CHEMICAL REVIEWS

Volume 97, Number 5 July/August 1997

Introduction: Molecular Recognition

"Molecular recognition", which became a popular phrase in the early 1980s, covers a set of phenomena that may be more precisely but less economically described as being controlled by specific noncovalent interactions. Such phenomena are crucial in biological systems, and much modern chemical research is motivated by the prospect that molecular recognition by design could lead to new technologies. Although "molecular recognition" is perhaps no longer at the cutting edge of chemical phraseology, I have used this term for the topic of this special issue of *Chemical Reviews* because of deficiencies in such alternatives as "host−guest chemistry", "supramolecular chemistry", and "self-assembly". These latter phrases are limited to intermolecular processes (the first two by definition, and the third by convention), while "recognition" can apply to both inter- and intramolecular phenomena. The importance of intramolecular recognition is clear to anyone who has pondered protein folding (see the review by Robertson and Murphy).

Noncovalently controlled phenomena are poorly understood. No one, for example, can design from first principles a small molecule that will bind tightly and specifically to a pocket in a protein of known structure, despite widespread interest in "rational drug design". Similarly, it remains impossible to predict a detailed protein folding pattern from a knowledge of amino acid sequence, even though enormous effort has been directed toward this goal.

Why such enduring mystery? One possibility is that we have not yet fully defined the repertoire of noncovalent interactions that underlie complex recognition events. Everyone knows that cations and anions attract one another, but the attraction between ions and the quadrupole of an aromatic ring has only recently come to be appreciated at the level of organic and biological chemistry (see the review by Ma and Dougherty). There may be other sources of attraction that are presently undervalued. A second intellectual difficulty with molecular recognition stems from our poor appreciation of the ways in which individual noncovalent forces compete with or reinforce one another in complex systems. Hydrogen bonds provide a case in point. Hydrogen bonds between uncharged groups are typically favored by <5 kcal/mol in nonpolar environments (e.g., an organic solvent, or the interior of a folded protein). The cost of converting a single *anti* butane unit to *gauche* is about 0.8 kcal/mol. Thus, the benefit of a single hydrogen bond can easily be undone by torsional strain. Chemists and biochemists delight in pointing out hydrogen bonds in high-resolution structures of their favorite molecules, but it is virtually impossible to perceive competing torsional strain in these structures; therefore, it is never obvious from visual inspection how much a given hydrogen bond, and its attendant conformational exigencies, contribute to the stability of an observed structure.

This issue of *Chemical Reviews* should be of interest to both the novice and the specialist in molecular recognition, because of the breadth of topics and approaches covered in the articles. The range of phenomena under the rubric of molecular recognition is so wide that no researcher active in one part of this field can stay current on developments in the many other parts. Therefore, any specialist is likely to find a great deal of new material in these reviews. The novice will find not only a wealth of new information, but also, and more importantly, a broad perspective on the goals currently under pursuit in laboratories that focus on noncovalently controlled phenomena.

Three major themes are manifested in the reviews collected here: (1) elucidation of the role of noncovalent interactions in biological contexts; (2) application of molecular recognition principles to practical goals; and (3) extrapolation from biological examples. This last theme stems from a marriage of the chemist's intrinsic desire to contrive new structures and functions, and a growing appreciation of Nature's remarkable uses of molecules. Many chemists view Life as an example of the sophistication that may be achieved in chemical systems. From this perspective, biology becomes an inspiration in the search for new chemistry, a motivation that is distinct from the elucidation of authentic biological processes at the chemical level (now fashionably referred to as "chemical biology"). The extrapolative mode of thinking leads chemists to try to devise complex new molecular functions, and very often this molecular-level engineering involves noncovalent interactions. Such efforts are frequently justified in terms of some distant practical goal, but most practitioners of such research, and those who read their papers, are drawn to the work because it is, well, cool.

Few of the articles in this issue fall solely into one of the three categories listed above, but one of the three themes is dominant in most articles. Elucida-

S0009-2665(97)00328-2 CCC: $28.00

tion of molecular recognition in biological contexts is covered in the reviews of Stites (protein−protein interactions), Robertson and Murphy (protein conformational stability), Davidson and Regen (interlipid interactions in membranes), Mader and Bartlett (mechanisms of protein-based catalysis, i.e., recognition of transition states), and Ma and Dougherty (cation−π interactions in model systems and in biological systems). The review on cyclodextrin complexation by Connors also belongs in this group, since the cyclodextrins are often viewed as model systems for more complex biological receptors. Connors focuses on the sources of cyclodextrin−ligand affinity, rather than on the design of new cyclodextrin-based agents.

Practical application of molecular recognition is represented by the reviews of Babine and Bender (protein-targeted drug design), Kool (DNA-targeted drug design), Chow and Bogdan (RNA-targeted drug design), and de Silva et al. (fluorescent sensor design). The extrapolative approach is dominant in the reviews by Diederich et al. (steroid complexation), Schmidtchen and Berger (anion complexation), Conn and Rebek (hydrogen bond-mediated construction of receptors), Linton and Hamilton (metal−ligand bond-mediated construction of receptors), Zeng and Zimmerman (dendrimer-based receptors and self-assembly of dendrimers), and Ikeda and Shinkai (calixarene-based receptors).

These reviews cover much of the best work on noncovalently controlled phenomena from around the world. Despite all of this excellent science, however, we are still far from being able to exert intellectual control over most such phenomena. Perhaps, then, the greatest value of this collection lies in the gaps in our knowledge implicitly revealed, and the prospect that astute readers will be inspired to fill those gaps.

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