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Density Functional Theory Calculations on Methylated β-Cyclodextrins

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Density functional theory studies at the B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p) levels have been used to determine the geometries and the enthalpies of formation of several methylated β-cyclodextrins.

Various degrees of methylation can be performed at the hydroxyl groups of β-cyclodextrin at the 2-, 3-, and 6-positions. The number of methyl groups and the position influence the physico-chemical properties of the derivatives as well as their inclusion ability. Large changes of the association constants with different guest molecules are accompanied with increase or decreased solubilities, as well as by a modification of the inclusion mechanisms. In this study three different types of methylated β-CDs were investigated: Heptakis(2-*O*-methyl)-β-cyclodextrin, heptakis(6-*O*-methyl)-β-cyclodextrin, heptakis(2,6-di-*O*-methyl)-β-cyclodextrin, and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin.

During building up the various β-CD derivatives C7-symmetry was used throughout. By applying systematic B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p) calculations, the oxygen-oxygen distances were scanned and all remaining geometry parameters were optimized. Three conformational minima were obtained. In the lowest energy conformation two homodromic hydrogen bond rings were formed, one with very short hydrogen bonds at the primary hydroxyls and a second at the secondary hydroxyls of the CD. Four orientations of the homodromic hydrogen bond rings, which are different in energy, have been taken into consideration: both hydrogen bond rims orientated counterclockwise (cccc) or clockwise (cwcw) and the primary rim clockwise and the secondary rim counterclockwise (cwcc) and vice versa (cccw). These four conformations were used to construct the methyl-derivatives of the β-CD molecules. For the optimization with both DFT methods no constraints were imposed on the molecules. To compare the calculated energies with related values obtained experimentally, the respective energies of five crystallographic structures have also been calculated.