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# Ribozymes

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The structural molecular biology of ribozymes took another great leap forward during the past two years. Before ribozymes were discovered in the early 1980s, all enzymes were thought to be proteins. No detailed structural information on ribozymes became available until 1994. Now, within the past two years, near atomic resolution crystal structures are available for almost all of the known ribozymes. The latest additions include ribonuclease P, group I intron structures, the ribosome (the peptidyl transferase appears to be a ribozyme) and several smaller ribozymes, including a Diels–Alderase, the *glmS* ribozyme and a new hammerhead ribozyme structure that reconciles 12 years of discord. Although not all ribozymes are metalloenzymes, acid-base catalysis appears to be a universal property shared by all ribozymes as well as many of their protein cousins.

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## Introduction

Ribozymes are enzymes whose catalytic centers are composed entirely of RNA and therefore do not require proteins for catalysis (although many exist naturally as RNA–protein complexes). Their discovery in the early 1980s provided a potential logical escape from the conundrum that plagues evolutionary molecular biology: which came first, information-encoding nucleic acids or proteins — including the enzymes needed to replicate nucleic acids? If RNA can do both, it is a potential self-replicase and the 'RNA world' hypothesis is based on the assumption that pre-biotic self-replicating molecules were composed of RNA.

Perhaps the most important (apparent) ribozyme is the ribosome, as the 23S RNA appears to comprise most if not all of the active site [1,2]; near atomic resolution structures of the *Escherichia coli* [3••] and *Thermus thermophilus* [4••,5••] 70S ribosomes have now provided us with many new structural insights. However, the main focus of this review will be to survey the many advances made in understanding the structural basis of ribozyme catalysis in other RNA systems. In reviewing these advances, it seems noteworthy that many of the most important ones emerged from laboratories that are not primarily known as structural biology research groups, but rather are laboratories that focus primarily on the RNA molecules themselves. Examples include Harry Noller's ribosome group, Norm Pace's RNase P group, Tom Cech's intron group and Scott Strobel's RNA chemistry group. The blurring of such distinctions will probably be a growing trend in the future of macromolecular structural studies and is an encouraging development.

All ribozymes were believed originally to be metalloenzymes, requiring $Mg^{2+}$ or other divalent metal ions for both folding and catalysis. A 'two-metal mechanism' had been proposed [6] in which hydrated $Mg^{2+}$ ions played the roles of general acids and bases. This prediction appears to have been correct for the group I intron (the specific context of the original proposal), as has now been revealed by Stahley and Strobel [7••] (described below), but perhaps the most striking result is that it does not generalize to all ribozyme systems. Acid-base catalysis appears to be a catalytic strategy so fundamental that it occurs in both protein and RNA enzymes; in many cases, it seems that the RNA itself, rather than acting as a passive scaffold for metal ion binding, is an active participant in acid-base catalysis in the sense that nucleotide functional groups, rather than metal complexes, often mimic the roles that amino acids play in the active sites of protein enzymes. Several of the small self-cleaving RNAs as a consequence do not strictly require divalent metal ions for catalysis [8] and no divalent metal ions have yet been observed in the active site of the peptidyl transferase, the ribozyme that is embedded in the ribosome.

## Ribonuclease P

Ribonuclease P (RNase P) was the first true RNA enzyme identified [9]. An RNA–protein complex, the catalytic subunit of bacterial RNase P is composed entirely of RNA (and it is thought that this is the case with the eukaryotic version as well). It processes precursor tRNAs and other RNAs required for cellular metabolism. Although structural fragments of RNase P have been previously elucidated, two structures of the entire catalytic RNA subunit finally appeared simultaneously in 2005, one from *Thermotoga maritima* at 3.85 Å resolution [10••] and the other from *Bacillus stearothermophilus* at 3.3 Å resolution [11••]. Both ribozyme structures were

obtained in the absence of bound substrate and protein non-catalytic subunit, so active site interactions between enzyme and substrate can only be inferred. The *B. stearothermophilus* fold is depicted in Figure 1. A model for the structure of eukaryotic RNase P has also been proposed based on these crystal structures [12].

## Group I intron

The group I intron was the first catalytic RNA discovered [13] and, in 1986, it was demonstrated to be a true enzyme [14]. Four group I intron crystal structures are now available, two of which fall into the current review period. Following publication of the *Azoarcus* [15] and *Tetrahymena* [16] group I intron ribozyme structures in 2004, two particularly noteworthy structures have appeared. In January 2005, the structure of a phage *Twort* group I ribozyme–product complex [17•] appeared (Figure 2a), followed in September by a second structure of the *Azoarcus* group I intron ribozyme [7••], which revealed evidence of a two-metal-ion mechanism in ribozyme catalysis (Figure 2b,c).

The folds of the various group I introns are quite similar [18•], permitting comparisons between molecular species. The first *Azoarcus* structure was in a pre-catalytic state, in which both exons (the substrate of the reaction in which adjacent exons are spliced as the intron excises itself) were present. The *Tetrahymena* group I intron structure represents a state in which the 3′-terminal ω-guanosine and a metal ion are present in the active site. The newer structures complement these two states with an enzyme–product complex, and a complex in which all substrate, ribozyme functional groups and predicted metal ions are present in the active site. These are observed as a cluster of two metal ions, each of which is coordinated to no less than five phosphate or ribose oxygens in the active site. The *Twort* ribozyme in addition reveals how the peripheral insertions that are characteristic of phage introns form a ring that completely envelops the active site (Figure 2a).

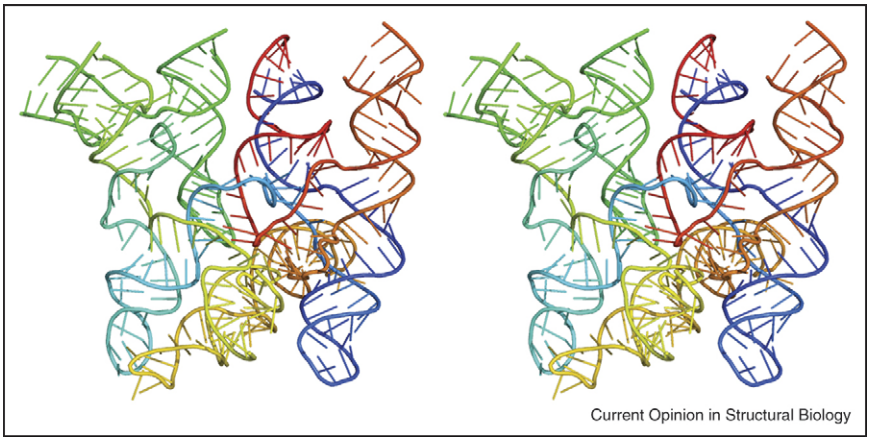
## A Diels–Alderase ribozyme

Possibly every crystallographer's favorite reaction from organic chemistry is the Diels–Alder reaction, as it reveals how orbital symmetry dictates reactivity between a diene and a dienophile. Proteins and RNAs have both been evolved *in vitro* that enzymatically catalyze this reaction. It is remarkable that RNA, originally thought to be incapable of enzymatic catalysis and then thought to catalyze primarily phosphodiester reactions, is capable of catalyzing carbon–carbon bond formation. The protein Diels–Alderase is a catalytic antibody whose structure is known. We now have the structure of a Diels–Alder ribozyme in both the unbound and enzyme–product complex states (Figure 3a), revealing that the ribozyme uses a combination of proximity, spatial complementarity and electronic effects (Figure 3b) to activate stereoselective catalysis, reminiscent of the protein Diels–Alderase [19•].

## The *glmS* ribozyme

The *glmS* ribozyme is a recently discovered ribozyme that is unique in the world of naturally occurring ribozymes in two respects. First, it is a ribozyme that is also a riboswitch. Second, the regulatory effector of the ribozyme, glucosamine-6-phosphate (GlcN6P), is actually a functional group that binds to the ribozyme active site and participates in the acid-base catalysis of RNA self-cleavage. The *glmS* ribozyme is derived from a self-cleaving RNA sequence found in the 5′-untranslated region (5′-UTR) of the *glmS* message; it cleaves itself, inactivating the message, when the cofactor GlcN6P binds. GlcN6P production is thus regulated in many Gram-positive bacteria via this ribozyme-mediated negative-feedback mechanism.

**Figure 1**




Stereo view of the fold of the RNase P RNA, as determined from *B. stearothermophilus*. The 5′ end of the molecule is in blue and the 3′ end is in red.



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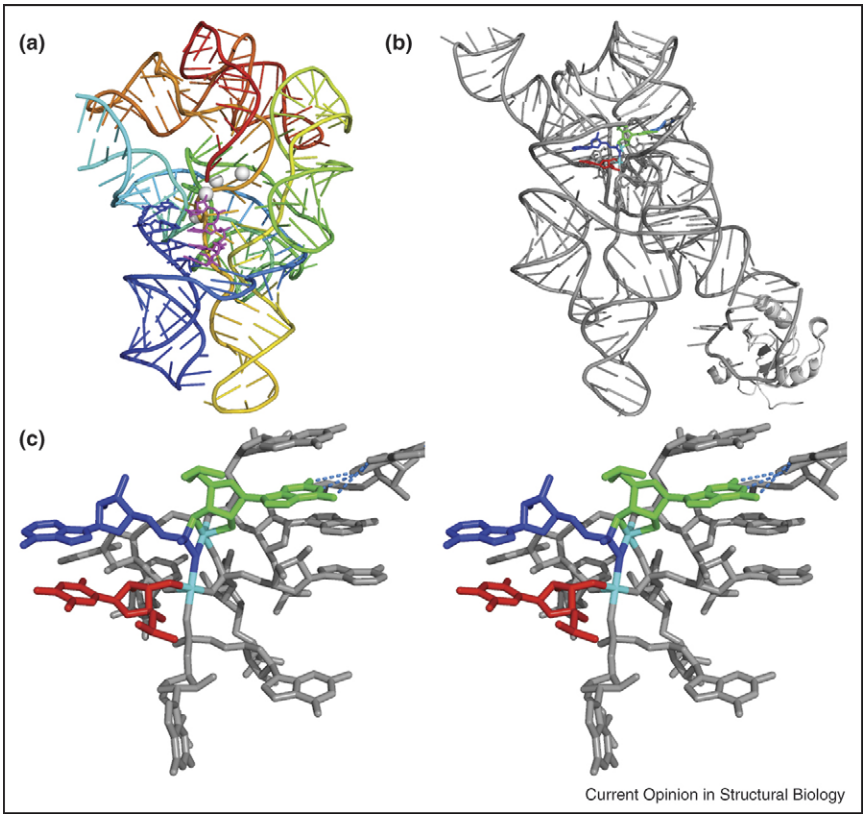
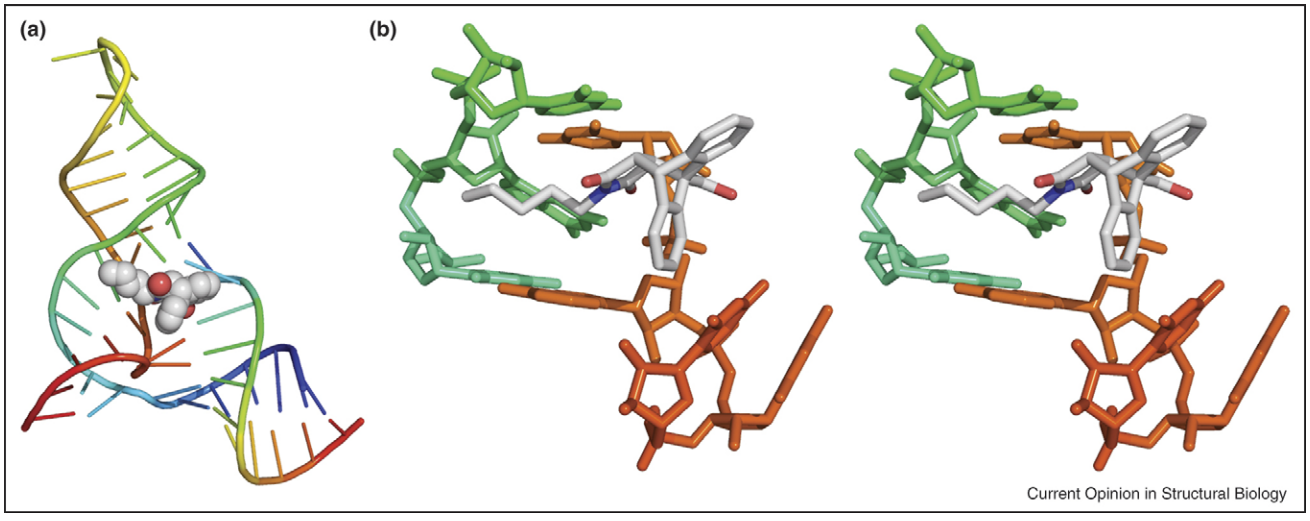
**Figure 2**




Group I intron structures. **(a)** Cartoon representation of the fold of the *Twort* group I intron. The 5′ end is dark blue and the 3′ end is red. Several observed $Mg^{2+}$ ions are depicted as grey spheres. **(b)** The previously reported *Azoarcus* group I intron structure (grey cartoon) shares many structural features with the *Twort* group I intron. The new *Azoarcus* structure reveals interactions between two $Mg^{2+}$ ions (cyan) at the active site and the 5′ end of the 3′ intron (blue), the 3′ end of the 5′ intron (red) and the ω-guanosine cofactor (green). **(c)** Close-up stereo view of the active site in (b). Hydrogen bonds between the residues (including the ω-guanosine) that comprise the cofactor-binding site are shown as light blue dotted lines.

**Figure 3**




Cartoon representation of the fold of the Diels–Alder ribozyme **(a)**. The 5′ end is colored blue and the 3′ end of the RNA is colored red, along with a space-filled representation of the bound adduct. **(b)** Close-up stereo view of the active site (same color scheme), depicting aromatic stacking and other interactions between the ribozyme and the Diels–Alder adduct.



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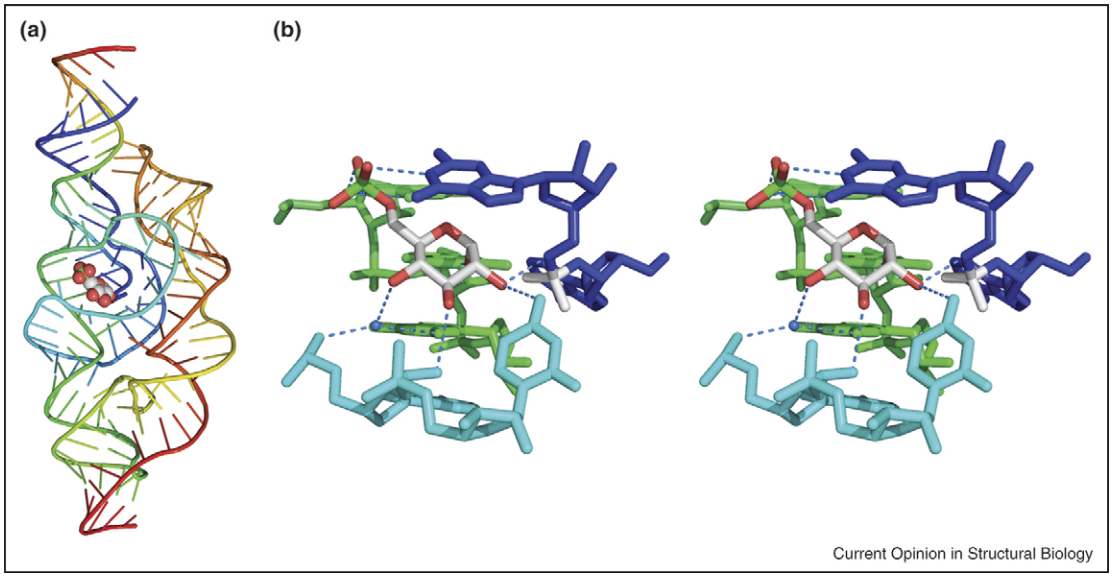
The structure of the *glmS* ribozyme is thus of particular interest both as a riboswitch and as an unusual catalytic RNA. As it is known to occur only in Gram-positive bacteria, it is also a potential antibiotic target. The structure of the *glmS* ribozyme is discussed in the context of riboswitches in an accompanying review by Ferré-D'Amaré and colleagues in this issue. Here, I focus on the structure from the point of view of catalysis.

Several structures of the *glmS* ribozyme are now available. The first set, solved by Klein and Ferré-D'Amaré [20••], comprises four ribozyme structures derived from *Thermoanaerobacter tengcongensis*, including 2′-$NH_2$- and 2′-deoxy-modified cleavage site structures (PDB codes 2GCS and 2H0S), an unmodified cleavage–product structure (PDB code 2GCV) without cofactor bound and a complex structure in which Gly6P, a highly homologous structural analogue of GlcN6P that is a competitive inhibitor of the ribozyme, is bound to the 2′-deoxy-modified *glmS* ribozyme (PDB code 2H0Z). An additional structure from *Bacillus anthracis*, solved by Cochrane, Lipchock and Strobel [21•], complements the original structures, as it was obtained with GlcN6P bound. Together, they provide a fairly complete structural analysis of how a riboswitch-ribozyme is activated.

The fold of the *glmS* ribozyme is that of a double pseudoknot, as depicted in Figure 4a. The cofactor-binding site is positioned immediately adjacent to the scissile phosphate, as seen in Figure 4b, a close-up stereo view in which several interactions between the RNA, the cofactor and the scissile phosphate are depicted. Because the inhibitor Gly6P differs from GlcN6P in only one non-hydrogen atom, it was proposed that most, if not all, of the interactions seen in the complex structure are representative of those with which the ribozyme binds its natural cofactor, GlcN6P. The *B. anthracis* structure indeed validates this claim. The differences are fairly subtle, but include the presence of a hydrogen bond to the C4-OH of the cofactor. The C2-$NH_2$ amine in GlcN6P and the corresponding C2-OH in Gly6P are positioned within hydrogen-bonding distance of the 5′-oxygen leaving group, together suggesting that GlcN6P is the general acid catalytic component of the self-cleavage reaction. G40 (G33 in the *B. anthracis* structure) in turn is positioned such that its N1 is within hydrogen-bonding distance of the nucleophilic 2′-OH at the ribozyme cleavage site, suggesting that G40 may be the general base component (similar to what is seen in the hammerhead ribozyme structure, described below).

Structures of the uncleaved RNA in the absence of the cofactor reveal that the substrate is positioned for in-line attack in a pre-formed active site. Binding of the cofactor then initiates the cleavage reaction by providing the acidic component to the catalyst. From a structural perspective, it does not appear that any metal ions are involved directly in the chemistry of catalysis.

**Figure 4**




Cartoon representation of the fold of the *glmS* ribozyme **(a)**. The 5′ end of each RNA strand is colored blue and the 3′ end of each strand is colored red, along with a space-filled representation of the bound cofactor. **(b)** Close-up stereo view of the active site (same color scheme), depicting the scissile phosphate as white atoms at the junction of the first two residues of the substrate strand (dark blue). Several stabilizing interactions with the inhibitor cofactor Gly6P and the RNA and solvent are indicated with blue dotted lines. The active cofactor GlcN6P differs from Gly6P in that the C2-OH is replaced with C2-$NH_2$, making the cofactor a general acid catalyst that potentially supplies the leaving-group oxygen with a required proton.



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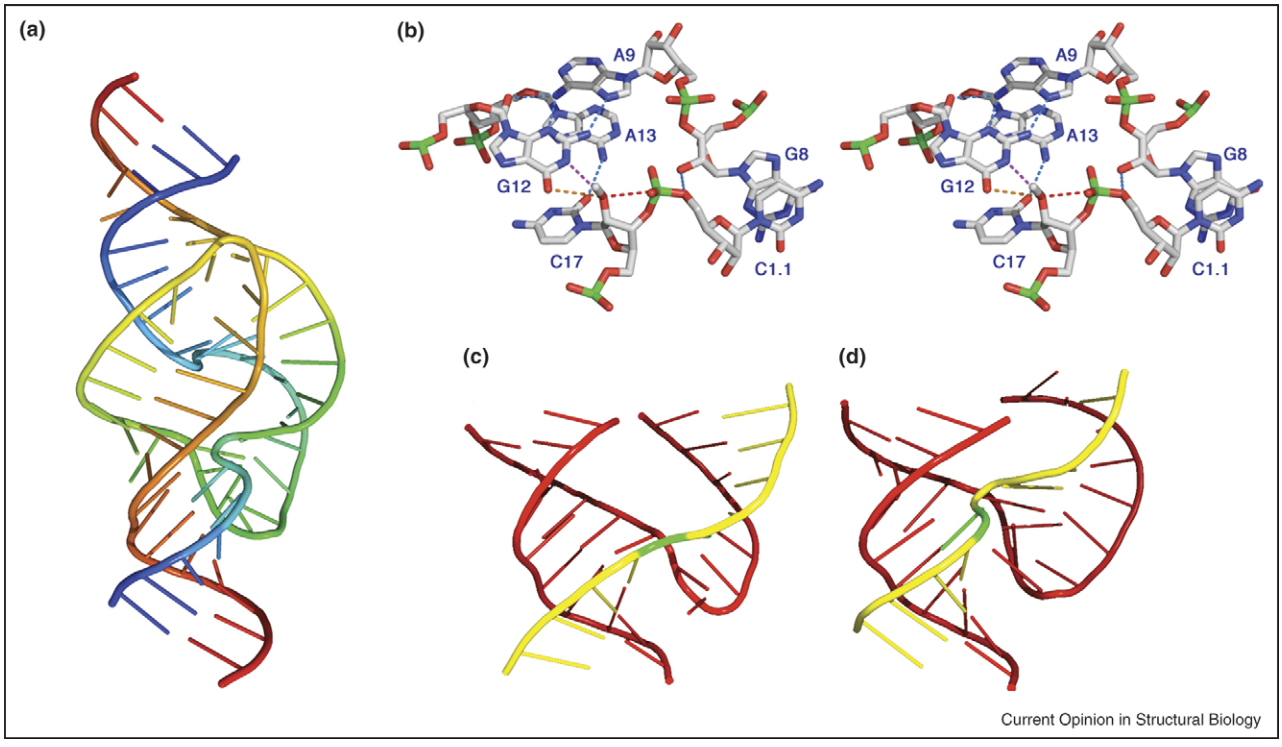
## The hammerhead ribozyme

Twenty years after the discovery of the hammerhead ribozyme [22] and twelve years after the original minimal hammerhead ribozyme structures appeared [23,24], the crystal structure of a natural, full-length hammerhead ribozyme that includes an only recently appreciated set of distal tertiary contacts has emerged [25••]. A growing body of biochemical evidence [26•,27•] suggested that the minimal hammerhead structures, which lacked these contacts, required a substantial conformational change before cleavage could take place. By contrast, unmodified minimal hammerhead ribozymes were observed to be catalytically active in the original crystals. These results appeared to be irreconcilable and led to much discord.

This paradox was resolved with the structure of the full-length hammerhead ribozyme (Figure 5a): the nucleophile is now found to be in line with the scissile phosphodiester bond; two invariant residues, G12 and G8, are positioned for base and acid catalysis (Figure 5b); and a third invariant residue, G5, positions the cleavage site nucleotide in the catalytic pocket. Two phosphates predicted to be close enough to be bridged by a divalent metal ion are in fact 4.3 Å apart and several additional troublesome biochemical observations are for the first time readily explained. Remarkably, when one compares the common sequence elements in the minimal and full-length hammerhead structures (Figure 5c,d), the global folds are quite similar and comparatively few low energy-barrier torsion angle conformational changes permit the cleavage site residues to rearrange into a manifestly active state. The distal tertiary contacts, absent in the minimal hammerhead construct (Figure 5c), stabilize in the full-length structure (Figure 5d) what must exist as only an evanescent fluctuation in the minimal hammerhead. This explains why cleavage was observable in crystals of the minimal hammerhead; the necessary conformational change could occur, transiently, within the confines of the crystal lattice, albeit inefficiently compared to the full-length ribozyme (which is estimated to be up to 1000-fold more catalytically active).

Several questions remain outstanding. Are divalent metal ions directly (i.e. chemically) involved in catalysis? (No $Mg^{2+}$ or $Mn^{2+}$ ions have yet been observed crystallographically to bridge the A9 and scissile phosphates, and the acid and base components of catalysis are accounted for.) Is the cleavage reaction microscopically reversible or does the ligation reaction proceed via a slightly different mechanistic pathway? (Perhaps G8 unpairs from C3 to catalyze ligation.) Are the distal contacts part of a conformational switch that regulates self-cleavage *in vivo* during virusoid replication? It is an attractive assumption, but requires experimental evidence.

**Figure 5**




The hammerhead ribozyme. **(a)** The global fold of the full-length hammerhead. **(b)** Stereo view of the active site. Comparison of the structural elements that the **(c)** minimal hammerhead and **(d)** full-length hammerhead share in common reveals that the newer full-length structure is framed in a familiar fold.



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## Conclusions

Until about 25 years ago, the question of how RNA might realize its catalytic potential did not even exist, apart from within the thoughts of Francis Crick and like-minded visionaries. It was not until 1994 that the first ribozyme crystal structure emerged and 12 years hence we now have an almost complete set of ribozyme crystal structures, including the peptidyl transferase. Universal principles are now beginning to emerge. It was once assumed that all ribozymes were obligate metalloenzymes, but it appears that the peptidyl transferase center and the *glmS*, VS, hairpin and hammerhead ribozymes all employ RNA moieties (and a metabolite cofactor in the case of *glmS*) to effect acid-base catalysis. Ribozymes are thus not merely a passive scaffold to which metal ions bind, but have instead been shown to be, in many cases, as sophisticated in their evolutionary design as their protein counterparts.

## Update

Very recently, a new ribozyme structure [28••] has been solved that offers a glimpse [29••] of how RNA may have catalyzed regiospecific RNA fragment assembly as a prerequisite to an 'RNA world' inhabited by self-replicating ribozymes. A 2.6 Å crystal structure of an *in vitro* evolved ligase ribozyme that catalyzes assembly of two RNA fragments reveals tertiary contacts that stabilize a flexible stem of the ribozyme at the ligation site, where an essential $Mg^{2+}$ ion coordinates three phosphates. The structure indicates that transition-state stabilization and general base catalysis are enzymatic strategies that readily arise as a consequence of *in vitro* evolution and artificial selection, suggesting that natural selection and evolution may have done likewise.

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