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Abstract:

Catalytic RNAs, or ribozymes, catalyze a variety of chemical reactions, primarily at phosphorus centers. Our laboratory is interested in learning how RNAs, with their highly charged backbone and limited chemical diversity, can assemble into a biologically active catalysts. The hepatitis delta virus ribozyme is a small hydrolytic ribozyme that uses a cytosine to facilitate general acid-base catalysis. Solution kinetic studies suggest that C75 has a histidine-like function with a pKa perturbed to near neutrality. Using Raman crystallography, we are able to directly measure the pKa of this active site residue. Group I introns are large, multidomain ribozymes that position magnesium ions to catalyze two phosphotransesterification reactions that resulting in self-splicing. We have determined the structure of a bacteriophage intron alone and in the presence of a protein splicing factor. These studies reveal an unexpectedly complex binding pocket for guanosine substrate, suggest a roll for substrate in organizing the ribozyme active site and demonstrate how a protein subunit can take over structural roles previously played by RNA.