THE SUGAR?*

- If H-Bond dynamics slow down trends are the result of transition state excluded volume (f) changes we can model our directly calculated anisotropy by scaling the bulk water time scale.



$$\frac{1}{\tau_r} = \frac{1}{\tau_{jump}}\left[1 - \frac{1}{5}\frac{\sin(5\Delta\theta/2)}{\sin(\Delta\theta/2)}\right] + \frac{1}{\tau_{frame}};\quad \tau_{jump} \propto \exp\left(\frac{\Delta G^*}{kT}\right) \approx \frac{\Omega^R}{\Omega^*}\exp\left(\frac{\Delta H^*}{kT}\right) \propto \frac{1}{\Omega^*};\quad \frac{\tau_{jump}^{sugar}}{\tau_{jump}^{bulk}} = \frac{1}{1-f};\qquad f=\ell_{🟨}/(\ell_{🟨}+\ell_{🟩});$$

Laage, Stirnemann and Hynes (2009) JPCB, 113, 2428-2435



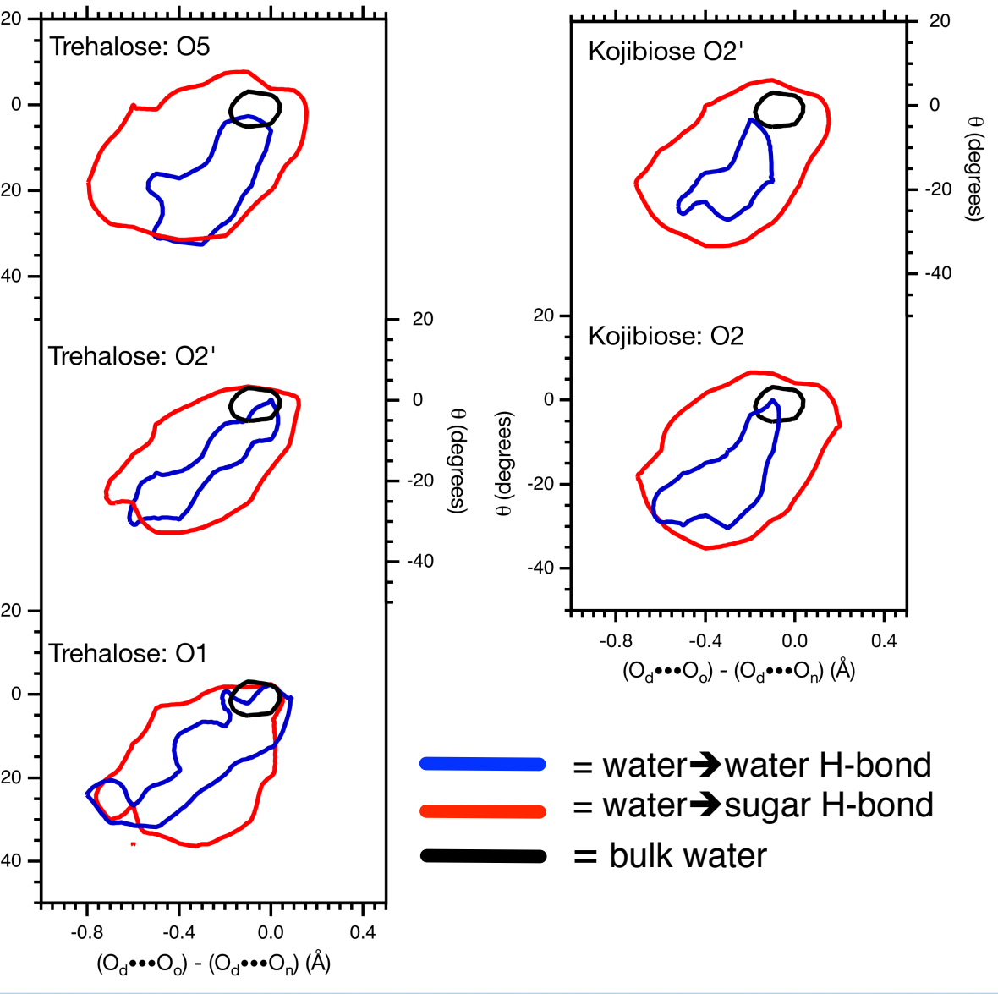
- Within 3.5 Å of individual sugar oxygens, water➔water H-bond anisotropies can be quantitatively modeled, with differences between measured and modeled $\tau_r < 1$ ps.
- For water➔sugar H-bonds, H-bond anisotropies are not well modeled.

- Changes in ΔG* arise mostly from changes in the volume of the transition state for water➔water H-bonds near the sugar but require changes in enthalpy of water➔sugar H-bonds.

Reference: Vila Verde, A. & Campen, R. K., Disaccharide Topology Induces Slowdown in Local Water Dynamics, *JPCB,* **2011**, *115*, 7069

WHY DOES THE RATE OF H-BOND EXCHANGE CORRELATE IMPERFECTLY WITH ΔG?*

Equiprobability curves of the transition state for OH rotation near different sugar oxygens



- The presence of the sugar induces broadening of the transition state, implying that the transition state for exchanges near the solute is different from bulk water.

4. CONCLUSIONS AND FUTURE WORK

- Slow down of water dynamics (translation and rotation) around Kojibiose and Trehalose correlates with local hydrophobicity.
- The rotational dynamics of water H-bonded to other waters and within 3.5 Å of Kojibiose and Trehalose can be well understood by accounting for a reduction in the total volume of the transition state and a broadening of the configurations making up that transition state relative to bulk water.
- The rotational dynamics of water H-bonded to Kojibiose and Trehalose can be understood only by accounting for a reduction in the total volume of the transition state, a broadening of the configurations making up that transition state relative to bulk water and enthalpic differences between water➔sugar and water➔water H-bonds.