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Computational insights about the dynamic behavior for the inclusion process of deprotonated and neutral aspirin in ?-cyclodextrin

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Abstract: Molecular dynamics was used to study the inclusion of neutral and deprotonated aspirin into the ?-cyclodextrin (?-CD) cavity. The molecular dynamic simulation allows following the time dependent behavior of the formation of the inclusion complex. For both complexes, we find a reasonable and a realistic pattern of the complexation. The calculations show a single pathway consisting of a no reversible binding process leading to the complexation of aspirin. Whereas for deprotonated aspirin it has been observed a reversible binding, in which one way leads to the binding form, and the reverse way to the unbinding form. Throughout the simulation, the penetration of aspirin (ASA) or deprotonated aspirin (ASA?) inside the cavity occurs only with a phenyl ring entering first through the wider or narrower rim. The determination of free energy using unbiased and biased simulations of the corresponding inclusion processes gives more favorable inclusion process of aspirin than deprotonated aspirin. The inclusion of the guest molecule is found deeply embedded within ASA:?-CD complex whereas it is partial in ASA?:?-CD complex. Also, the orientation A of both complexes is found more favorable of ca. 1.9 kcal/mol, and of ca. 0.8 kcal/mol, respectively for neutral and deprotonated complex. Aspirin molecule establish one H-bond between the hydrogen carboxylic atom and one oxygen atom of primary hydroxyl group of ?-CD; this H-bond is detected during about 20% of the simulation period. In addition, we found that water molecules in the first solvation layer are implied with hydrogen carboxylic atom and the keto oxygen atoms within H-bonds. While, water molecules of the second solvation layer is in interact with the O1 and O2 oxygen atoms of aspirin. Accordingly, based on the obtained results we can consider that the hydrophobic/hydrophilic interactions are the most important driving forces of the complexation assisted by stabilizing H-bonds.

Keywords : Aspirin, Cyclodextrin, Inclusion complexes, Molecular dynamic simulation, Umbrella sampling, Hydrogen bonding