Structural basis for Diels-Alder ribozyme catalyzed carbon-carbon bond formation

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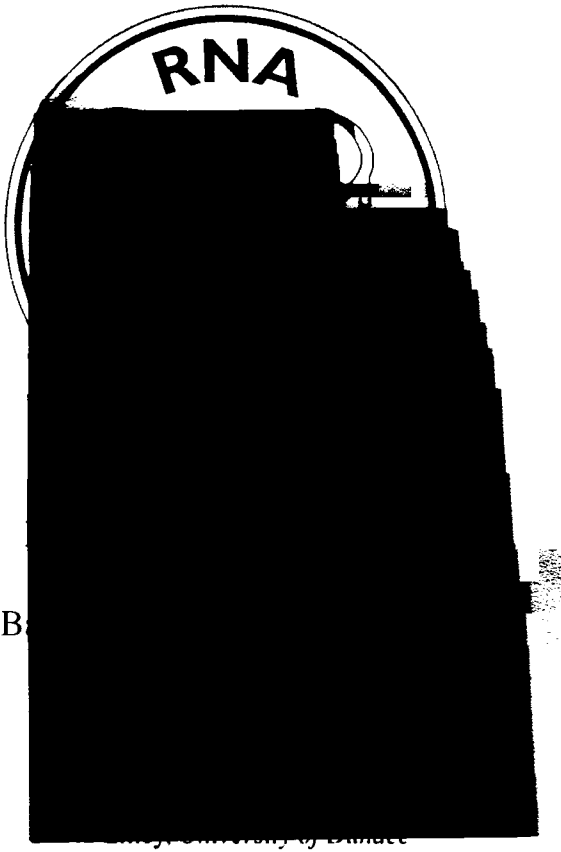
The natural ribozymes catalyze a narrow range of chemical reactions namely phosphodiester transfer and peptide bond formation. *In vitro* selection, however, have demonstrated that ribozymes are capable of accelerating a much broader reaction spectrum. For instance, ribozyme can catalyze enantioselective carbon-carbon bond formation by Diels-Alder reaction between maleimide and anthracene molecules. Nevertheless, the majority of structural efforts have focused on the natural ribozymes. To obtain a comprehensive picture of the catalytic abilities and limitations of RNA, we have determined the 3.0 and 3.5 Å crystal structures of the 49 nt Diels-Alder ribozyme in free form and bound with the reaction product. The RNA adopts λ-shaped nested pseudoknot architecture different from the known ribozyme structures. A hydrophobic pocket located in the center of the structure shows precise shape-complementarity to the reaction product. RNA folding and product binding are dictated by extensive stacking and hydrogen-bonding, while stereoselection is governed by the shape of the catalytic pocket. Catalysis is apparently achieved by a combination of proximity, shape complementarity, and electronic effects. Similar structures of the free and bound ribozymes suggest pre-formation of the catalytic pocket. Modeling shows that the pocket can accommodate bound substrates and transition state, therefore the reaction does not require major conformational changes. Diels-Alder ribozyme, though equipped with a much less varied arsenal of functional groups than proteins, shows remarkable structural parallel with the independently evolved catalytic pocket of the protein catalyzing similar reaction.

RNA 2005

THE TENTH ANNUAL MEETING OF THE RNA SOCIETY



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