426m Toward the Transition State: Further Docking Studies on Family 47 Alpha-1,2-Mannosidases

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Alpha-1,2-Mannosidase from the endoplasmic reticulum (ERMan), a Family 47 glycosyl hydrolase, is a key enzyme in the *N*-glycan synthesis pathway. Catalytic-domain crystal structures of human and yeast ERMans have been determined, the former without ligands, with the inhibitors 1-deoxymannojirimycin and kifunensine, and with a thiodisaccharide substrate analog. Both inhibitors were bound at the base of the funnel-shaped active site as the unusual $^{1}C_4$ conformer, while the substrate analog glycone is a $^{3}S_1$ conformer. In the current study, AutoDock was used to dock alpha-D-mannopyranosyl-(1,2)-alpha-D-mannopyranose with its glycone in chair ($^{1}C_4$, $^{4}C_1$), half-chair ($^{3}H_2$, $^{3}H_4$, $^{4}H_3$), skew-boat ($^{O}S_2$, $^{3}S_1$, $^{5}S_1$), boat ($^{2,5}B$, $^{3,O}B$, $B_{1,4}$, $B_{2,5}$), and envelope (^{3}E, ^{4}E, E_3, E_4) conformations into the yeast ERMan active site. Both docked energies and forces on docked ligand atoms were calculated to determine how the ligand distorts to the transition state. From these, we can conclude that 1) both $^{1}C_4$ and $^{O}S_2$ can be the starting conformers; 2) the most likely binding pathways are $^{1}C_4$ to $^{3}H_2$ to $^{O}S_2$ to $^{3,O}B$ to $^{3}S_1$ to ^{3}E and $^{O}S_2$ to $^{3,O}B$ to $^{3}S_1$ to ^{3}E with $^{1}C_4$ and $^{O}S_2$ as starting conformers, respectively; 3) the transition state is likely to be close to a ^{3}E conformation.