specific binding was demonstrated and it promises to give considerable insight into the requirements for optimal catalysis. Another area in which the organic chemical approach has made enormous contributions to our understanding of enzymes is that of stereochemistry; D. Arigoni (ETH, Zurich) described an elegant series of studies of biological methylation reactions using S-adenosyl methionine labelled with a chiral methyl group (—CHDT).

F. M. Richards (Yale University) described computations of the solvent-accessible surface area of proteins; contrary to earlier generalisations, the surface of a protein is made up of polar and non-polar groups in roughly equal proportions. Richards showed that calculations of changes in surface area can be used to estimate 'hydrophobic' interactions, and that they could form the basis of a program which searched for optimal helix–helix contacts, and which worked well for myoglobin—an encouraging step towards an algorithm for protein folding. He also pointed out that calculations of the packing density of atoms in a protein lead to a 'solid-like' picture of the interior of a protein. This raised the question of flexibility in proteins which was taken up by a number of other speakers throughout the meeting. D. M. Blow (Imperial College, London) discussed crystallographic evidence for large scale flexibility in some proteins, particularly Huber's work on trypsinogen and his own on tyrosyl tRNA synthetase, in which about a third of the subunit fails to give rise to any interpretable electron density. K. Wüthrich (ETH, Zürich) and R. J. P. Williams (University of Oxford) drew attention to NMR evidence for mobility in proteins, principally at the level of single residues. It seems clear that proteins in general are more flexible than the 'solid-like' description implies, although the degree of flexibility varies substantially, not only from one protein to another but within one protein—as exemplified by pancreatic trypsin inhibitor. As pointed out by Wüthrich, this protein is both rigid, in that several peptide NH protons fail to exchange with the solvent on a timescale of years, and flexible, in that the aromatic rings of its tyrosine residues are able to 'flip' through 180° at rates of the order of $10^3\,s^{-1}$. The possibility that flexibility is in some way essential to catalysis was discussed both by Williams and also by B. Vallee (Harvard University) in describing his studies of arsanilazo-tyrosine 248 carboxypeptidase. Optical absorption, circular dichroism and resonance Raman spectroscopy were used to obtain structural information on the environment of the 'probe', which could then be related to individual kinetic steps in catalysis.

Turning to substrate binding, C-I. Brändén (Uppsala) described crystallographic work on liver alcohol dehydrogenase, including studies of a ternary complex, enzyme.NAD^+.*p*-bromobenzyl alcohol. In this enzyme, the substrate binds at the bottom of a very deep pocket, lined exclusively with hydrophobic residues, where it coordinates to the zinc atom—the only specific enzyme–substrate interaction that is apparent, thus explaining the very broad specificity of the enzyme. Brändén reported that it is very difficult to say from the crystal structures why substrates bind 2–3 orders of magnitude more tightly in the presence of coenzyme; a subtle change in the electronic structure of the zinc may be involved. H. Gutfreund (University of Bristol) described transient-state kinetic studies of the alcohol dehydrogenase reaction, presenting evidence for proton release accompanying the binding of NAD^+. This proton may well originate from a 'charge relay' system, comprising Asp 293–His 151–Ser 48–(water or alcohol)–zinc, at the active site. An interesting, though as yet unexplained, generalisation noted by Brändén is that in almost all enzymes having a parallel β-sheet structure, the C-terminal part of the sheet contains an anion binding site; in dehydrogenases the pyrophosphate of the coenzyme binds here, in carboxypeptidase the carboxylate of the substrate, and in rhodanese a thiocyanate ion.

Several other speakers took up the question of the specificity of binding in a pharmacological context; G. C. K. Roberts (National Institute for Medical Research, London) discussed the origins of the very tight binding of inhibitors to dihydrofolate reductase, emphasising the role of conformational changes, while M. Halsey (Clinical Research Centre, London) described studies of the binding of general anaesthetics to haemoglobin. T. Blundell (Birkbeck College, London) showed how the combination of the crystal structure with studies of modified insulins makes it possible to define those regions of the molecule which most probably interact with the receptor.

The reactivities and pK_a values of side chains on enzymes can be markedly altered from those of the free amino acids, and this can make a significant contribution to the observed rate enhancement. D. C. Phillips (University of Oxford) and Williams described a combined onslaught, by crystallography and NMR, on lysozyme, asking whether one could predict the reactivity of pK_a of a side chain from its environment as revealed by crystallography. While the exchange rate of the indole NH protons of the tryptophan residues, for example, correlated well with their solvent accessibility, this was not the case for iodination of the tyrosine residues—the most readily iodinated tyrosine was neither the most solvent accessible nor the one with the most 'normal' pK_a.

Perhaps the most remarkable example of a special environment for a side chain of an enzyme was described by B-M. Sjoberg (Stockholm). Ribonucleotide reductase contains a stable free radical, which is most probably involved in the activity of the enzyme, and which is formed on the side chain of a tyrosine residue, the spin density being located on carbons 1, 3 and 5 of the aromatic ring. The stability of such a radical during purification and handling of the protein is really quite extraordinary.

In his summary, Lipscomb noted that, though we are fairly sure we understand the general principles governing the behaviour of enzymes, we do not know exactly how things work in any individual case. This clearly applies not only to catalytic activity but also to the details of specificity and reactivity. The fact that precise chemical questions can be asked about such systems, if not yet answered, is a mark of the progress that has been made, but theoretical advances will be required before we can properly relate structure and energetics. □

A hundred years ago

On Monday afternoon a powerful shock of earthquake was felt in the island of Jersey. It was so strong as to cause houses to totter and bells to ring. Its course was from east to west. There was at the time a heavy gale from the south-west in the English Channel. At 11.55 A.M. the same day a shock, lasting about four seconds, was felt at Eastern Alderney. No doubt it was the same earthquake which was felt at Brighton, Blackheath, Fareham, and St. Leonards, as reported in yesterday's *Times*, and at Paris, Havre, and Rouen, as stated by the *Times* Paris correspondent. Mr. Dobson, writing to us from the Royal Victoria Hospital, Netley, Southampton, states that the first shock occurred there at seven minutes to twelve o'clock exactly, and lasted about five or six seconds. It was sufficiently strong to cause the door to shake with some violence, and many objects in the room continued to vibrate for a considerable time.

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