Enzymatic Reactions in Thrombin

Another challenging area in life science research is thrombin catalysis and

inhibition. A thrombin complexed with a thrombin receptor peptide was used to study the cleavage reaction of the Arg-Ser bond in the receptor. To simulate the physiological conditions as closely as possible, a water environment was placed around the protein structure yielding up to 21895 atoms for the full system (Fig. 10). Classical molecular dynamics simulations and subsequent QM/MM minimisations of snapshots taken from the production run after equilibration provided detailed insights into conformational aspects. Each optimised snapshot structure was then taken as a starting point to investigate the first step of the reaction which proceeds by a proton transfer from Ser195 to His57 and a concomitant nucleophilic attack of the Ser195 oxygen atom at the carbonyl carbon of Arg1 to yield a tetrahedral intermediate. These calculations which are still in progress employ the AM1/CHARMM method with an electrostatic embedding scheme.

Summary

Taken together the three enzyme modelling examples outlined above illustrate the versatility and broad functionality of ChemShell. The results from the first two studies have already been published (TIM see J. Phys. Chem. B 2002, 106, 1758-1767, PBBH see Phys. Chem. Chem. Phys. 2001, 3, 688-695).

The QUASI Partners

The European Union has funded a collaboration to develop QM/MM techniques for industrial applications. The project combines software development work of three academic groups active in the area.

- The chemistry group at the Max Planck Institut für Kohlenforschung, Mülheim (DE).
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The QM/MM schemes and the ChemShell software were applied to study several enzymatic reactions. This

relative energies towards variations in the QM/MM model, including the choice of the QM method, the size of the QM region, the size of the optimised MM region, and the treatment of the QM/MM boundary through various link atom and connection atom schemes. The QM methods that were applied in combination with the MSI-CHARMM force field range from semiempirical (AM1) to density functional (B96, B3LYP) and ab initio (MP2) methods. The most extensive QM calculations involving 279 QM atoms and 2162 basis functions. From a mechanistic point of view the results support a four-step proton transfer pathway via an enediol, with involvement of His65, since the alternative direct intramolecular proton transfer in the enediyolate is disfavoured by the protein environment.

Enzymatic Reactions in Interfaces

The Software Approach

The project has implemented the QM/MM methodology by integrating a number of computational chemistry packages, including those developed by the partners and some commercial applications.

The control module in the QUASI software is a Tcl-based computational chemistry interpreter, providing:

- Shell model QM/MM A solid state embedding scheme coupling quantum chemistry methods with a classical representation based on the shell model has been developed within QUASI.
- QM/MM coupling Different coupling models are available, including mechanical and polarized (electrostatic) embedding of the QM region.
- MD Module A range of integration methods (derived from code within the DL_POLY package, and a Monte Carlo driver.
- Geometry Optimiser An optimiser, based on the delocalised internal coordinate approach, for the treatment of macromolecular systems.
- Studies of Enzyme Reactivity

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work (jointly carried out by BASF and MPI für Kohlenforschung) made extensive use of the comprehensive QM/MM functionality of ChemShell for life science research.

Enzymatic Reactions in Transesphosphatase Isomerase (TIM)

Systematic QM/MM calculations were performed for the TIM catalysed conversion of dihydroxyacetone phosphate into glyceraldehyde 3-phosphate (see Fig. 8). The primary objective was to investigate the sensitivity of optimised structures and

102 QM atoms) and could not have been accomplished without the HDLC optimiser that has been developed in the QUASI project and implemented in ChemShell.

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inhibition. A thrombin complexed with a thrombin receptor peptide was used to study the cleavage reaction of the Arg-Ser bond in the receptor. To simulate the physiological conditions as closely as possible, a water environment was placed around the protein structure yielding up to 21895 atoms for the full system (Fig. 10). Classical molecular dynamics simulations and subsequent QM/MM minimisations of snapshots taken from the production run after equilibration provided detailed insights into conformational aspects. Each optimised snapshot structure was then taken as a starting point to investigate the first step of the reaction which proceeds by a proton transfer from Ser195 to His57 and a concomitant nucleophilic attack of the Ser195 oxygen atom at the carbonyl carbon of Arg1 to yield a tetrahedral intermediate. These calculations which are still in progress employ the AM1/CHARMM method with an electrostatic embedding scheme.

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The Catalytic Cycle - From CO₂ to Methanol

The QUASI software is designed for use on high-performance parallel computer systems, and is available for use on a variety of platforms, including Cray T3E, IBM SP2, and Beowulf-class commodity clusters. Parallel performance of the code is excellent, making the routine study of large systems possible.

Introduction and Background

Norsk Hydro is a major producer of nitrogen based fertilizers, resulting in the emission of NOx. NOx contributes to the catalytical destruction of stratospheric ozone, in addition to being a greenhouse gas, corresponding to 310 CO₂ equivalents. Thus, effective conversion into harmless products is an industrial process of increasing importance.

Software Interfaces (cont’d)

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High-Performance Simulation

The QUASI software is designed for use on high-performance parallel computer systems, and is available for use on a variety of platforms, including Cray T3E, IBM SP2, and Beowulf-class commodity clusters. Parallel performance of the code is excellent, making the routine study of large systems possible.

Application: Modelling NOx and N₂O Decomposition in Zeolites

Figure 1 shows the zeolite structure of ZSM-5 with copper ions coordinated to the framework oxygens. The copper ions are shown as green spheres, and the framework oxygens are shown as red triangles.

Catalytic Cycle

By using the QM/MM scheme we have been able to characterize the energetics of the individual steps in the CO₂ decomposition reaction. The catalytic cycle of CO₂ decomposition for the oxygen end adsorption is given in Figure 3.

Adsortion Energies

We have studied the adsorption energies for NO and N₂O adsorption at different Cu ion sites including two- (I₂) and three-coordinated (M₇ and Z₆) sites. The calculated adsorption energies indicate that the most stable forms of adsorbed NO and N₂O bind through the nitrogen end in accordance with experimental findings. However, the O-bound adsorption mode for N₂O is believed to be more important in the decomposition pathway. Comparing the different Cu sites within the zeolite framework, we find lower adsorption energies for the ring sites (Z₆, M₇) as compared to the I₂ site, in agreement with other theoretical studies. The effect can be traced to the geometry of the adsorbed complex. The structure of the I₂ sites remains essentially unchanged upon coordination, whereas the ring coordinated Cu⁺ (Z₆, M₇) has to give up the extra coordination to non-AO₄ framework oxygens to bind NO or N₂O. This reduces the total binding energy.

Transition State

Preliminary results show that there is a difference in activation barrier (18 kcal/mol) between the gas phase model and QM/MM model. The N-O bond distance shows the largest geometry difference. The QM/MM result gives an elongated and more activated adsorbate complex. This causes a higher activation barrier when using the QM/MM scheme.

Summary

By using the QM/MM methodology, we predict that there is a difference in adsorption energies among the different sites. The zeolite environment has an impact on the adsorbate structure compared to the bare gas phase calculations. This also influences the transition states and further calculations are currently in progress.

Application: Understanding the Chemistry of Oxide Surfaces

For improvements to be made in long standing industrial catalytic processes an understanding of the atomistic mechanism of the reactions is required. A variety of experimental techniques can be used to study sorption and reaction processes, but when both catalyst and reactant mixtures are multicomponent, mechanisms are particularly complex, and often controversial. Computational techniques can be used to gain valuable insight and interpret experimental evidence.

Industrial Methanol Synthesis

A large quantity of methanol, in excess of 22 million tonnes worldwide, is produced annually using the multicomponent Cu/ZnO/Al₂O₃ catalyst and feed gas, CO₂/CO/H₂. Many experimental studies of this process have been performed but without any definite reaction mechanism being established. The rate-determining step is thought to be the hydrogenation of adsorbed intermediates, for example the formate ion, at the active sites.

Active Site

Proposed mechanisms for methanol synthesis require the chemisorption of CO₂ before hydrogenation via formate or HCOOH-(formic acid) as shown in Figure 6. Our calculations show that Cu⁺ is the most stable forms of adsorbed NO and N₂O, and feed gas, CO₂/CO/H₂. CO₂ before hydrogenation via formate to methanol. The nature of the active site for sorption/catalysis of CO₂ remains unclear; as a test system (model catalyst) it has been proposed to use clean oxygen terminated surfaces of CO₂.

Catalytic Cycle

The proposed catalytic cycle is summarised in Figure 5. We start with the adsorption of CO₂ and H₂ to upon adsorption retains its linear structure. Upon adding an electron the molecule breaks and the extra electron populates an antibonding level. The interaction with the surface stabilises the radical CO₂⁻ species.

The reaction then proceeds via the hydrogenation of the adsorbed CO₂⁻ by surface hydrogen, to the formate ion. Further hydrogenation can proceed either through the formation of H₂CO₃ or HCOOH (formic acid) as shown in the figure. Experiment does not detect these species, which suggests a short lifetime and therefore high reactivity. Computational techniques allow us to differentiate and investigate these different scenarios. Further hydrogrogenation and interactions of the resulting species with the surface and possible surface defects lead to a large amount of possible intermediates. We show examples of a methione ion (CH₃O⁻) chemisorbed to the surface and physisorbed methanol. To complete the catalytic cycle, methanol is removed from the surface and the active site is recycled by desorption of carbon dioxide and water.

Adsorbed Copper

We have investigated the interaction of copper clusters with the surface of zincite, as the active site of the industrial catalyst is known to involve copper. Although such catalysts have been used for many years the role of copper is still largely unknown.

The following unresolved questions are of interest: i) the nature of the interaction of Cu with the ZnO surface, ii) the electronic state of the active copper sites (0, +1, +2), iii) the surface morphology of the catalytically active Cu clusters — (111), (110) or (10-11)-like.

We have attempted to address these issues by investigating the adsorption of a single Cu ion in different charge states. Our calculations show that Cu⁺ and Cu²⁺ ions are ideal anchor sites. Larger clusters have then been built up using the single Cu ion as a seed.

As a promising example we show the embedding of a Cu₂⁺ cluster (Fig 6) anchored on the (0001)-Zn terminated surface of zincite as compared to the gas phase geometrhythm shown in Fig 7.

Summary

The application of computational methods to such complex materials and their catalytic activity clearly demonstrates the power of the solid-state embedding scheme available in ChemShell. A paper giving further details on the catalytic cycle has recently been published in Angew. Chem. Int. Ed., 2001, 40, p 4437-4440.

Figure 1: The QM/MM methodology allows us to study the relative reactivity of different sites.

Within the framework of QUASI, Norsk Hydro has studied the catalytical abatement of nitrogen oxides and in particular NOx using metal-exchanged zeolites. Cu exchanged ZSM-5 is among the most active materials for the ambient temperature treatment of the off-gas (230-250°C) in nitric acid production. Therefore it was chosen as a good starting point to gain a more detailed understanding of the reaction mechanism which so far has been limited.

Figure 2: N₂O adsorption on M₇ and Z₆ sites.

Figure 3: Catalytic cycle of N₂O decomposition on 12 Cu sites in ZSM-5, energies in kcal/mol.

Figure 4: The effect of the zeolite environment on TS can be elucidated by using the QM/MM method.

Figure 5: The Catalytic Cycle - From CO₂ to Methanol

Figure 6: Cu²⁺ cluster embedded on the (0001)-Zn surface.

Figure 7: Cu²⁺ gas phase cluster