

THE CONFORMATIONAL ITINERARY OF GLYCOPYRANOSYL OXACARBENIUM IONS

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The glycopyranosyl oxacarbenium ion is the presumed intermediate or transition state in most proposed mechanisms for glycosidases or glycosyltransferases. It is also a widely held belief that small molecules that mimic these ions should function as inhibitors for these enzymes. However primarily due to the short lifetimes of such oxacarbenium ions it is difficult to experimentally determine their structures and properties. We address these issues using Density Functional Theory (DFT) quantum calculations for static structures and the Projector Augmented Wavefunction (PAW) method for dynamical investigations. We will present results for 2,3,4,6-tetra-*O*-methyl-D-glucopyranosyl (**1**) and mannopyranosyl (**2**) oxacarbenium ions. We have shown that these two ions likely exist in at least 2 conformations with ⁴H₃, ⁵S₁ and ⁴H₃, ³E pairs for **1** and **2** respectively. For **1** both ions have O-2 pseudoequatorial and this equatorial preference from a limited number of examples is about a 10 kJ mol⁻¹ stabilizing effect. Unexpectedly all 4 ions have the O-2 methyl group *syn* to the H-2 methine. This effect is stabilizing by more than 10 kJ mol⁻¹. These two factors are sufficiently large in magnitude (DFT) that they likely have mechanistic implications for glycosyl processing enzymes and the design of inhibitors for them. Current studies focus on the interconversion pathways between these ions. These studies use a new constrained ab initio dynamical method based on PAW calculations. We have tested this method by finding the inversion barriers of neutral model systems as well as 1,2,3,4,6-penta-*O*-methyl-D-glucopyranose. In all cases where experimental values are available the agreement is good. This method allows for pseudorotation in a natural way because the constraints are based on the normal modes of six membered rings. We present the conformational itineraries of all molecules including **1** and **2** using a spherical representation based on the 3 canonical conformations ¹C₄ chair, ^{1,4}B boat and ⁰S₂ skew boat. The results confirm our static calculations and suggest a pseudorotational pathway of interconversion with distinct differences for **1** and **2**. These pathways should be of interest to the mechanistic studies of glucopyranosyl and mannopyranosyl processing enzymes.