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Computational Modelling of pH-Responsive Nanovalves in Controlled-Release System

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Abstract : A category of nanovalves system containing the α-cyclodextrin (α-CD) ring on a stalk tethered to the pores of mesoporous silica nanoparticles (MSN) is theoretically and computationally modelled. This functions to control opening and blocking of the MSN pores for efficient targeted drug release system. Modeling of the nanovalves is based on the interaction between α-CD and the stalk (p-anisidine) in relation to pH variation. Conformational analysis was carried out prior to the formation of the inclusion complex, to find the global minimum of both neutral and protonated stalk. B3LYP/6-311G**(d, p) basis set was employed to attain all theoretically possible conformers of the stalk. Six conformers were taken into considerations, and the dihedral angle (θ) around the reference atom (N17) of the p-anisidine stalk was scanned from 0° to 360° at 5° intervals. The most stable conformer was obtained at a dihedral angle of 85.3° and was fully optimized at B3LYP/6-311G**(d, p) level of theory. The most stable conformer obtained from conformational analysis was used as the starting structure to create the inclusion complexes. 9 complexes were formed by moving the neutral guest into the α-CD cavity along the Z-axis in 1 Å stepwise while keeping the distance between dummy atom and OMe oxygen atom on the stalk restricted. The dummy atom and the carbon atoms on α-CD structure were equally restricted for orientation A (see Scheme 1). The generated structures at each step were optimized with B3LYP/6-311G**(d, p) methods to determine their energy minima. Protonation of the nitrogen atom on the stalk occurs at acidic pH, leading to unsatisfactory host-guest interaction in the nanogate; hence there is dethreading. High required interaction energy and conformational change are theoretically established to drive the release of α-CD at a certain pH. The release was found to occur between pH 5-7 which agreed with reported experimental results. In this study, we applied the theoretical model for the prediction of the experimentally observed pH-responsive nanovalves which enables blocking, and opening of mesoporous silica nanoparticles pores for targeted drug release system. Our results show that two major factors are responsible for the cargo release at acidic pH. The higher interaction energy needed for the complex/nanovalve formation to exist after protonation as well as conformational change upon protonation are driving the release due to slight pH change from 5 to 7.

Keywords : nanovalves, nanogate, mesoporous silica nanoparticles, cargo
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