Ab Initio Conformational Space Study of Model Compounds of O-
Glycosides of serinediamide

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Relative stabilities of rotamers of the N-acetyl-O-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-L-seryl-N’-methylamide (1) and eleven analogous molecules containing β galactose, α- and β-mannose, glucose, and L-threonine were calculated to learn whether they could explain the natural preference for 1 in linkages between the carbohydrate and protein in glycoproteins. The lowest energy rotamers of four O-glycoside models of serine diamide were identified with a Monte Carlo search coupled with molecular mechanics (MM2*). These rotamers were further optimized with an *ab initio* level of theory (HF/6-31G(d)). Subsequently, B3LYP/6-31+G(d) single point energies were calculated. The most favorable interactions are present in 1 and in its glucose analogue. The monosaccharide base for the carbohydrate antenna is anchored to the serine residue with an AcNH…O=C-NHMe hydrogen bond in the most stable rotamers. The mannose containing analog and the beta anomers are considerably less stable according to the *ab initio* energy values. The three analogs have HF/6-31G(d) energies that are 4-6 kcal mol\(^{-1}\) higher, and the single point B3LYP/6-31+G(d)//HF/6-31G(d) calculations yield preferences of 3-5 kcal mol\(^{-1}\) for 1. The most stable L-threonine analogs behave very similarly to the corresponding serine analogs. The ZPE and thermal correction components of the calculated \(\Delta H^{298}\) and \(\Delta G^{298}\) values are relatively small (< 0.4 kcal mol\(^{-1}\)). However, the T\(\Delta S^{298}\) term can be as large as 2.6 kcal mol\(^{-1}\). The entropy terms stabilize the \(\alpha\) anomers relative to \(\beta\) anomers, and ManNAc relative to GalNAc. The largest stabilization effect is observed for one of the rotamers of the \(\alpha\) anomer of ManNAc.