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Molecular recognition, most often mediated by specific protein-protein or protein-nucleic acid interactions, is a key component in nearly all biological processes. Three-dimensional structural analyses have revealed that the interfaces that occur between biological macromolecules typically display significant geometric and electrostatic complementarity, tightly packed hydrophobic clusters, and a number of ordered interfacial water molecules. In spite of the wealth of three-dimensional structural information presently available, it is also clearly evident that structural information alone is insufficient to define the chemical principles which underlie specific high-affinity association between biological macromolecules. As an example, alanine scanning mutagenesis studies of the interaction of peptide hormones with the extracellular domains of their cognate receptors has shown that while some residues are critical to recognition, others play only a marginal role in conferring binding energy and specificity. More recently, NMR relaxation measurements made on a number of interacting systems has challenged the conventional notion that complex formation is universally accompanied by a large positive enthalpy owing to the spatial restriction of sidechains that occurs upon complexation.

Through advances in methodology and instrumentation over the past ten years, multinuclear multidimensional NMR spectroscopy has emerged as powerful tool for studying macromolecular structure and function in solution. The overall goal of the research underway in the Hinck laboratory is directed toward applying the powerful analytical capabilities NMR as a tool for studying protein-protein and protein-nucleic acid interactions in solution. Research efforts in this laboratory are directed toward a) using novel NMR methods for mapping the interaction surface between two interacting macromolecules and b) investigating the molecular basis of their association by studying the molecular dynamics of backbone and sidechain atoms in protein interfaces, by analyzing perturbations in the pK_as of ionizable groups which occur upon complex formation, and by investigating the role of hydrogen bonds and ordered solvent molecules in facilitating specific high affinity protein-protein association. There are two different model systems that we are presently studying: (1) The three major isoforms of transforming growth factor-beta (TGF-b1, -b2, and -b3) and their interactions with the ligand binding domains of the TGF-b type II (TbR2), type IIB (TbR2b), and type I (TbR1) signaling receptors, and (2) Signal recognition particle protein SRP-19 and its interaction with helix 6 and helix 8 domains of SRP RNA.