Computational Investigation of Enthalpy-Entropy Compensation in Complexation of Glycoconjugated Bile Salts with β-Cyclodextrin and Analogs

The inclusion complexes of glycoconjugated bile salts with beta-cyclodextrin (beta-CD) and 2-hydroxypropyl-beta-cyclodextrins (HP-beta-CD) in aqueous solution were investigated by molecular dynamics simulations to provide a molecular explanation of the experimentally observed destabilizing effect of the HP substituents. Good agreement with experimental data was found with respect to penetration depths of CDs. An increased degree of HP substitution (DS) resulted in an increased probability of blocking the cavity opening, thereby hindering the bile salt from entering CD. Further, the residence time of water molecules in the cavity increased with the DS. Release of water from the cavity resulted in a positive enthalpy change, which correlates qualitatively with the experimentally determined increase in complexation enthalpy and contributes to the enthalpy-entropy compensation. The positive change in complexation entropy with DS was not able to compensate for this unfavorable change in enthalpy induced by the HP substituents, resulting in a destabilizing effect. This was found to originate from fixation of the HP substituents and decreased free rotation of the bile salts within the CD cavities.