

SUBTLE BUT SYSTEMATIC ANOMERIC PREFERENCES IN SACCHARIDE INTERACTIONS

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Saccharides, particularly hexoses, are essential to a plethora of biochemical processes and find applications in diverse fields. In aqueous solutions, hexoses predominantly exist in two rapidly interconverting cyclic forms (α and β anomers, respectively), with negligible contribution from the linear form. Although interactions of different anomers play crucial roles in processes such as enzymatic recognition and receptor binding, the relatively weak nature of saccharide interactions and the dynamic α/β equilibrium make it challenging to systematically study anomeric binding preferences.

In this work, we address this gap by examining the interactions of several hexoses, including a subset of their derivatives that are methylated at anomeric carbon, which prevents mutarotation and locks the saccharide in a single anomeric state. We explored saccharides' binding to various amino acids (representing nearly every chemical subtype) as well as their self-association. Combining experimental osmotic coefficient measurements with extensive all-atom molecular dynamics simulations (including free energy calculations and corresponding osmotic coefficient predictions), we observed a consistent pattern: α -anomers exhibit slightly stronger interactions with amino acids and with themselves than corresponding β -anomers. These differences, while small and sometimes near the limits of experimental uncertainty, emerged consistently across dozens of saccharide–saccharide and saccharide–amino acid combinations tested in our work. Our simulation analyses suggest that subtle differences in the solvation shell are responsible for this trend. Specifically, the axial orientation of the anomeric hydroxyl group in α -anomers (a consistent feature in the hexoses studied) leads to a less structured saccharide's solvation shell compared to β -anomers, where the hydroxyl group adopts an equatorial position. This eventually favors stronger solute–solute contacts for α -anomers. Furthermore, molecular dynamics simulations show that this trend is even more pronounced in short oligosaccharide sequences composed exclusively of either α or β units. Overall, our findings underscore how minor structural differences can have detectable impact on carbohydrate interactions in aqueous environments. These insights not only deepen our understanding of carbohydrate chemistry but also offer valuable guidance for studying protein–carbohydrate and ligand–receptor interactions.

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