C-terminal and N-terminal zinc finger region of NC. These results agree with earlier experimental work that suggests the same.

Another notable aspect of this study is the use of the relative proton potential as a descriptor to predict proton affinity of titratable sites of the ovomucoid third domain (OMTYK3). The agreement between experimental pK_a and relative proton potentials of these residues is very encouraging with a linear correlation coefficient of −0.996. There is a wealth of experimental pK_a data and high-resolution x-ray crystallographic data available for other therapeutically important protein targets. A systematic study of all these targets to confirm the predictive ability of relative proton potential is in order. In related studies, Rajamani and Reynolds have also used linear-scaling QM[60,61] implemented in the computer program DivCon to model protonation states of catalytic aspartates in β-secretase.[62] These studies suggest that the aspartates prefer the monoprotonated state in the presence of the inhibitor, whereas in its absence they favor the dideprotonated state. Raha and Merz, again using DivCon, have also formulated a scheme to calculate the proton affinity of the catalytic aspartates of HIV-1 protease in the presence and absence of inhibitors bound to the proteases and discussed the results in light of their binding affinity calculations.[63]

Polarization and charge transfer

Although the role of polarization and charge transfer in macromolecular interaction is well known, only recently has it been quantified in SBDD by the use of QM methods. Hensen and coworkers, using QM/MM methods, have studied the interaction of HIV-1 protease with three high-affinity inhibitors: nelfinavir, mozenavir, and tripnavir.[64] They find that polarization of the ligand by the enzyme environment contributes to up to 39% of the total electrostatic interaction energy. Based on their analysis they propose modifications to one of the inhibitors that can possibly lead to increase in binding affinity. In a similar study, Garcia-Viloca et al. have investigated the role of polarization of the substrate tetrahydrofolate, and the cofactor NADPH, at various stages of dihydrofolate reductase catalyzed hydride transfer reaction.[65] The authors find that polarization contributes to 4% of the total electrostatic interaction and stabilizes the transition state by 9 kcal/mol over the reactants.

Charge transfer in receptor ligand interaction in the context of SBDD has been studied in significant detail by Raha and Merz.[63] In their recent study of 165 noncovalent protein/ligand complexes, they find that in 11% of the complexes more than 0.1 electron units of charge is transferred from the protein to ligand. In the 49 metalloenzyme complexes, there is on average up to 0.6 electron units of charge transferred between the protein and the ligand. The direction of CT depends on the protein/ligand complex. For example, in matrix metalloproteases (MMP), charge is transferred from the protein to the ligand, whereas in human carbonic anhydrase (HCA) and carboxypeptidases (CPA) charge is transferred from the ligand to protein. All these studies indicate that QM effects are important in protein/ligand interaction and cannot be ignored in SBDD efforts that hope to discover potent inhibitors to protein targets in silico.

Catalysis, QM, and SBDD

The mechanism of recognition of substrates by enzymes, followed by catalysis and product formation, has drawn considerable interest from the drug discovery community as these enzymes are potential targets for therapy. As a result, a thorough understanding of the mechanism with respect to catalysis can lead to effective inhibitor design strategies. QM has come to play a leading role in this area, because the very nature of mechanistic enzymology makes it suitable for sophisticated investigation via use of QM. Recent reviews in this area describe the emerging field of computational enzymology and detail modeling techniques and important advances that involve QM/MM and DFT based approaches.[3,4]

Review of the literature for the past year indicates a host of enzymes that have been the subject of mechanistic investigation using QM-based methods and a thorough review is beyond the scope of the overall topic of this article. However, we touch on two enzymes that have been the subject of detailed investigation and are important SBDD targets. These are β-lactamase and chorismate mutase.[66–70] From the point of view of RBDD, β-lactamases have been particularly well studied to elucidate their mechanism of resistance to β-lactam antibiotics. In one such comprehensive study, Hermann et al. have modeled the acylation mechanism of class A β-lactamase enzyme TEM1 using semiempirical QM/MM and hybrid DFT to correct the semiempirical energies.[71] The insights gleaned from this study will be valuable in the design of β-lactam antibiotics that are not hydrolyzed by β-lactamases. Merz and coworkers have also used QM/MM, DFT, and quantum chemical solvation methods to study the mechanisms and binding preferences of a class of β-lactam antibiotics for these enzymes.[69,72]

Quantitative uses of QM in RBDD

Although QM can provide valuable insights and a different perspective regarding the interaction between receptor and ligand in structure-based drug design, the holy grail of computational drug discovery still remains the ability to accurately calculate the free energy of binding between a protein and its small-molecule inhibitor and thereby discover new inhibitors in silico. Part of this problem involves the prediction of the correct binding mode or "pose" of the inhibitor when bound to a protein target. Several docking programs have been reasonably successful in obtaining the correct binding mode.[73] However, calculating the binding free energy or the correct score has proven to be challenging.[74] This is not surprising, considering that the free energy of binding between two molecular systems depends on a complex interplay of interactions between them and the medium they exist in. Computational