Modellazione moleculare e calcoli di energia libera di binding per complessi di inclusione ciclodestrina-farmaci antitumorali

Maurizio Fermeglia, Marco Ferrone and Sabrina Pricl[?]

Computer-aided Systems Laboratory - CASLAB, Department of Chemical Engineering, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy

The more stable structures of 1:1 host-guest complexes between BCD and six anticancer drugs belonging to different classes of action were studied first by means of molecular mechanics/molecular dynamics using a continuum solvent model (GB/SA). The main driving forces for complexation are dominated by nonbonded van der Waals interactions between the host and the guest, although the relative orientation of the dipole moments and the presence of topical H-bonds between the polar parts of the drugs and the OH groups of the BCD rims play a further role in stabilizing these supermolecular assemblies. The calculations of the energetic components of the nonbonded potential energy showed that, under the conditions considered, all inclusion complexes should in principle be stable and, in the case of asymmetrical molecule, no preferential way of insertion was detected, exception made for Hexahydro-TMC69, for which the Octyl *OH prim* conformation was favored with respect to the alternative Octyl *OH sec* by approximately 18 kJ/mol.

Further, in the case of the two biggest molecules considered, Thiocolchicine and Hexahydro-TMC69, the energetical gain in the formation of 2:1 complexes was also calculated from simulation. The results clearly indicated that, under the conditions considered and in excess of BCD, the 2:1 host-guest complex stoichiometry is favored for both these two active principles. The computational results obtained so far are in good agreement with similar, published studies on BCD inclusion compounds *in vacuum*.

Notwithstanding this fact, the absence of an explicit solvent and the neglect of the entropic contribution does not allow for a reliable estimate of the complexation energy. Therefore, the dynamic behavior of the same 1:1 and 2:1 host-guest complexes has been simulated using a combination of molecular mechanics energy derived from MD simulations in explicit solvent, and solvation free energy derived from a continuum solvation model. Accordingly, we have calculated reasonable absolute free energies of binding for all BCD/drug complexes formation.

In general, the energetic analysis reveals that the van der Waals interactions and the nonpolar contributions to solvation always provide the basis for the favorable absolute free energy of binding. On the other hand, a delicate balance exists between the always favorable gas-phase electrostatics term and the unfavorable change in electrostatic contribution to the solvation. Indeed, by counteracting the favorable electrostatic interactions that form between the drug and the BCD cavity binding site, the desolvation of the molecular components plays an important role in determining the effect of the electrostatics, as a whole, on the formation of the BCD/anticancer complexes.

The results obtained from this study can then suggest the conclusion that, although

[?] E-mail:sabrinap@dicamp.units.it; Web-site: http://www.caslab.units.it

the results obtainable using continuum solvation models can be used in a predictive, comparative manner among a series of compounds, in order to investigate in detail the influence of the solvent on the interaction of the host and its guests, and to calculate reliable values for the free energy of binding, simulations in explicit water must be performed. In any case, the results we obtained by applying our simulation technique are in good agreement with published values of binding constants for analogous compounds in BCD.

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