Affordable Modelling of H-bonded Solutes Using MD-ONIOM2.

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Modelling of compounds with acidic protons in polar solvents is especially complicated as hydrogen bonding between the solute and solvent molecules adds extra complexity to the electronic environment. MD-ONIOM2 is a computationally affordable method that gives good predictions. This uses standard molecular dynamics (MD) to first model the dynamics of solute-solvent interactions and find the solvation shell. The solute molecule and its solvation shell is then optimised quantum mechanically using the ONIOM2 method. ONIOM2 treats the solute molecule at a higher level of theory, and the whole solute-solvation shell system at a lower level of theory.

MD-ONIOM2 has been used previously to model the anti-HIV drug molecule, nevirapine in DMSO solution [1], and to predict its 1H-NMR chemical shifts with good accuracy (<±0.4ppm). This included one acidic amine-proton whose NMR shift was poorly predicted with a gas-phase model and with IEFPCM. MD-ONIOM2 is now being used to model other amines in DMSO solution to demonstrate its application in the general study of dynamic solvent-solute interactions, including solutes with multiple acidic protons.

With this model, the system consists of an optimised solute molecule placed in a box of solvent with periodic boundary conditions. Standard MD is run to simulate the dynamic interactions, including the formation of H-bonds. Radial distribution functions (RDFs) of the solvent atoms around the acidic amine protons show the number of solvent molecules in the solvation shell. From the final 1ns of the production period, a snapshot of the system is taken every 100ps for ONIOM2 calculations which optimise the structure of the system within the solvation shell using [2]:

$$E_{\text{High, Solvated}} \approx E_{\text{ONIOM2}} = E_{\text{High, Solute}} + E_{\text{Low, Solvated}} - E_{\text{Low, Solute}}$$

and generate the NMR shift of each proton from the corresponding:

$$\sigma(^1H_i)_{\text{ONIOM2}} = \sigma(^1H_i)_{\text{High, Solute}} + \sigma(^1H_i)_{\text{Low, Solvated}} - \sigma(^1H_i)_{\text{Low, Solute}}$$

where High = high level of quantum theory,
Low = low level of quantum theory,
Solute = solute molecule only,
Solvated = solute with solvent molecules in the solvation shell.
$\sigma(^1H_i)$ = shielding tensor of the i^{th} proton in the solute molecule

The 10 NMR shifts for each proton are averaged for final NMR shift values.

To date, aniline, N-methylaniline, acetamide and valerolactam have now been successfully modelled. The dynamics show the H-bonded solvent molecules, as expected around the acidic anime protons, and their exchange with the bulk. Also, the different NMR shifts of the *cis*- and *trans*- protons in acetamide were found. In addition, this model is computationally affordable giving final results in 3-4 days running on a modern standalone PC.

REFERENCES

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