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Original scientific paper

On the dynamics of some small structural motifs in rRNA upon ligand binding

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Abstract: The present study characterizes using molecular dynamics simulations the behavior of the GAA (1186–1188) hairpin triloops with their closing c–g base pairs in large ribonucleoligand complexes (PDB IDs: 1njn, 1nwy, 1jzx). The relative energies of the motifs in the complexes with respect to that in the reference structure (unbound form of rRNA; PDB ID: 1njp) display the trends that agree with those of the conformational parameters reported in a previous study[1] utilizing the *de novo* pseudotorsional (η,θ) approach. The RNA regions around the actual RNA–ligand contacts, which experience the most substantial conformational changes upon formation of the complexes were identified. The thermodynamic parameters, based on a two-state conformational model of RNA sequences containing 15, 21 and 27 nucleotides in the immediate vicinity of the particular binding sites, were evaluated. From a more structural standpoint, the strain of a triloop, being far from the specific contacts and interacting primarily with other parts of the ribosome, was established as a structural feature which conforms to the trend of the average values of the thermodynamic variables corresponding to the three motifs defined by the 15-, 21- and 27-nucleotide sequences. From a more functional standpoint, RNA–ligand recognition is suggested to be presumably dictated by the types of ligands in the complexes.

Keywords: rRNA; ligand binding; small motifs; molecular dynamics; thermodynamics.

INTRODUCTION

Tertiary structures are of vital importance in providing a structural basis for and support of biological hypotheses. Folded RNA molecules are constructed from extensive networks of interactions between various molecular building blocks, RNA motifs. Hence, knowledge of the structural and functional features of RNA

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motifs is indispensable for understanding the form and stability of the tertiary structure of RNA. In a previous study[1] the conformational differences between hairpin triloops in large ribonucleoligand complexes, induced by ligand binding to an unbound form of rRNA, were extensively explored using a pseudotorsional (η,θ) approach.[2] Even though the differences between the compared structures were detectable using various representations of the RNA structure, such as Cartesian coordinates,[3] standard backbone torsion angles[4] and root-mean-square deviation (RMSD),[5] a reduced representation of RNA conformational space based on pseudotorsions (η,θ) of two virtual bonds of individual nucleotides is more likely to register conformational peculiarities with a higher sensitivity.[6] Two pseudotorsions around these virtual bonds, extending from P to C4' and from C4' to P of the adjacent nucleotide,[7] are η (C4'$_{i-1}$ − P$_i$ − C4'$_i$ − P$_{i+1}$) and θ (P$_i$ − C4'$_i$ − − P$_{i+1}$ − C4'$_{i+1}$).[2] The (η,θ) strategy has been shown to be a useful means of classifying small structural motifs, such as triloops.[1] A more general attempt to correlate the measured η–θ parameters to a single-point, AMBER force-field conformational energies of all the nucleotides in the database was undertaken, but no meaningful relationship was found.[8] Herein, the question of how our previous conformational study[1] of some hairpin triloops (Fig. 1) is lined up with their molecular dynamics (MD) is addressed.

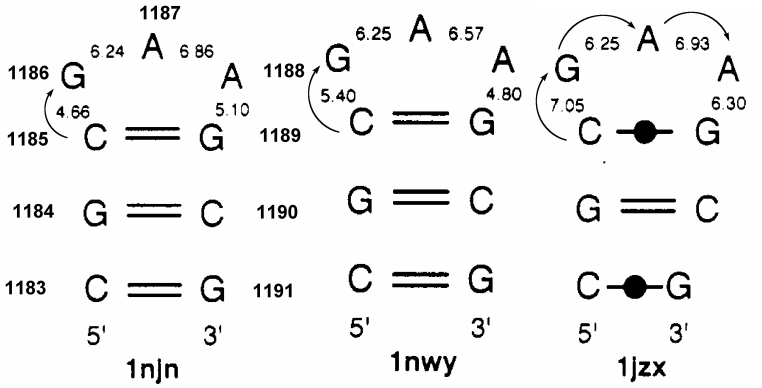

Fig. 1. Two-dimensional representations of the triloop tertiary structures in accordance with the geometric nomenclature of Leontis and Westhof.[9] The symbols are: = – GC *cis* canonical Watson–Crick base pair, –●– – *cis* Watson–Crick/Watson–Crick edge-to-edge basepair, and → – change in strand orientation. The numbers denote the phosphate···phosphate distances in angstroms (Å).

RESULTS AND DISCUSSION

To investigate the conformational differences between the cGAAg (1185– –1189) motifs in the large ribonucleoligand complexes 1njn, 1nwy and 1jzx, with respect to that in the reference structure 1njp, the difference in nucleotide morphologies based on the values of the pseudotorsion angles, η and θ, for two RNA

worms of the same length was previously observed.[1] For a single nucleotide with sequence position *i*, the difference is given by

$$\Delta(\eta,\theta) \equiv \sqrt{(\eta_i^{\mathrm{A}} - \eta_i^{\mathrm{B}})^2 + (\theta_i^{\mathrm{A}} - \theta_i^{\mathrm{B}})^2} \quad (1)$$

where A and B are the two structures being compared. Nucleotides with $\Delta(\eta,\theta) < 25°$ are considered to be structurally similar to each other, while those with $\Delta(\eta,\theta) > 25°$ are not.[6] For the particular motifs in 1njn, 1nwy and 1jzx, the average (av) values of $\Delta(\eta,\theta)$ were 1, 15 and 110°, while the average RMSDs involving all atoms were 0.05, 0.85 and 5.36 Å, respectively. Notably, a near linear relationship between the average RMSD and the average difference in the pseudotorsion angles $\Delta(\eta,\theta)$ was found.[1] In the present work, the trends associated with the structural features are complemented with the dynamics of these motifs.

All the optimization procedures and MD simulations were performed by the Hyperchem molecular modeling system for Windows.[10] As the starting geometries were far from minimum, steepest descent optimizations of the motif structures with an RMS gradient of 0.01 kcal $Å^{-1}$ mol^{-1} were performed before the MD computations. Each optimized structure was subsequently placed in a periodic box of 30×30×30 $Å^3$ containing 892 water molecules associated with a minimum distance of 2.3 Å between solvent and solute atoms. The AMBER force field was chosen with the following options: dielectric (epsilon) = constant, scale factor = 1, 1−4 scale factors – electrostatic = 0.9, van der Waals = 0.9 and cutoffs = none. The MD procedure with several options was specified to simulate molecular movement so that it was possible to observe equilibrium properties and kinetic behavior. 50 picoseconds (1 ps = 1×10^{-12} s) without changing the simulation temperature were chosen as a run time. A time interval of 0.002 ps between evaluations of the total energy and temperature of the system was chosen as the step size. At the start of the run time, atomic velocities are adjusted to give a simulation temperature of 300 K. To stabilize the temperature during the run time, constant temperature simulations with a bath relaxation time of 0.5 ps were performed. In this context, the average kinetic, potential and total energies of the motifs in both the complexes and the free form of RNA (reference structure) were observed. The plots showing the relative, total and potential energies of the motifs in the complexes with respect to that in the reference structure are depicted in Fig. 2. The relative potential energies indicate that the stability order, from the highest to the lowest, of the motifs is: 1njn, 1nwy and 1 jzx. By adding the kinetic energies, the same trend displayed by the "relative total energy *vs.* time" plot is quite clear.

Since sugar puckers and torsion angles are unknown in the 2.5–3 Å resolution range, which is typical for large nucleic acids, it was therefore difficult to study most of the recurrent motifs, such as sharp turns, U-turn, *etc.*[11] A conformational strategy rooted in the pseudotorsion (η,θ) approach was proposed to be

a possible way to bypass the difficulties for small constitutive parts of large RNAs.[1] The agreement between the trends of conformational parameters recently reported[1] and the trends of the MD energies reported herein speaks in favor of the previous proposal.

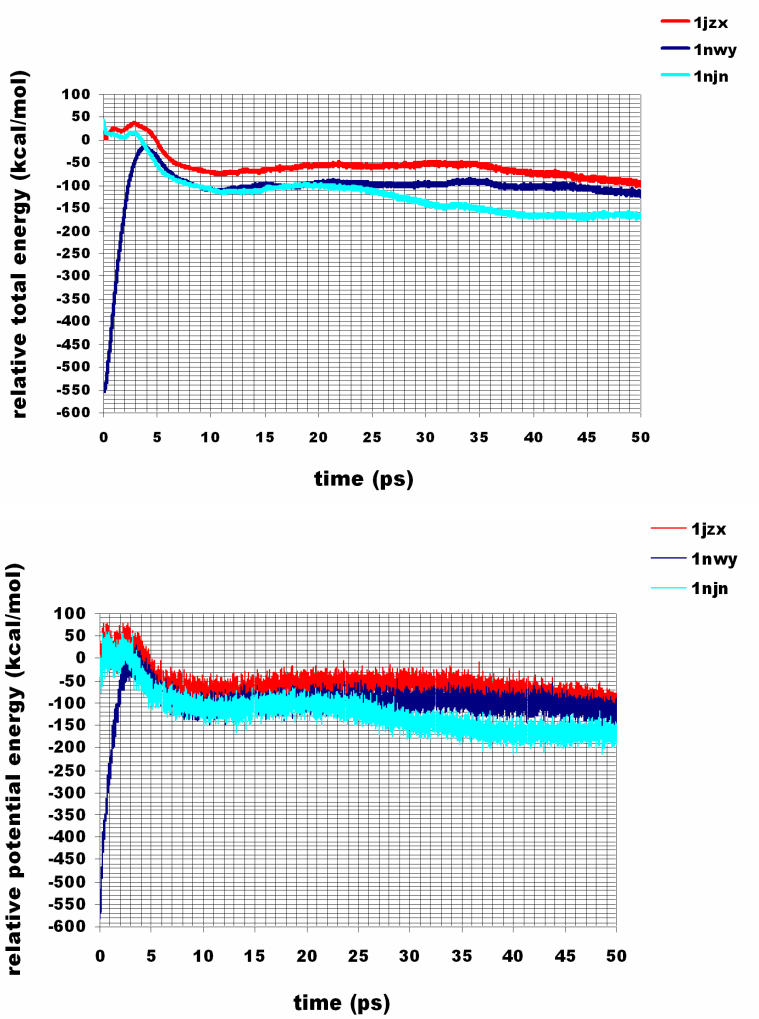

Fig. 2. Relative total and potential energies of the cGAAg (1185–1189) motifs in the complexes (PDB IDs: 1njn, 1nwy, 1jzx) with respect to that in the unbound form of rRNA (PDB ID: 1njp).

The interaction motifs of various hairpin loops were hypothesized as possible targets for the binding of proteins.[12] The indications were primarily related to the extent of loop flexibility. Consequently, the investigations were presumably true for loops having a larger number of nucleotides, such as 4, 5, *etc*. As the local behavior of hairpin triloops was not quite clear, the structural features

induced by the binding of ligands of a number of triloops in rRNA were investigated.[1] In this context, all RNA residues in contact with the ligands and all RNA regions experiencing considerable conformational changes upon ligand binding were identified. As the bound complexes are conceivable as ribosomal states at various stages of translation, the ligands were found to be far (in the range of 20 Å) away from the triloops, interacting primarily with other parts of the ribosome.[1] For the complexes under study, 1njn, 1nwy and 1jzx, the RNA residues with the highest values of $\Delta(\eta,\theta)$ in contact with the ligands are A2581, A1354 and A764 respectively.[1] The "$\Delta(\eta,\theta)$ *vs.* sequence position" plot, taken in the immediate vicinity of the A2581, A1354 and A764 residues in the complexes, shows their corresponding $\Delta(\eta,\theta)$ values to be 232.1, 45.8 and 47.1°, respectively (Figs. 3–5). The particular binding sites can be viewed as the maximum-entropy sites involved in bonding. There is a more intuitive understanding that conformational changes within various localized regions along a large biological macromolecule are a direct consequence of the overall response of the macromolecular structure to the binding of a ligand. Thus, it is quite interesting to gain more insight into what is the impact of the binding of ligands, manifested by the maximum-$\Delta(\eta,\theta)$ sites A2581, A1354 and A764 in the large ribonucleoligand complexes 1njn, 1nwy and 1 jzx, on the localized behavior of the cGAAg (1185––1189) motifs.

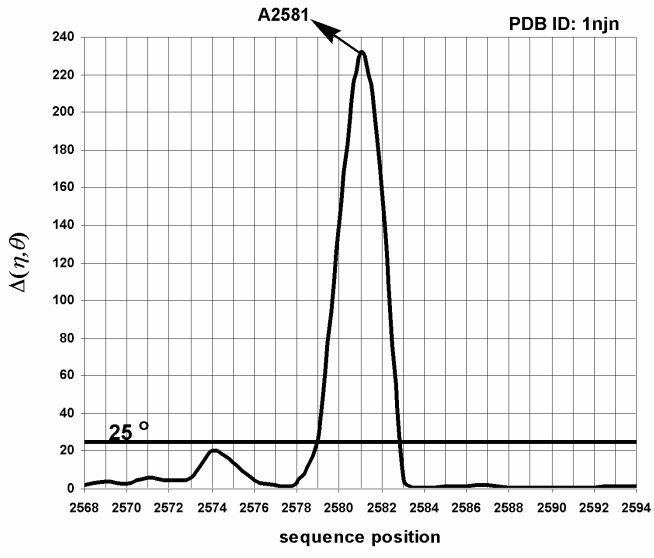

Fig. 3. $\Delta(\eta,\theta)$ *vs.* sequence position in the immediate vicinity of the ligand binding site A2581 having a maximum value of 232.1° among all of the RNA residues in contact with the ligand. The line at 25° indicates a threshold above which nucleotides in the complexes are considered to have different conformations relative to those in the reference structure (PDB ID:1njp).

There is some controversy in the literature on key factors dictating RNA–ligand recognition. The first major aspect is that the nature of RNA–ligand interactions is considered as a determinative factor influencing ligand specificity. Thus, the structural variability of RNA, as well as the ability of the RNA mole-

cule to distort upon ligand binding may play a crucial role in RNA–ligand interactions.[13] The second major aspect is related to the sequence-specific binding of RNA.[14] The previously raised question is hereafter addressed in light of these two main standpoints.

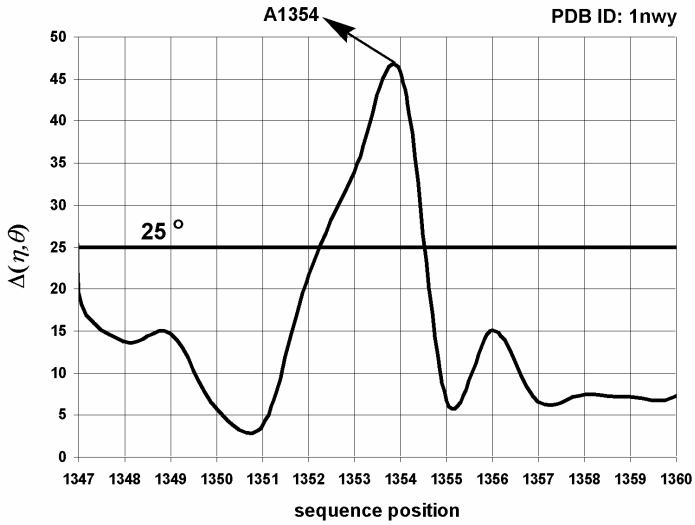

Fig. 4. $\Delta(\eta,\theta)$ *vs.* sequence position in the immediate vicinity of the ligand binding site A1354 having a maximum value of 45.8° among all of the RNA residues in contact with the ligand.

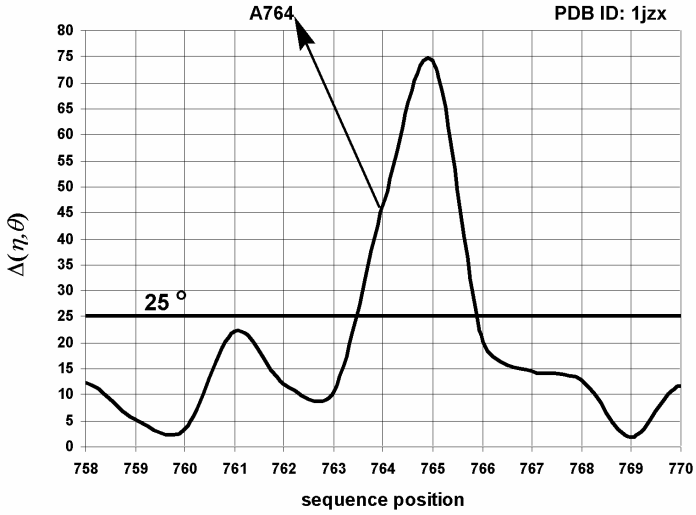

Fig. 5. $\Delta(\eta,\theta)$ *vs.* sequence position in the immediate vicinity of the ligand binding site A764 having a maximum value of 47.1° among all of the RNA residues in contact with the ligand.

In the context of the first aspect, the RNA–ligand binding sites and the nature of particular contacts in the complexes 1njn, 1nwy and 1jzx were identified

by the ENTANGLE program.[15] In general, no hydrogen bonds, or electrostatic and stacking interactions were detected. In 1njn, 4 hydrophobic contacts, having an average bond length of 4.70 Å, were found between atoms of the A2581 residue and atoms of the ligand. In 1nwy, atoms of the A1354 residue make 5 hydrophobic contacts with atoms of the ligand, having an average bond length of 4.51 Å. In 1jzx, atoms of the A764 residue participate in 6 hydrophobic contacts with atoms of the ligand, having an average bond length of 4.17 Å. Hence, 4, 5 and 6 hydrophobic contacts in the complexes are associated with average bond lengths of 4.70, 4.51 and 4.17 Å, respectively. To our chemical perception, the larger the number of contacts is, the smaller an average bond length of the contacts is, and the larger $\Delta(\eta,\theta)$ for a particular ligand binding site is. If the ability of RNA to deform upon ligand binding is, quantitatively, conceivable through the values of $\Delta(\eta,\theta)$ of 232.1, 45.8 and 47.1° for A2581, A1354 and A764, respectively, we note that the trends both of the number of hydrophobic contacts and of their average bond lengths do not agree with the trend of $\Delta(\eta,\theta)$ values. Note also the average values of $\Delta(\eta,\theta)$ for 15- and 21- and 27-nucleotide sequences around the A2581, A1354 and A764 sites, which are placed right in the middle of the sequences. For 15-nucleotide sequences, the average values of $\Delta(\eta,\theta)$ are 40.6, 14.9 and 17.7°, respectively. For 21-nucleotide sequences, the average values of $\Delta(\eta,\theta)$ are 29.8, 29.4 and 16.2°, respectively. For 27-nucleotide sequences, the average values of $\Delta(\eta,\theta)$ are 23.6, 24.1 and 34.7°, respectively. Therefore, a common chemical intuition based upon the nature of contacts of the A2581, A1354 and A764 residues only conforms to the case of 27-nucleotide sequences. Moving away from the particular binding sites, noteworthy are the average values of $\Delta(\eta,\theta)$ of 1, 15 and 110° for the cGAAg (1185–1189) motifs in the complexes 1njn, 1nwy and 1jzx, respectively. Clearly, the nature of contacts of the A2581, A1354 and A764 residues is in agreement with the trends both of $\Delta(\eta,\theta)$ values and of MD energies for small cGAAg (1185–1189) motifs being both about 20 Å away from the specific ligand binding sites and involved in interactions with other parts of the ribosome.

A simple measure for the determination of the strain of a triloop (Å), such as:

$$\frac{1}{4}\sum_{k=1}^{i+3}\left|P_kP_{k+1}-5.9\right| \qquad (2)$$

was previously introduced.[1] While P_kP_{k+1} is the phosphate···phosphate distance between two consecutive nucleotides, k and k+1, 5.9 Å stands for the phosphate···phosphate distance of the C3'-*endo* conformation.[16] Interestingly, the trend of the strains, 0.82, 0.66 and 0.73 Å, of the cGAAg (1185–1189) motifs in the 1njn, 1nwy and 1jzx complexes, respectively, does not agree with the chemical elucidation of the binding of ligands, which is primarily manifested through the trend of the average bond lengths, 4.70, 4.51 and 4.17 Å, of the A2581, A1354 and A764 contacts, respectively.

In the context of the second aspect, to probe the sequence-specific binding of RNA, nucleotide sequences containing 15, 21 and 27 nucleotides in the immediate vicinity of the maximum-$\Delta(\eta,\theta)$ ligand binding sites, A2581, A1354 and A764, were chosen as the input required to generate the corresponding secondary structures. The particular binding sites were initially placed right in the middle of the sequences, so that 7, 10 and 13 nucleotides were on each side of A2581, A1354 and A764, giving total sequence lengths of 15, 21 and 27 nucleotides. No restrictions were imposed on the process of generating the secondary structures by means of the Vienna RNA package V1.1.[17] The G–U pairing, based on the base pair (BP) probability algorithm of McCaskill,[18] was allowed in terms of the G–U wobble BPs.[9,19] Energy parameters were taken from the literature.[20–22] The secondary structure coordinates were calculated with Naview[23] within the Vienna RNA package,[17] while the employed dynamic programming algorithm was that of Zuker and Stiegler.[24] The calculated secondary structures for 15-nucleotide sequences are shown schematically in Fig. 6, while those corresponding to the 21- and 27-nucleotide sequences are given in the Supplementary Material, due to insufficient space in the present article. Note that the positions of A2581, A1354 and A764 are within various loops in Fig. 6, as generally expected for RNA residues in contact with ligands.

Base pairing defined by the secondary structures, consequently, was essential information for the determination of the thermodynamic parameters using the two-state conformational model of RNA sequences, as implemented within the framework of the Mfold V3.2 web server.[25,26] The very basic idea of a two-state model is that hairpin formation and more complex secondary structures of nucleic acids can be described in terms of rate of formation, stability, and control of secondary structure. The two states, ordered and disordered structures, are connected by a melting curve having a characteristic sigmoid shape. At low temperatures, all base pairs are formed, while at high temperatures no base pairs are formed. At any intermediate temperature, both the free energy of base pair formation and the nature of not fully paired intermediates influence the fraction of unpaired bases. At the melting temperature, T_m, depending solely on the free energy of base pair formation and not on the intermediates, paired and unpaired bases are present equally. Since enthalpy (ΔH) and entropy (ΔS) can be computed from the melting curve, it is straightforward to calculate ΔH and ΔS if no presence of the intermediates is assumed.[27] The core algorithm of the Mfold software package predicts a minimum free energy, as well as free energies for foldings containing desired base pairs. The minimum folding energy of a sequence was calculated by the zipfold server. The 'T_m' server was employed to estimate two-state melting temperature. Only available RNA folding parameters, version 2.3, were used to calculate the enthalpy of this folding using the appropriate nearest neighbor parameters. The enthalpy calculations were followed by the estimation of ΔS and T_m using a 2-state model as discussed above.[25]

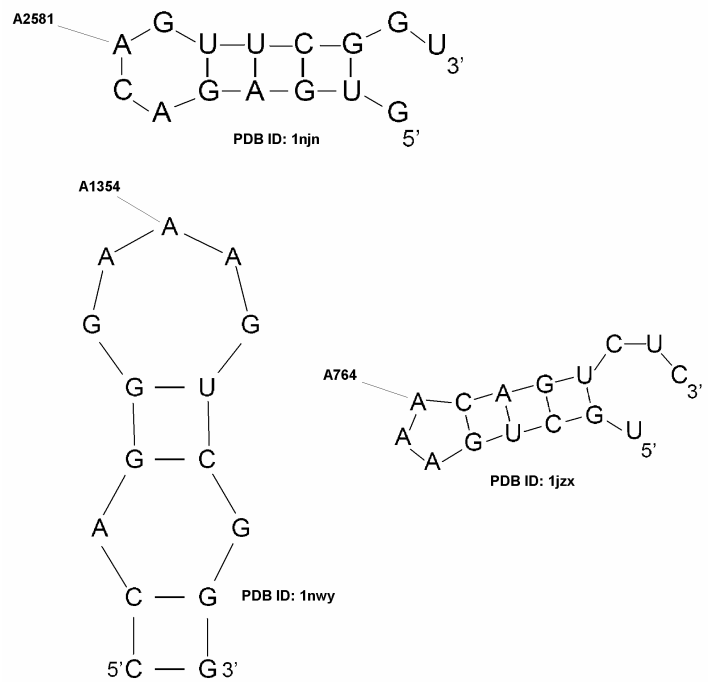

Fig. 6. Secondary structures generated by the RNAdraw program[17] for 15-nucleotide sequences in the immediate vicinity of the maximum-$\Delta(\eta,\theta)$ ligand binding sites, denoted by A2581, A1354, and A764. Secondary structures for sequences having 21 and 27 nucleotides around the same ligand binding sites in the complexes are given in the Supplementary Material due to insufficient space in the present paper.

The calculated values of these parameters for the sequences of various lengths are given in Table I. The trend of the ΔG values, −2.9, −1.1 and −3.2 kcal mol^{-1}, for the 15-nucleotide sequences does not agree with that of the average values of $\Delta(\eta,\theta)$ of 1, 15 and 110° for the cGAAg (1185–1189) motifs in the complexes 1njn, 1nwy and 1jzx, respectively. However the trends of the ΔG values for both the 21- and 27-nucleotide sequences, −7.7, −5.1 and −4.8 kcal mol^{-1} and −9.2, −5.5 and −5.1 kcal mol^{-1} are in agreement with that of $\Delta(\eta,\theta)_{av}$ for the cGAAg (1185–1189) motifs in the complexes 1njn, 1nwy and 1jzx, respectively. Note that the trends of the ΔG values are in accordance with those of the E_{ss} values for all of the sequences with the same number of nucleotides in the series of complexes. It is indicative that, by moving away from the ligand binding sites with the maximum value of $\Delta(\eta,\theta)$, the trends displayed by ΔG and E_{ss} tend to be lined up with both those of the $\Delta(\eta,\theta)_{av}$ values for very distant cGAAg motifs and of the energies of the motif MD. To further probe this indication, the average energies of the secondary structures and the average $\Delta(\eta,\theta)$ for the sequences of various lengths are given in Table II. Clearly, only for the sequences of 27 nu-

cleotides do the $E_{\text{ss-av27}}$ and $\Delta(\eta,\theta)_{\text{av27}}$ values display trends that agree with those of the $\Delta(\eta,\theta)_{\text{av}}$ values and MD energies associated with the cGAAg (1185––1189) motifs.

TABLE I. Values of the thermodynamic variables, based on a 2 state model, for sequences of various lengths in the immediate vicinity of the maximum-$\Delta(\eta,\theta)$ ligand binding sites, A2581, A1354 and A764, in the complexes 1njn, 1nwy and 1jzx

PDB ID (Sequence Range), Sequence Length Sequence	ΔG kcal mol^{-1}	ΔH kcal mol^{-1}	ΔS cal kmol^{-1}	T_{m} °C	E_{ss}[a] kcal
1njn (2574–2588), 15 GUGAGAC(A2581)GUUCGGU	–2.9	–30.2	–91.5	56.6	–1.3
1nwy (1347–1361), 15 CCAGGGA(A1354)AGUCGGG	–1.1	–24.4	–78.3	38.2	–1.1
1jzx (757–771), 15 UGCUGAA(A764)CAGUCUC	–3.2	–30.2	–90.6	59.8	–2.8
1njn (2571–2591), 21 GUCGUGAGAC(A2581)GUUCGGUCUC	–7.7	–55.1	–158.9	73.5	–6.7
1nwy (1344–1364), 21 CGCCCAGGGA(A1354)AGUCGGGACC	–5.1	–52.0	–157.4	57.0	–4.3
1jzx (754–774), 21 GCCUGCUGAA(A764)CAGUCUCGGA	–4.8	–59.6	–183.5	51.5	–3.5
1njn (2568–2594), 27 AACGUCGUGAGAC(A2581)GUUCGGUCUCUAU	–9.2	–62.6	–179.2	76.1	–7.9
1nwy (1341–1367), 27 GUCCGCCCAGGGA(A1354)AGUCGGGACCUAA	–5.5	–49.2	–146.7	62.2	–5.1
1jzx (751–777), 27 GGUGCCUGCUGAA(A764)CAGUCUCGGAUGA	–5.1	–76.7	–240.2	46.1	–3.7

[a]Energy of the secondary structure (ss) calculated by the Vienna RNA package V1.1.[17]

TABLE II. Values of both the average (av) energies of the secondary structures ($E_{\text{ss-av}}$) and of the average $\Delta(\eta,\theta)$ for sequences of various lengths in the immediate vicinity of the maximum-$\Delta(\eta,\theta)$ ligand binding sites, A2581, A1354 and A764, in the complexes 1njn, 1nwy and 1jzx

$E_{\text{ss-av}_{\text{sequence length}}}$ / kcal $\Delta(\eta,\theta)_{\text{av}_{\text{sequence length}}}$ / °	PDB ID: 1njn	PDB ID: 1nwy	PDB ID: 1jzx
$E_{\text{ss-av}_{15}}$	–0.08	–0.07	–0.19
$\Delta(\eta,\theta)_{\text{av}_{15}}$	40.57	14.90	17.74
$E_{\text{ss-av}_{21}}$	–0.32	–0.21	–0.17
$\Delta(\eta,\theta)_{\text{av}_{21}}$	29.87	29.38	16.21
$E_{\text{ss-av}_{27}}$	–0.29	–0.19	–0.14
$\Delta(\eta,\theta)_{\text{av}_{27}}$	23.66	24.11	34.73

The three nucleotide sequences of various lengths centered on the maximum-$\Delta(\eta,\theta)$ ligand binding sites, A2581, A1354 and A764, are essentially three distinct structural motifs in each of the complexes, if observed from a structure––function standpoint. Consequently, their thermodynamic variables and energies

change in different ways, as previously discussed. In every single complex, it is useful to find an average measure as a representative characteristic for the three motifs of 15, 21 and 27 nucleotides. Based upon the values of ΔG and E_{SS} in Table I for three sequences in each complex, the calculated average ΔG values are −6.6, −3.9 and −4.4 kcal mol^{-1}, while the average E_{SS} values are −0.23, −0.15 and −0.17 kcal in the 1njn, 1nwy and 1jzx complexes, respectively. Interestingly, the trends of ΔG and E_{SS} are in line with that of the cGAAg (1185–1189) motif strain, 0.82, 0.66 and 0.73 Å in 1njn, 1nwy and 1jzx, respectively. This is in contrast to the finding that the values of the strains of triloops do not follow the trend of the average bond lengths, 4.70, 4.51 and 4.17 Å, of the A2581, A1354 and A764 contacts, respectively, as previously discussed in the context of the first aspect of RNA–ligand recognition. Therefore, the nature of RNA–ligand contacts is presumably determined by the types of ligands involved in bonding, which are the antibiotics, sparsomycin, azithromycin and clindamycin in the 1njn, 1nwy and 1jzx complexes, respectively.

CONCLUSIONS

The considerations are well-correlated with the understanding that conformational changes, induced within localized regions of an rRNA structure, are associated with the overall response of the rRNA structure to the binding of a ligand at sites which are quite far (in the range of 20 Å) away from the localized regions. Due to the structural variability of RNA, the overall response is conceivable as the RNA capability of distorting upon ligand binding.

SUPPLEMENTARY MATERIAL

Secondary structures generated by the RNAdraw program[17] for 21- and 27-nucleotide sequences in the immediate vicinity of the maximum-$\Delta(\eta,\theta)$ ligand binding sites, denoted by A2581, A1354, and A764, in the 1njn, 1nwy and 1jzx complexes, respectively, are available electronically from http://www.shd.org.yu/JSCS/ or from the corresponding author on request.

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ИЗВОД

ДИНАМИКА МАЛИХ СТРУКТУРНИХ МОТИВА У рРНК УСЛЕД ВЕЗИВАЊА ЛИГАНДА

АЛЕКСАНДРА РАКИЋ[1] и ПЕТАР М. МИТРАШИНОВИЋ[2]

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Тронуклеотидне петље GAA (1186–1188) затворене са спареним c–g базама у великим рибонуклеотидним комплексима (PDB кодови: 1njn, 1nwy, 1jzx) су анализиране у овом раду помоћу молекуларно-динамичких симулација. Трендови релативних енергија ових мотива у комплексима у односу на мотив у слободној (без лиганда) структури рРНК (PDB код: 1njp)

се поклапају са трендовима конформационих параметара базираних на псеудоторзионом (η,θ) прилазу из претходног рада.[1] Идентификоване су области структуре рРНК које се налазе у непосредној близини контаката са нејизраженијим конформационим променама при везивању лиганда. Одређени су термодинамички параметри базирани на конформацијском моделу "два стања" секвенци рРНК са 15, 21 и 27 нуклеотида око ових везивних места лиганада. Са више структурног становишта, деформација тронуклеотидне петље, која је далеко од ових везивних места и укључена у интеракције са осталим деловима рибозома, установљена је као структурна особина која одговара трендовима просечних термодинмичких параметара за три мотива дефинисана секвенцијама од 15, 21 и 27 нуклеотида. Са више функционалног становишта, типови лиганада у комплексима су предложени као важан фактор који детерминише рРНК–лиганд препознавање.

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