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PERSPECTIVE

Maximizing RNA folding rates: A balancing act

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ABSTRACT

Large ribozymes typically require very long times to refold into their active conformation in vitro, because the RNA is easily trapped in metastable misfolded structures. Theoretical models show that the probability of misfolding is reduced when local and long-range interactions in the RNA are balanced. Using the folding kinetics of the *Tetrahymena* ribozyme as an example, we propose that folding rates are maximized when the free energies of forming independent domains are similar to each other. A prediction is that the folding pathway of the ribozyme can be reversed by inverting the relative stability of the tertiary domains. This result suggests strategies for optimizing ribozyme sequences for therapeutics and structural studies.

Keywords: group I intron; ribozyme; RNA folding; RNA structure

INTRODUCTION

Ribozymes have been useful models for many aspects of RNA structure and function, setting the stage for probing the molecular details of even more complex systems. One example is the assembly of ribozymes into their active or native conformations from unfolded RNA. Recent work on the folding kinetics of ribozymes has extended the results of experiments conducted in the 1970s, namely that small hairpins form with time constants (τ) of 10 to 100 μs, and that tertiary interactions can form in 10–100 ms under conditions in which they are stable, such as in the presence of Mg^{2+} (reviewed in Draper, 1996; Brion & Westhof, 1997). However, it has been widely observed that many RNAs fold much more slowly in vitro ($\tau = 100$ s), because of competition with alternative conformations whose stabilities are similar to that of the native structure (Fresco et al., 1966; Uhlenbeck, 1995; Treiber & Williamson, 1999).

Large ribozymes typically contain several domains of tertiary structure, and one domain is often more stable than the others. Here, we argue that disparity in the folding energetics of different segments of the ribozyme structure favors the formation of long-lived (and partially misfolded) intermediates. Conversely, folding times are shortest when the tertiary interactions in each domain are energetically balanced.

FOLDING KINETICS OF LARGE RIBOZYMES

The well-studied *Tetrahymena* group I ribozyme can be divided into two principal domains of tertiary interactions and several peripheral helical regions (Fig. 1; Kim & Cech, 1987; Michel & Westhof, 1990). The folded structure of the domain containing paired (P) regions P4, P5, and P6 is stabilized by tertiary interactions between a three-helix junction (P5abc) on one side and helices P4 and P6 on the other (Cate et al., 1996). This domain is independently stable (Murphy & Cech, 1993) and folds at a rate of 1 s^{-1} at low ionic strength (Sclavi et al., 1998). In contrast, the region containing P3, P7, and P9, which is much less stable and not able to fold independently (Celander & Cech, 1991; Doherty & Doudna, 1997), requires minutes or hours to form in vitro due to misfolding of nucleotides in P3 (Pan & Woodson, 1998). Thus, the formation of active ribozyme is limited by slow reorganization of residues in the P3–P9 domain, which make up half of the catalytic core (Zarrinkar & Williamson, 1994, 1996; Sclavi et al., 1998).

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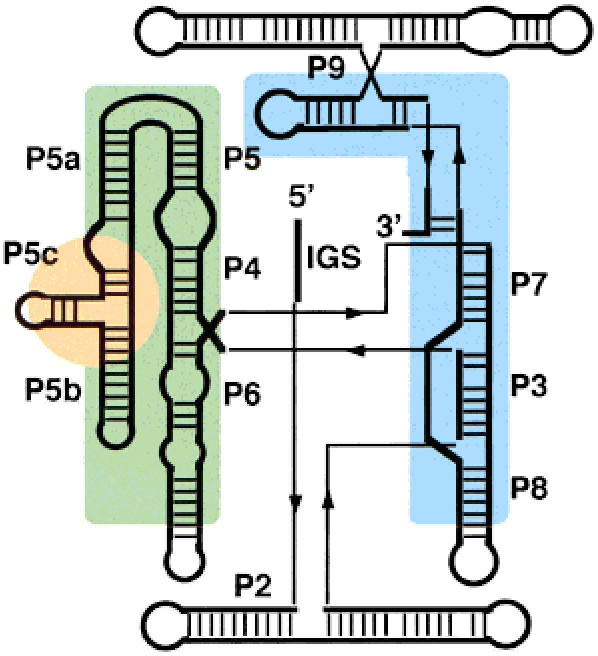
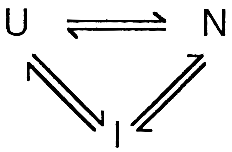


FIGURE 1. Structure of the *Tetrahymena* ribozyme. Adapted from Cech et al. (1994). Paired (P) regions are numbered 5′ to 3′. The domain containing P4–P6 (green) is more stable and folds more rapidly than the P3–P9 domain (blue). Tertiary interactions between a three-helix junction (P5a, P5b, and P5c) define a stable subdomain within the P4–P6 RNA.

Similarly, the tertiary structure of *Bacillus subtilis* RNase P ribozyme can be divided into two domains (Pan, 1995; Loria & Pan, 1996). The catalytic domain alone folds with a time constant of ~150 ms in vitro (Fang et al., 1999). However, a second domain that is required for specific recognition of pre-tRNA substrates folds much more slowly and increases the folding time for the active wild-type ribozyme to ~2–4 min by populating metastable intermediates (Zarrinkar et al., 1996; Pan & Sosnick, 1997).

KINETIC PARTITIONING AND TOPOLOGICAL FRUSTRATION

Because the folding of large RNAs often involves metastable intermediates, it is useful to ask whether the probability that an RNA will fold rapidly can be predicted from the properties of the native structure. We base our analysis of the folding process on a kinetic partitioning mechanism (KPM) (Thirumalai & Woodson, 1996) that is derived from free energy landscape models initially developed to describe protein folding (Dill & Chan, 1997). As sketched in Scheme I, this model proposes that a fraction of the RNA population folds rapidly to the native state (N) without forming long-lived intermediates, while the remainder of the molecules become trapped in metastable intermediates that contain some non-native interactions (I). The transition from these misfolded intermediates to the native RNA structure is slow, because the RNA must at least partially unfold before the active or native structure of the RNA is formed (Pan et al., 1997). The need to partially unfold the RNA is consistent with observations that slow conformational transitions are accelerated by raising the temperature or by adding denaturants (Pan et al., 1997; Pan & Sosnick, 1997; Rook et al., 1998).



SCHEME 1. Three-state folding mechanism.

A prediction of this model is that folding rates will be optimal only when the interactions formed during the folding process are compatible with a unique structure, and the competition between native and non-native interactions is minimized. In large ribozymes, the structures of independent folding domains are largely determined by nucleotides that are relatively close to each other in the primary sequence. By contrast, the assembly of these domains into a functional structure re-

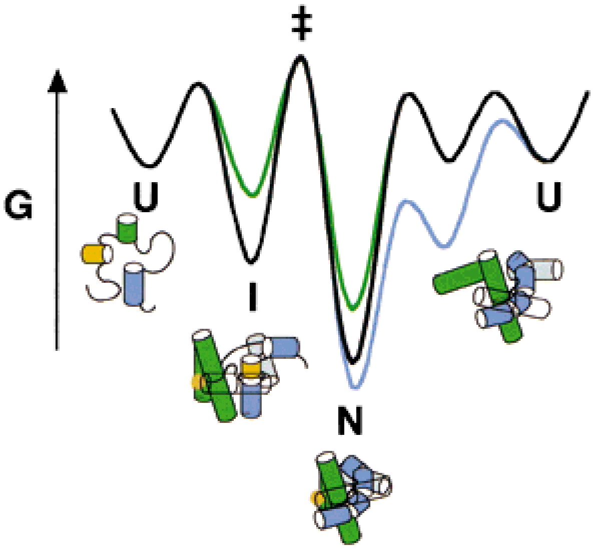


FIGURE 2. Kinetic partitioning mechanism for folding of the *Tetrahymena* ribozyme. The unfolded (U) RNA is represented by an ensemble of structures in the absence of $MgCl_2$. The majority of the population folds *via* intermediates (I) that are stabilized by native interactions in the P4–P6 domain (green cylinders) and misfolded structures in P3 (yellow). The slow transition from I to the native structure (N) requires partial or complete unfolding of the RNA, corresponding to a large transition state energy ($\Delta G_{I\ddagger}$). A small fraction of the wild-type RNA folds rapidly. Stabilization of P3 by the mutation U273 to A enables ~80% of the RNA to form N without populating the I states (right). Mutations that change the energy levels of I and N may also change the position of the transition state, which we do not indicate here for simplicity. The transition state itself is a collection of related structures.

quires tertiary interactions involving nucleotides that are far apart in the sequence. This distinction between local and long-range interactions is captured by hierarchical models of RNA structure (Brion & Westhof, 1997). In general, there is a greater propensity to form local structures because these are entropically favorable. An example of this is rapid folding of the P5abc subdomain of the *Tetrahymena* ribozyme in the absence of long-range interactions with P2 or with the P3–P9 domain. Local structure is more likely to be stable in RNA than in proteins because the base pairs that define RNA secondary structure are strong relative to tertiary interactions (Banerjee et al., 1993; Herschlag, 1995; Draper, 1996).

The seemingly opposing demands of forming local structure and establishing long-range interactions that define global conformation results in "topological frustration" (Thirumalai & Woodson, 1996). This term, borrowed from condensed matter physics, expresses the inability of individual residues to simultaneously satisfy all energetically favorable interactions with their neighbors (Toulouse, 1977). One example of topological frustration is the competition between two base pairings of the P5c helix, only one of which is compatible with native tertiary interactions in the P5abc subdomain (Wu & Tinoco, 1998). Another example is misfolding of P3, in which the two strands joining P7 and P8 base pair with each other instead of pairing with nucleotides 170 residues upstream to form the native P3 pseudoknot (Pan & Woodson, 1998). The incorrect pairing is kinetically preferred over P3, at least in part because it involves short-range rather than long-range contacts.

If local interactions in one part of the ribozyme dominate the energetic landscape (such as P5abc or mispaired P3), then their premature formation stabilizes intermediate structures and slows down the overall folding rate. Conversely, if interactions throughout the RNA have roughly similar energetics, then the native structure is more likely to form cooperatively and rapidly, with few or no apparent intermediates.

TRANSITION STATES AND THE STABILITY OF DOMAINS

The idea that folding should be most rapid when interactions in the RNA are energetically balanced can be illustrated by considering the folding kinetics of the *Tetrahymena* ribozyme. The overall free energy for forming the native structure from unfolded states, ΔG_{UN}, can be expressed as

$$\Delta G_{UN} \approx \Delta G_{46} + \Delta G_{39} + \Delta G_{interface} - T\Delta S_{interdomain}, \quad (1)$$

where ΔG_{46} and ΔG_{39} are the free energies of folding the P4–P6 and P3–P9 domains, $\Delta G_{interface}$ is the free energy of favorable interdomain interactions (including long-range interactions outside of the catalytic core such as P14), and $T\Delta S_{interdomain}$ takes into account the entropy lost when the orientation of the two domains is fixed. The time constant τ of the transition from I to N is determined by the height of the free energy barrier, $\Delta G_{I\ddagger}$,

$$\tau = \exp\left(\frac{\Delta G_{I\ddagger}}{RT}\right), \quad (2)$$

where $\Delta G_{I\ddagger}$ is the free energy difference between I and the transition state (Fig. 2).

Metastable folding intermediates in RNA are stabilized by many native (as well as some non-native) interactions (Pan & Woodson, 1998; Treiber et al., 1998). Because the transition state is expected to share some features with I and N, changes in $\Delta G_{I\ddagger}$ (due to mutations, for example) may be predicted from changes in the relative free energies of I and N (or U and N for mechanisms not involving I), as demonstrated for the *Tetrahymena* pre-rRNA (Pan et al., 1999). Hence, the transition state energy is proportional to ΔG_{UN}, and $\Delta G_{I\ddagger}$ can be estimated from $\Delta G_{I\ddagger} \approx -\Delta G_{UN}$.

This conclusion is reached by considering that the folded structures of biological macromolecules are stabilized by many noncovalent interactions, which are on the order of a few k_BT (0.5–2 kcal/mol). Because this energy is comparable to the entropy lost when an ordered structure is formed, the folded state is only marginally stable (for the Mg^{2+}-dependent transition of the *Tetrahymena* pre-rRNA, $\Delta G_{UN} \approx 4.5$ kcal/mol $= 7.5$ k_BT). Typical free energy barriers in RNA folding result from the same types of noncovalent interactions. Hence, these barriers are also minimized by compensating enthalpy and entropy changes. Because many of the interactions that stabilize I are native contacts, the free energy penalty for partially unfolding I must scale with the stability of N.

Assuming that $\Delta G_{interface}$ and $\Delta S_{interdomain}$ do not depend on the stabilities of the individual domains and contribute less to the stability of I, then the transition state energy $\Delta G_{I\ddagger} \approx -(\Delta G_{46} + \Delta G_{39})$. It follows from equation (2) that the overall folding time is determined by the relative values of ΔG_{46} and ΔG_{39}. In the limits in which one domain is much more stable than the other,

$$\tau \approx \begin{cases} \exp\left(\frac{-\Delta G_{46}}{RT}\right) \text{ when } \Delta G_{46}/\Delta G_{39} > 1 \\ \exp\left(\frac{-\Delta G_{39}}{RT}\right) \text{ when } \Delta G_{46}/\Delta G_{39} < 1 \end{cases} \quad (3)$$

MAXIMIZING FOLDING RATES BY MODULATING DOMAIN STABILITY

We may now consider three folding regimes in which the relative free energies of forming the P4–P6 and P3–P9 domains vary with respect to one another.

1. $\Delta G_{46}/\Delta G_{39} > 1$. Because the P4–P6 domain is more stable than P3–P9 in the wild-type ribozyme, the

folding pathway is characterized by intermediates in which tertiary interactions within P4–P6 are formed (Celander & Cech, 1991; Zarrinkar & Williamson, 1994; Sclavi et al., 1998) but P3 and P7 are misfolded (Pan & Woodson, 1998; Pan et al., 2000). Let us assume that formation of the native interface between the two domains requires some loosening of interactions within each domain. Because P3 and P7 appear to be disordered and to contain few stable tertiary contacts in the I states, the P3–P9 domain is expected to be more flexible than the P4–P6 domain. Hence, the minimum barrier for the I-to-N transition is expected to be dominated by ΔG_{46}, so that equation (3) reduces to $\tau \geq \exp(\alpha \Delta G_{46})$, where α is a scaling factor that is proportional to $-1/RT$. This estimate for τ neglects contributions from non-native interactions to the stability of I, which moderately increase $\Delta G_{I\ddagger}$ and τ.

This situation corresponds to the left side of the curve in Figure 3, in which the folding time becomes progressively shorter as the stability of the P4–P6 domain is decreased. In a search for fast-folding mutants, Treiber et al. (1998) found that mutations that destabilized tertiary interactions within the P5abc region of the P4–P6 domain increased the folding rate of P3 and P7 up to fivefold at 37 °C. Similarly, mutations that disrupt base pairing between the loops of P5c and P2 increase the overall folding rate of the ribozyme (Pan & Woodson, 1999).

2. $\Delta G_{46}/\Delta G_{39} < 1$. If interactions in the P3–P9 domain are more stable than those in the P4–P6 domain, then according to the reasoning above, we expect the free energy barrier for forming the native structure to be proportional to ΔG_{39}, and $\tau \approx \exp(\alpha \Delta G_{39})$. This situation is illustrated by the right side of the curve in Figure 3. A key prediction of this model is that it should be possible to reverse the order in which the domains fold by introducing mutations that significantly stabilize P3–P9 relative to the P4–P6 domain.

3. $\Delta G_{46}/\Delta G_{39} \approx 1$. Figure 3 shows that the trends above converge when the stabilities of the two domains are roughly equal. Generally, we expect that the folding time, $\tau \approx \exp(2\alpha \Delta G_{39})$ will approach a minimum when $\Delta G_{46} \approx \Delta G_{39}$. We have recently found that a mutation in the P3 helix of the *Tetrahymena* ribozyme increases the stability of the P3–P9 domain so that it folds at similar Mg^{2+} concentrations as the P4–P6 domain (Pan et al., 2000). As predicted by this model, the overall folding rate is increased 10- to 50-fold by this mutation, and the majority of the RNA (~80%) reaches the native state without becoming trapped in metastable intermediates (Fig. 2).

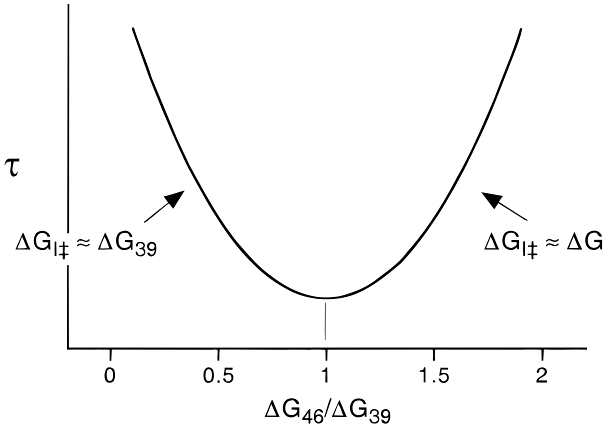


FIGURE 3. Relationship between folding times (τ) and relative domain stabilities ($\Delta G_{46}/\Delta G_{39}$). On the right side of the graph, the minimum kinetic barrier $\Delta G_{I\ddagger}$ is proportional to the stability of the P4–P6 domain, ΔG_{46}. This corresponds to the folding kinetics of the wild-type ribozyme. On the left, the minimum barrier depends on the free energy for folding the P3–P9 domain, ΔG_{39}. The shortest folding times are predicted to occur when these trends converge ($\Delta G_{46}/\Delta G_{39} \sim 1$). The complete curve can be approximated by the sum of the terms in equation (3).

Although the examples above ignore contributions to the transition state energy from interactions at the domain interface, a similar analysis is obtained if the ratio $\Delta G_{46}/\Delta G_{39}$ is compared to $(1 + \beta/\Delta G_{39})$, where $\beta = \Delta G_{interface} - T\Delta S_{interdomain}$. If $\beta > \Delta G_{39}$, then the overall folding rate will be dominated by interdomain interactions and will be less sensitive to the energetics for folding the independent domains. We also acknowledge that the RNA folding problem has been simplified in this analysis, and other factors are likely to influence folding rates. Nonetheless, this model qualitatively accounts for existing folding data on large RNAs.

PROSPECTS FOR THE DESIGN AND EVOLUTION OF RIBOZYMES

This analysis predicts that the folding kinetics of RNAs can be optimized by smoothing out differences in the energetics of local interactions, as illustrated by experiments on the *Tetrahymena* ribozyme. Similar results might also be achieved by adjusting external conditions such as Mg^{2+} concentration (Fang et al., 1999; Pan et al., 1999; Rook et al., 1999). In contrast, overstabilizing local elements of secondary or tertiary structure is predicted to decrease the global folding rate.

The arguments presented in this article also highlight the fact that secondary and tertiary interactions must be compatible for efficient assembly of independent folding domains, as illustrated by the coupling of secondary and tertiary folding in the P5abc RNA and a complex pseudoknot in the *Escherichia coli* α operon (Gluick & Draper, 1994; Wu & Tinoco, 1998). As the helices become increasing stable and rigid, rearrangement of the secondary structure becomes less probable and may impede the formation of tertiary interactions. Thus, optimal folding rates require a balance between secondary and tertiary interactions, an idea that was proposed some time ago by Go (1983) in the context of protein folding.

Many group I ribozymes (and other RNAs) contain structural elaborations that reinforce the central fold (Michel & Westhof, 1990; Westhof et al., 1996). These peripheral "stability elements," such as the P5abc three-helix junction, appear to lengthen the folding time of the *Tetrahymena* ribozyme (Treiber et al., 1998; Pan & Woodson, 1999; Russell & Herschlag, 1999). This differs from the idea that a stable nugget of tertiary structure, which in this case is outside of the structural core, functions as a scaffold upon which the rest of the structure is built. Interestingly, the stabilizing function of the P5abc region is replaced by the protein CYT-18 in group I introns from *Neurospora* mitochondria (Mohr et al., 1992; Caprara et al., 1996). This hints at the possibility that RNA–protein complexes offer the advantage of a more flexible assembly process, in which the RNA–RNA interactions remain fluid until they are solidified by binding of proteins (e.g., see Buchmueller et al., 2000).

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