Caught in the act – modelling how a biological catalyst works

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Essentially all of the multitude of biochemical reactions in a cell depend on enzymes to make them 'go'. Dissecting how these biological catalysts work will be vital to understanding biological processes at the molecular level, and also promises technological benefits in the form of new drugs, genetic analysis and catalytic processes. Central to enzyme catalysis is the nebulous 'transition state' of a chemical reaction, in which bonds are partly formed and broken. Biologists have theorized for many years that enzymes are able to recognise and stabilize transition states, and that this stabilization is at the heart of enzyme catalysis. However, transition states are extremely unstable and short-lived, making it impossible to study them directly in systems as large and complex as enzymes. The challenge is to analyse the groups and interactions involved in a biological reaction 'as it happens' within the protein structure of the enzyme. Now quantum chemical modelling on the CSAR T3E has provided a detailed picture of a reaction in an important enzyme, showing at the atomic level how transition state stabilization is achieved[1].

Para-hydroxybenzoate hydroxylase (PHBH) is an important enzyme in the microbial biodegradation of a wide variety of aromatic chemicals, including pollutants and lignin, a major component of wood and so among the most abundant of all biopolymers. PHBH acts by oxygenating its substrates (adding a hydroxyl (OH) group to the aromatic ring), and is a key member of an important class of oxygenase enzymes. Its mechanism has been investigated in a collaboration between computational chemists at the School of Chemistry, University of Bristol, and biochemists and toxicologists at Wageningen University, The Netherlands. Using the computational power of the CSAR T3E it has been possible to model the vital reaction step in the enzyme.

The reaction was modelled starting from a protein structure determined by X-ray crystallography. Using a technique combining quantum mechanics calculations with a simpler ('molecular mechanics') description of the protein, it was possible to model how the bonds break and form, and how the structure of the enzyme and the reacting groups change during the reaction[1].

The results showed that a specific interaction with the enzyme is found only at the transition state. This has the effect of stabilizing the transition state relative to the reactants, lowering the barrier to reaction. A hydrogen bond is formed between a group in the enzyme (the backbone carbonyl of a proline amino acid residue) and the hydroxyl group as it is transferred onto the substrate. The active site of the enzyme is exquisitely well organized to stabilize the transition state, in a way that was not at all obvious until the reaction was modelled. The calculations indicate that this interaction lowers the barrier by a catalytically significant amount. The results also appear to agree well with biochemical experiments[2]. What is particularly exciting is that this catalytic motif seems to be a common feature of this family of enzymes, so the finding may be useful in understanding their biodegradation processes more generally[1,3].

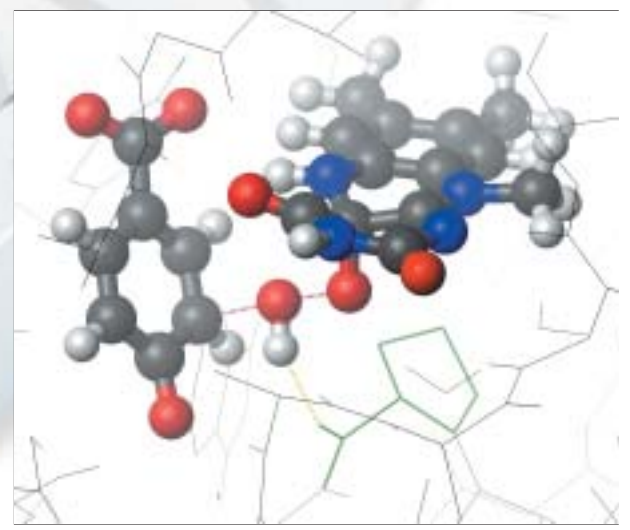

Figure 1: How a biological reaction happens: this picture shows the transition state in the enzyme para-hydroxybenzoate hydroxylase, as found by modelling. An OH group (centre) is transferred from a cofactor (right) to the substrate (left) (reacting groups shown as balls and sticks), and is stabilized by an interaction with a key group in the enzyme (shown in green).

Biological oxygenation reactions are the focus of a lot of current research, both from the point of view of understanding the challenging chemistry involved, and with a view to practical applications of biocatalysts. These computational results show the potential of high-

level modelling for analysing the fascinating and little understood mechanisms of enzyme catalysis.

References

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MSc in Applied Numerical Computing
http://www.maths.man.ac.uk/DeptWeb/MScCourses/NA/NewNAMSc.html
The Departments of Mathematics at the University of Manchester and UMIST jointly run an MSc in Applied Numerical Computing that provides training in the use and development of reliable numerical methods and corresponding software. The programme covers the underlying mathematical ideas and techniques, scientific and high-performance numerical programming (including MPI and OpenMP), the use and design of mathematical software, and options in a number of application areas. The course involves both taught work and a dissertation. It is supported by EPSRC and industrial partners.

MSc in Advanced Computer Science
http://www.cs.man.ac.uk/Study_subweb/Postgrad/ACS-CS/syllabus/acs/acs.html *&*
MSc in Computational Science
http://www.cs.man.ac.uk/Study_subweb/Postgrad/cpn.asp
Both of these courses are taught by the internationally renowned Centre for Novel Computing within the Department of Computer Science, and are supported by industrial partners. The MSc in Computational Science is aimed at graduates in the Physical Sciences, Engineering and Mathematics who have an understanding of the role of differential equations in the modelling of physical phenomena. The course concentrates on the high-performance computational aspects of such modelling and simulation, including algorithmic aspects, visualization, the development of software and the use of massively parallel machines for fast simulation.

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