Accounting for Intra-molecular Hydrogen-bond Formation in Modeling Aqueous Solutions of Glycine Homopeptide Using the SAFT-γ Mie Equation of State

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The phase transitions and closely related non-equilibrium formation of gels of therapeutic peptides in solutions are of direct relevance to the peptide-drug development. From a modelling stand-point, a theoretical progress can deliver accurate predictions of complex phase behaviour, including solid–liquid solubility and liquid–liquid de-mixing, and can account for detailed molecular features. We implement SAFT-γ Mie which is a group-contribution approach based on a heteronuclear model of fused segments interacting via the Mie potential. These segments also feature association sites when necessary to interpose directional interactions that mimic hydrogen bonds. This approach accounts for chemical functionality, ring size, molecular size, connectivity, and strong polar interactions. The SAFT-γ Mie approach [1] has been shown to deliver accurate predictions of the solubility of pharmaceuticals including the pH-solubility profiles of ionisable active ingredients. [2], [3] This theory is used to predict the solid–liquid solubility of glycine homopeptides (up to hexaglycine) in water. In peptides, intramolecular bonding and the zwitterionic nature of the molecules critically affect the observed solubility, and lead to complex phase transitions, which pose a stringent test to modelling approaches. The deviations in the SAFT-γ Mie solubility prediction from the experimental data motivate an assessment of the impact of intramolecular hydrogen bonding in the theoretical approach. Eight conformers of neutral diglycine are considered, based on the number and type of hydrogen bond: each with a different intramolecular bond between –NH or =O groups of the peptide-bond group (C=ONH) and the end groups (NH_2 and COOH) in the glycine peptides. When the two functional groups consisting of donors and acceptors are involved in an intramolecular bond, the association sites are deactivated and are inaccessible by other associating groups. The models which provide the best prediction of the diglycine solubility are when intramolecular hydrogen bonds are considered as the following cases: (i) [–NH and $–NH_2$], [=O and –COOH] and (ii) [$–NH_2$ and =O], [–NH and COOH]. These models are extended to glycine homopeptides up to the aqueous solution of hexaglycine. The results indicate that it is challenging to capture the solubility predictions for all neutral conformers of the glycine homopeptides by considering any choice of the model for the intramolecular hydrogen bonding. As a next step, the zwitterionic form of glycine homopeptides will be modelled to assess the impact of presence of charged species in aqueous solutions on the solubility predictions.

References

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