In this talk, I will first introduce Vibrational Sum-Frequency Spectroscopy (VSFS), a nonlinear, ultrafast laser spectroscopy that is capable of selectively detect molecular vibrations on or near surfaces and interfaces. This unique surface-specificity allows us to study absolute orientations of molecules on various surfaces of importance in fields including biophysics, materials science and environmental science. For example, our recent results show that H2O is intrinsically more surface active than D2O. This surface-specific isotopic effect results in isotropic fractionation with significant implications in environment chemistry. VSFS has also been used to elucidate how a biomacromolecule aligns itself as well as the surrounding small molecules, such as water, salts, and osmolytes.