Preface

We have been fascinated by enzymes since we were students in the 1960s and the 1990s. In the early days the mantra – "there's nothing magic about enzymes" – simply added to the fascination. Of course "*like magic*" in these postromantic times simply means (to quote the Oxford English Dictionary) "*without any apparent explanation; with incredible rapidity*": simple maybe, but it's hard to think of a more intriguing starting point for a research career. And we still would like to understand – as well as possible – how enzymes work.

At one level we can already explain enzyme catalysis: what an enzyme does is bind, and so stabilize selectively, the transition state for its specific reaction. But our current level of understanding fails the more severe, practical test – the creation of new systems with catalytic efficiencies to rival those of natural enzymes. As researchers, mostly in chemistry but at defining points in biochemistry departments, our approach has been experimental: applying the methods of contemporary organic chemistry, enzymology and more recently molecular biology, to develop systems that model or – better – mimic enzymes: and in particular their catalytic efficiency.

We settled on the title of this book only after some discussion, and some definitions are in order. An enzyme *model* simply models an aspect, sometimes more than one aspect, of the chemistry of a particular enzyme. At the next level, we expect enzyme *mimics* to catalyze reactions of substrates free in solution, by mechanisms that are demonstrably enzyme-like, involving both binding and catalysis. However, to call the most successful systems artificial enzymes seems no longer appropriate. As protein chemistry develops in countless new directions, existing protein structures can provide appropriate starting points for new catalysts, which are not exactly artificial. We propose the term model enzyme. Everyone expects that their model aeroplane should at least fly! And

From Enzyme Models to Model Enzymes
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ribozymes (Chapter 5), which qualify as successful systems, are serious candidates to have been Nature's models for all enzymes.

Our first intention was to write a short student text, introducing the area of enzyme models for readers from the many disciplines that offer a basic grounding in chemistry and biochemistry. The project evolved as we wrote, reflecting the ways the subject is developing, to take advantage of the availability of new and powerful biological methodologies. The resulting text is still short, and still intended to be accessible to the same readership: but attempts in a final chapter to put recent developments in the perspective of the major body of work that has gone before: to trace the underlying logic of these developments, and to identify the lessons to be learned. So that as we understand and come to terms with the limitations of classical approaches to "design-based" model systems, we learn how to complement – and perhaps even replace – them with new and emerging methods: based on the successful development of enzymes by natural evolution, and using iterative approaches to make the best use of design and selection. It is in the nature of science that the very recent work we review may well be superseded by even more remarkable results in this fast moving field.

We have been helped, encouraged and inspired by our students, colleagues and teachers, too numerous to mention, from all over the world: but we must acknowledge our special debts of gratitude to the late Bill Jencks, who could turn physical organic chemistry into biological magic.

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