CYCLODEXTRIN AS A TEMPLATE FOR MOLECULAR ASSEMBLY: INCLUSION COMPLEXES WITH ANTI-CANCER DRUGS

Maurizio Fermeglia, Alessia Lodi and Sabrina Pricl

Department of Chemical Engineering, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy and ICS-UNIDO, Area Science Park, Pardiciano 99, 34100 Trieste, Italy

Supermolecular assemblies involving cyclomalto-oligosaccharides (cyclodextrins) have mostly made use of the host-molecular properties of these compounds. In particular, encapsulation of drugs by means of monomolecular inclusion complex formation offers a new form of dosage and its importance in pharmaceutical formulation has been fully realized. Anti-cancer drugs belonging to the main categories of action are suitable, in principle, for inclusion as guest within some cyclodextrin. It has been proposed that some of the well known deleterious effects of such drugs can be improved by their inclusion within a cyclodextrin molecule, resulting in a reduced concentration of the free drug in non-target physiological environment.

In this work we present the results obtained from extensive molecular dynamics simulations on host-guest inclusion complexes between β-cyclodextrin and 5 known different anti-cancer drugs (i.e. pipobroman, melphalan, thiocolchicine, acivicin, 7-chlorocamptothecin) belonging to the different classes, such as alkylating agents, antimitotic agents, nucleic acid anti-metabolites and topoisomerase inhibitors. Further, we considered a new, potentially active antitumor antibiotic, hexahydro-TMC-69 from *Chrysosporium sp* TC1068, which showed cytotoxic activity *in vitro* against various tumor cell lines.

All simulations were run, both on isolated complexes and in water environment, in a temperature interval encompassing the physiological range. The conformational properties and the energetics of the host-guest systems were examined and the binding free energy for the complexes obtained.

As a general result, all complexes seem to be stable in the physiological temperature range. The thermodynamic parameters for the different possible mechanisms of inclusion for each drug do not differ considerably, so that the drugs have the possibility of entering both through the primary or the secondary hydroxyl side.