plexes cationic ligands. This spherand also constitutes the substrate binding site of a series of enzyme mimics[2,3] whose molecular recognition features have been analyzed in this laboratory.[4] The rationale behind Cram's design of the spherand was to provide a binding site that was optimally "preorganized" for substrate binding (i.e., one in which very little energy would be spent in conformational reorganization to accommodate the substrate). We probe this design concept at the molecular level by using (1) molecular mechanics analysis to study the energetics of the complexation process, and (2) molecular dynamics simulation to investigate the degree of structural rigidity of the spherand.

Our molecular mechanics results show that the energy change of the spherand during complexation is generally quite small, especially when compared to the binding energy of the cation. In addition, we have found that the spherand undergoes very little structural change upon complexation of the cation. In agreement with the experimental results, some ligands are found to "perch" above the cyclic urea oxygens of the spherand, whereas others "nest" inside. It is the latter situation that exhibits the largest conformational change in the macrocycle.

Superposition of "snapshots" of the spherand from the molecular dynamics simulation also illustrates the structural rigidity of the macrocycle. This, together with the molecular mechanics results, illustrates the structural "preorganization" of the spherand for the cation ligands.

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Simulations of Receptor Activation Mechanisms As a Guide for Drug Design

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Dramatic new developments in the fields of molecular and structural biology offer new leads and exciting prospects for the design of therapeutic agents and other molecules with predetermined biological activities. Most important in this respect is the insight that the new findings have provided on details of structure function relationships for many key proteins, including soluble enzymes and even some membrane-bound systems. However, practical methods for the design of drugs and other biologically active molecules are hampered by the nearly complete lack of structural information, at the detailed atomic level, for molecules of membrane-bound receptors and effectors. This lack of information makes the design effort dependent on inferences from the molecular pharmacology of drug-receptor interactions. Insofar as part of this interaction depends on the process of recognition of a small molecule by a protein, these design efforts can further be aided by models based on the biochemistry of enzyme-substrate interactions.

In its ability to combine disparate insights in a rigorous frame at the molecular level, theoretical chemistry is irreplaceable in the quest for understanding the chemical basis for the action of various ligands in biological systems. Such understanding is essential for the success of any method of molecular design, for it relates the molecular properties of the ligands to specific chemical reactivities that determine their interactions in biological systems. The set of chemical reactivities that determine the selectivity of the ligands for specific receptors constitutes the molecular determinants for recognition of the ligand. Another, possibly different, set of reactivities could be most important for triggering the consequence of the binding that leads to the response.

A strategy for the design of biologically active ligands with selective affinity can begin with a search for molecular determinants for recognition of a series of ligands with known affinities for a receptor. Chemical intuition and theoretical insight can be used to infer on the chemical nature of the species that are most likely to match these reactivities and to form stable, discriminant interactions with the ligands. Such species are candidates for the receptor sites that recognize and bind the ligands, and proteins containing such putative recognition sites can be identified in the Protein Data Bank. When the formation of complexes with ligands is simulated computationally with the methods of theoretical chemistry, important insight can be gained concerning the likely consequences of the complexation. Such consequences could constitute a triggering mechanism for receptor activation. The inferences are a basis for design of receptor activating agents (i.e., agonists), as opposed to receptor blocking agents (i.e., antagonists). Our ongoing work on the molecular pharmacology of receptors for the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) illustrates such a complex strategy for heuristic design, based on the molecular details of drug–receptor interactions and including the consideration of whole protein environments in simulations of receptor-triggering mechanisms.