# Biochemical Reactions and Molecular Recognition

Professor Chris Easton

One theme of our research involves the analysis of chemical reactions, particularly those occurring in biochemical systems. Results of these studies are being exploited to develop new synthetic methods and to produce physiologically active compounds with potential as pharmaceuticals. The other main field of research is in the area of supramolecular chemistry and molecular recognition, and involves the design and synthesis of molecular hosts tailored to form inclusion complexes with specific guests. Applications of this chemistry in the development of catalysts, molecular reactors, and photochemical and thermal switches are being pursued.

Highlights of our recent results include the development of:
(i) enzyme inhibitors to regulate the biosynthesis of peptide hormones;
(ii) methods to quantify and predict the susceptibility of amino acids and peptides to free-radical degradation;
(iii) oxidation-resistant amino acids and peptides;
(iv) a prototype molecular ratchet and molecular reactors to control the regioselectivity of electrophilic aromatic substitution and carbon-carbon bond forming reactions; and
(v) novel spectroscopic techniques to analyse melamine-urea-formaldehyde and related resins.

Personnel highlights in 2003 included the graduation of PhD students H. Onagi and S.B. McNabb, and the submission of a PhD thesis by M. Gebara–Coghlan and an MPhil thesis by P.G. Dumanski. H. Onagi was awarded a Postdoctoral Fellowship at Scripps Research Institute and S.B. McNabb a Japan Society for the Promotion of Science Postdoctoral Fellowship. M. Gebara–Coghlan and P.G. Dumanski took up positions with Therapeutic Goods Administration and Environment Australia. A.J. Herlt joined us as a highly skilled technical officer. M.M. Cieslinski was awarded prizes for her presentations at the 19th RACI Organic Chemistry Conference and the RACI NSW Organic Chemistry Group's 24th Annual One-Day Symposium, and L. Barr received an award to present a lecture at the Southern Highlands Conference on Heterocyclic Chemistry. B.J.W. Barratt received the Jim O'Donnell International Travel Award of the RACI and gave an invited lecture at the Gordon Conference on Free Radicals.

## Amino Acid and Peptide Free Radicals and Synthesis

Secondary metabolism of amino acids and peptides frequently gives rise to unusual products that would not be expected on the basis of laboratory precedent. This has prompted studies of the fundamental free radical reactions that may be involved. Consequently methods to assess the susceptibility of amino acids and peptides to radical degradation have been developed, and radical-resistant amino acids and peptides have been designed. Free radical reactions are associated with enzyme catalysis and a range of pathological and physiological conditions. Results of our studies therefore have potential in regulating biochemical processes and treating human diseases. Accordingly we are exploiting the results of our research to develop inhibitors of peptidylglycine α-amidating monooxygenase, for regulating the biosynthesis of mammalian peptide hormones and treating disease states associated with the over-production of these hormones. We are also developing prohormones to address hormone deficiencies. Other results are being applied to the synthesis of novel amino acids and peptides. *(with B.J.W. Barratt, Y.-C. Tsai, L.Y.F. Chow, A.C. Cruickshank, A.J. Herlt, I. Li, N.A. Lorimer, S.B. McNabb, A.J. Mortimer, L. Radom, J.S. Simpson, Z.I. Watts, and M.J. Davies [Heart Research Inst.,*

*Sydney], A. Rauk [U. Calgary, Canada], A. Wright, M. Taylor [ANUTECH Pty Ltd], [Business ACT])*

## Supramolecular Chemistry and Molecular Recognition

This work exploits cyclodextrins as the basis for the construction of molecular hosts and involves the preassembly of molecules to:
(i) alter their behaviour and properties;
(ii) produce materials for chemical processing; and
(iii) construct molecular devices.
Our early work in this area resulted in pharmaceutical formulations that are in everyday clinical use worldwide. In more recent studies modified cyclodextrins are being developed and exploited as molecular scaffolds for the construction of catalysts, molecular switches, and photochemical devices, and as templates to control the regio- and stereo-selectivity of reactions of included guest molecules. We have been able to design and prepare modified cyclodextrin hosts that display increased molecular recognition on binding of guest molecules. By attaching reactive groups to cyclodextrins it has also been possible to produce catalysts with applications in chemical process technology. Another application of cyclodextrins involves their use to control the assembly of the components of chemical reactions, to facilitate the reactions and alter the outcomes. The cyclodextrins thereby act as reaction vessels, but at the molecular level. In this regard, we have developed demonstration systems to alter by more than 4000 times the ratio of indigo and indirubin produced in competing condensation reactions and to reverse the regioselectivity of nitrile oxide cycloaddition processes. The latter reactions are also markedly accelerated compared to the analogous reactions in free solution. We have also been exploring the synthesis of cyclodextrin rotaxanes, catenanes, knots and daisy chains of various topologies. Where these have more than one ground state conformation, and the different states can be accessed using external stimuli, they form the basis of molecular devices such as ratchets and motors, temperature and light sensors, photochemical frequency switches and molecular tweezers. Crystal structures of cyclodextrin host-guest complexes and rotaxanes show that these may be designed to exploit the cyclodextrins as insulators of molecular filaments formed by the guests. This has potential, for example, in the development of microelectronic systems, where the guests form conducting wires only in one direction. *(with L. Barr, M.M. Cieslinski, R. Dawson, P.G. Dumanski, A.J. Herlt, N.A. Lorimer, H. Onagi, M.-H. San and J.S. Simpson, and S.F. Lincoln, J.S. Locke, B.L. May [U. Adelaide], G.W. Simpson [CSIRO Molecular Science, Melbourne], R. Faulkner [Australian Vinyls Pty Ltd, Melbourne])*

## Other Collaborative Research

Another collaboration involves studies of the structure of melamine-urea-formaldehyde resins, and the search for alternative reagents and improved processes. We are also investigating the use of nitrile oxides in the stereocontrolled synthesis of polyfunctional molecules, particularly in order to develop a synthesis of the triol pharmacophore of the antioxidant scymnol. Other biochemical molecular recognition processes are also being studied, including the design and development of compounds to inhibit and stimulate ion-flux through calcium ion channels. *(with P.A. Coghlan, M. Gebara–Coghlan, M. Nairn, A. Philbrook, J. K. Robinson, and J. Altin [Lipotek Pty Ltd], J.M. Broadbent [McFarlane Laboratories Pty Ltd, Melbourne], A. Dulhunty, M. Casarotto [JCSMR, ANU], N. Dunlop, G. Ryan [Orica Ltd and the UnIChe program], A. Ferrante, A. Poulos [Adelaide Medical Centre for Women and Children], G.W. Simpson [CSIRO Molecular Science, Melbourne])*

**http://rsc.anu.edu.au/research/easton.php**