REVIEW

On the wobble GoU and related pairs

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ABSTRACT

The wobble GoU pairs have been implicated in several biological processes where RNA molecules play a key role. We review the geometrical and conformational properties of wobble GoU pairs on the basis of available crystal structures of RNAs at high resolution. The similarities with the wobble A⁺oC pairs and UoU pairs are illustrated, while the differences with the recently discovered bifurcated G•U pairs are contrasted.

Keywords: A⁺oC; covariations; GoC; stacking; twist; wobble

INTRODUCTION

The prevalence and importance of non-Watson–Crick base pairs in RNA folding is recognized. However, among them, the GoU wobble pair first suggested by Crick more than 30 years ago, enjoys a special status (Crick, 1966). First, the usual definition of secondary structure includes the GoU wobble pairs, together with the common Watson–Crick pairs for delimiting the helical regions. Secondly, the GoU wobble pairs are slightly nonisosteric, in contrast to the remarkable isostericity of the Watson–Crick pairs. Finally, highly conserved GoU pairs are observed in various RNAs associated with diverse functions. A critical GoU pair is a major determinant in *Escherichia coli* tRNA^{Ala} for aminoacylation activity (Hou & Schimmel, 1988; McClain et al., 1988; Park et al., 1989; Frugier & Schimmel, 1997) and for the regulation of the expression of the ribosomal protein S15 (Benard et al., 1998). In group I introns (Cech et al., 1981; Michel & Westhof, 1990; Strobel & Cech, 1995), the 5' splicing event occurs 3' of a highly conserved GoU pair, whereas in the HDV ribozyme (Tanner et al., 1994; Been & Wickham, 1997), the self-cleavage takes place 5' of a conserved GoU pair. Small inorganic complexes (Chow & Barton, 1992) or organic molecules (Burgstaller et al., 1997) specifically photocleave GoU base pairs embedded within a helical track.

The geometry of wobble pairs

In wobble GoU pairs, the U points into the deep groove of an RNA helix (equivalent to the major groove of a

B-DNA helix, towards the top of the drawing on Fig. 1), forming a hollow surface in the shallow groove side (equivalent to the minor groove of a B-DNA helix). Geometrically, the movement of the U provokes an asymmetry in the angles subtended at the glycosyl carbon atoms C1'; in Watson–Crick pairs those angles are equal (around 55°) whereas, in GoU pairs, the angle at the U is increased (around 70°) and that at the G decreased (around 40°), leading to a sum of the angles roughly equal to that of a Watson–Crick pair (110°). This difference in the angles subtended at the C1' atoms is the origin of the nonisostericity of GoU pairs; that is, with the C1' atoms of the G of a GoU pair superimposed on the C1' of the U of a UoG pair, the C1' atoms of the paired bases will not superimpose (Fig. 2). At the same time, the displacement of the U introduces a concave irregularity in the surface of the shallow groove of the RNA helix. Such cavities favorably stabilize water molecules or other hydrophilic atoms (Westhof, 1988). Indeed, crystallographic studies of tRNAs (Westhof et al., 1988) and of oligonucleotides at high resolution (Holbrook et al., 1991; Auffinger & Westhof, 1998; Masquida et al., 1999; Mueller et al., 1999) have confirmed the systematic presence of a hydration site linking the amino group of the G to the carbonyl O2 and hydroxyl O2' of the U in GoU pairs (Fig. 3).

Phylogenetic analysis shows that GoU pairs exchange most frequently with the standard Watson–Crick pairs and, depending on the sequence environment or function, with AoC pairs (Rousset et al., 1991; Gautheret et al., 1995). Geometrically, with the A protonated at the N1 position, an A⁺oC pair is isosteric to a GoU pair (Doudna et al., 1989). Crystal structures of oligonucleotides containing wobble mismatches within helices confirmed the similarity between GoU and A⁺oC (Jang et al.,

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FIGURE 1. Schematic representations of a standard wobble GoU pair, the isosteric A⁺oC pair, and the “bifurcated” G•U pair. Notice the rotation (of about 45°) and slight translation of the U from the standard wobble to the bifurcated G•U pairs. The hydrogen bonding donor and acceptor sites are indicated by arrows, as well as the weak C-H donor sites. Observe the strong donor/acceptor switch in the deep groove between the wobble GoU and A⁺oC pairs. In all those pairs, the glycosyl bonds adopt a *cis* arrangement (the C1' atoms are on the same side of the H-bonds linking the two paired bases. For clarity, we will denote wobble pairs with the standard geometry by o between G and U, with all other non-Watson–Crick pairs noted by •, whereas the Watson–Crick pairs will be noted A–U and G=C.

1998; Pan et al., 1998). Evidently, the nature of the donor and acceptor groups surrounding the two wobble pairs is different in both the shallow and deep groove sides (Fig. 1). In Figure 4, the values of the twist angles between a wobble pair and its flanking pairs, as calculated from the available X-ray data, are given. A striking regularity is observed: the twist angle 5' of the pyrimidine of a RoY wobble pair is always larger than the usual 33°, whereas the twist angle 3' of the pyrimidine is always smaller (Masquida et al., 1999; Mueller et al., 1999; Trikha et al., 1999). This underwound-overwound pattern of the twist angles around GoU pairs has been observed also in NMR structures (White et al., 1992; Allain & Varani, 1995b). The increase and the decrease is such that the average value is close to 33°. The same behavior is observed in the motifs of tandem

wobble pairs (Trikha et al., 1999). Some values for the A⁺oC tandem are still missing, but one can expect similar trends. It was shown previously that NUCLIN-NUCLSQ (Westhof et al., 1985), a geometrical and stereochemical refinement program which does not consider the polarization terms responsible for specific stacking patterns, gives the same trends in twist angles (Masquida et al., 1999). Thus, it appears that the observed trends in twist angles reflect geometry more than energetics. Some C•A pairs, especially at the ends of helices before a hairpin or internal loop, are structurally not related to wobble UoG pairs but rather to sheared G•A pairs (Leontis & Westhof, 1998a). A well studied example is the one occurring between positions 32 and 38 at the end of the anticodon helix in tRNAs (Auffinger & Westhof, 1999). In such pairs, the

FIGURE 2. The nonisostericity of wobble GoU pairs. A superimposition of the glycosyl bonds of the G and the U of GoU and UoG pairs leads to a distance of about 4 Å between the C1' atoms of the paired residues. However, if the C1' atoms are superimposed, the N2 amino groups superimpose well with an angular deviation of the two N-H bonds.

N6 of A makes bifurcated H-bonds to the carbonyl O2 of the C. Other examples occur in 16S rRNAs (e.g., positions 152•169, 996•1045, and 1402•1500).

It was noticed some time ago by Mizuno & Sundaralingam (1978) that the unusual stacking geometries of GoU base pairs is especially marked at the ends of helices where 5'-GoU-3' stacks well with the preceding base pair in contradistinction with 5'-UoG-3', which presents a poor stacking overlap with a preceding base pair (Fig. 5). Statistics on rRNAs indicate that there is indeed a preference for the stacked 5'-GoU-3' base pair at the ends of helices (Van Knippenberg et al., 1990; Gautheret et al., 1995). Thermodynamically also, helices ending with 5'-GoU-3' base pairs are more stable than those ending with the opposite base pair (He et al., 1991; Wu et al., 1995). There is, however, an interesting exception when the wobble pair closes a hairpin loop (Giese et al., 1998).

Tandem of GoU pairs have been discussed (Gautheret et al., 1995) and analyzed (Tripathi et al., 1999). In Figure 6, the stacking patterns of the three types of

FIGURE 3. Pockets of hydration densities around 10 wobble GoU pairs evaluated on the basis of an analysis of five high resolution crystal structures. Potential H-bonds between hydrophilic groups and potential C-H...O H-bonds are, respectively, represented by solid and dashed lines. Like in Watson-Crick pairs, there are five hydration sites in the deep groove and three in the shallow groove; however, their precise location and peak forms differ depending on the type of base pair. The characteristic hydration site of wobble GoU pairs is located between the three groups N2(G), O2(U), and O2'(U). That site could be already seen in low resolution crystal structures of tRNAs (Westhof et al., 1988). In contrast to Watson-Crick pairs, the site close to O2'(G) is poorly populated and there is no specific hydration of N3(G). Notice the difference in conformational mobility between the 5'-phosphate of G and U; the 5'-phosphate of G adopts sometimes the *trans/trans* conformation instead of the *gauche⁺/gauche⁻* conformation for the torsions about C(4')-C(5') and O(5')-P (Moras et al., 1986; Westhof & Sundaralingam, 1986). Thus, the C8-H...O(5') contact is less well defined than the C6-H...O(5') contact in GoU wobble pairs. A comparison of GoU pairs in tRNA crystal structures has been made (Moras et al., 1986). Adapted from Auffinger & Westhof (1998).

motifs, idealized from available crystal structures or modeled using NUCLIN-NUCLSQ (Westhof et al., 1985), are represented. For the motifs of UoU tandems, only motif I has been observed crystallographically (Lietzke et al., 1996); the other two have been calculated. Another structure (Baeyens et al., 1995) presents a distorted motif I of UoU pairs, but also, interestingly, two examples of a mixed motif I involving a 5'UoG3' pair stacked on a UoU pair. The similarities between the tandem of GoU pairs, UoU pairs, and mixed motifs have been discussed on the basis of sequence alignments in 5S rRNA loop E (Leontis & Westhof, 1999b). As noticed by Gautheret and coworkers (1995), in motif I the unstacked sides of the tandem face each other so that cross-strand stacking occurs, whereas in motif II, they face the flanking base pairs with intrastrand stacking within the tandem. In addition, in motif I, the natural right-handedness of RNA helices is well preserved, which is less so in motif II. Clearly, motif III presents an intermediate situation. As further remarked by Tripathi and coworkers (1999), the alternation of low/high twist values around an isolated GoU pair can be used to evaluate the twist values in the three tandem motifs (see Fig. 6). In other words, the geometry around a base pair is determined primarily by its immediately preceding and following base pairs, a structural valida-

Twist (°)

FIGURE 4. Twist variations around GoU base pairs in crystal structures (the standard deviations are given in parentheses). The most frequently observed tandem in rRNA sequences is the one noted as motif I and the least frequently observed one is noted motif II. The values available from crystal structures containing A⁺oC and UoU base pairs are also given. The values were calculated using the program CURVES (Lavery & Sklenar, 1988). As noted by Trikha and coworkers (1999), the use of the FREEHELIX program (Dickerson, 1998) reverses the magnitudes of the twist angles. This is related to the choice made in CURVES for the defining vectors, which implies the local dyad axis and, thus, the angles at the C1' atoms (an increase/decrease of about 15° at the G/U). The stars (*) indicate the U residues that protrude in the deep groove. The crystal structures used in the averages have the following NDB (Nucleic Acid Data Base) identification: AH077 (Biswas et al., 1997), AH089 (Biswas & Sundaralingam, 1997), AR0008 (Trikha et al., 1999), AR0009 (Muel-ler et al., 1999), AR0011 (Shi et al., 1999), AR0019 (Masquida et al., 1999), URL050 (Lietzke et al., 1996), AR0001 (Jang et al., 1998), AR0002 (Pan et al., 1998).

tion of the nearest-neighbor model proposed several years ago that forms the basis of secondary structure prediction (Tinoco et al., 1971). Energetically, however, those purely geometrical aspects ought to be completed by water and ion binding, the strength of which depends in subtle ways on geometry. For example, it was noticed a long time ago that sodium chelation is geometrically favored in the shallow groove of ApU but not of UpA (Seeman et al., 1976). Similarly, tandem of GoU pairs, especially of the type 5'-GU-3'/3'-YG-5' (Hermann & Westhof, 1998), are magnesium binding sites in the deep groove (Allain & Varani, 1995a; Cate & Doudna, 1996; Correll et al., 1997).

The bifurcated G•U pairs

Those general considerations should, however, be modulated by recent data from X-ray structures. The crystal structure of the loop E of eubacterial rRNA convincingly shows that pairs between G and U do not exist solely as standard wobble pairs, but adopt also what has been called a bifurcated geometry (see Fig. 1) (Correll et al., 1997). According to chemical nomenclature, such pairs ought to be called "chelated" (Jeffrey, 1997). In those base pairs, the O4 of the U points to hydrogen atoms

FIGURE 5. Stacking of a 5'-UoG3' pair on its following base pair, the unstacked configuration, but with interstrand stacking (right), and of a 5'-GoU3' pair on its preceding base pair, the stacked configuration, but with intrastrand stacking (left). The example is taken from the crystal structure of [r(CGUGAUCG)dC]₂ (Masquida et al., 1999).

bound to the N1 and N2 of the G. Such base pairs are not well accommodated within a regular helix, and, instead, they occur close to other types of non-Watson-Crick pairs (e.g., *trans* Hoogsteen). A reexamination (Allain & Varani, 1995b) of the NMR structure of the stable tetraloop UUCG (Varani et al., 1991) has led to the conclusion that the closing U•G base pair is a *trans* bifurcated U•G pair (the O2 of U interacts with the G) and not a *trans* wobble U•G pair (in both cases, the guanine adopts the *syn* conformation about the glycosyl bond). Another example is present in tRNA structures between the invariant residues G18 and Ψ55 in which the O4(Ψ55) (equivalent to O2 of U) points towards the N1 and N2 of G18 (see Leontis & Westhof, 1998a). In the former example, the strands are antiparallel and, in the latter, parallel. For completeness, the wobble pairs in the *trans* conformation are shown in Figure 7. Notice first that the *trans* A•C pair does not require protonation of the adenine and, second, that the *trans* wobble pairs G•U and A•C pairs are isosteric.

The phylogenetic analysis of sequence variations in structural motifs known at high resolution allows us to infer dictionaries of pairings that are isosteric (or almost isosteric), that is, that are able to substitute for each other while preserving the three-dimensional structure of the motif (Leontis & Westhof, 1998, 1999). The observed substitutions and covariations are gathered in isostericity matrices (Fig. 8) (Leontis & Westhof, 1999a). The matrices for wobble GoU pairs in tandem are clearly different from those of bifurcated G•U pairs in 5S rRNAs. Thus, for a wobble GoU pair, the conservative substitutions are

FIGURE 6. Stacking patterns in the three motifs of tandem GoU and UoU pairs, following the nomenclature introduced by Gautheret et al. (1995). Notice the interstrand or cross-strand stacking in motif I, the intrastrand stacking in motif II and the intermediate situation in motif III. Only motif I has been observed for UoU pairs (Lietzke et al., 1996). The other two motifs have been built by analogy with the UoG motifs and refined using NUCLIN-NUCLSQ (Westhof et al., 1985).

UoU, UoC, CoC, but interestingly not CoU. The covariation between GoU and UoU pairs is exemplified by an analysis of the twist angles of tandem UoU pairs (see Fig. 6). On the contrary, the bifurcated G•U pair, which is isosteric with the bifurcated G•G pair, is often substituted by A•A or A•C pairs, in which probably the amino group of one base (either N6(A) or N4(C)) points to the pyrimidine ring N1 nitrogen of the A.

CONCLUSIONS

Functionally, it is interesting to notice that the specific cleavages, in group I introns (Bevilacqua et al., 1994) or the HDV ribozymes, and the photocleavages induced by small inorganic (Chow & Barton, 1992) or organic molecules (Burgstaller et al., 1997) all occur at the step with a low twist angle (i.e., 3' of the U or 5' of

the G) where unstacking of the base pairs occurs (Fig. 9). As discussed above, a GoU pair presents, within the helical continuity, a polar cavity partially occupied by a water molecule 3' of the U on the shallow groove side. A molecular model of the GoU recognition by isoalloxazine (which induces cleavage upon light irradiation) showed how a carbonyl group of the isoalloxazine displaces the water molecule while a N-H group H-bonds to the ribose hydroxyl of the U, positioning above the following 3' ribose the orbitals of the isoalloxazine moiety which, upon excitation to the triplet state, will abstract one sugar proton, leading to breakage of the sugar-phosphate chain (Burgstaller et al., 1997). In the other instances as well, the reactive species might (1) recognize the environmental niche and (2) be able to approach closer the sugar-phosphate backbone to promote catalytic cleavage. At the same time, on the gua-

FIGURE 7. The wobble pairs in the *trans* conformation of the glycosyl bonds (i.e., the sugars are on either sides of the H-bonds). If such pairs were inserted in a continuous helix, the two strands would be parallel (assuming standard and invariant conformations of the nucleotides as in a regular A-RNA helix). In such a parallel helix, the two grooves would geometrically be identical in depth and width, a severe drawback for specific recognition. Notice that pairs involving the Watson–Crick sites between the noncomplementary bases G/U and A/C are isosteric either in *cis* or in *trans* configurations in contrast to the Watson–Crick pairs between the complementary bases G/C and A/U, which are isosteric only in the *cis* configuration.

nine side, close to the 2-amino group, there exists a binding pocket for a negatively charged group like a phosphate or a sulfate group (Masquida et al., 1999), which might help in the trapping of the transition state.

Further, the propagation of the high versus low twist angles is such that, after superimposition of the C1' atoms of the GoU and UoG pairs at the base of a regular helix, a deviation up to 2 Å can be observed 5 bp away from the wobble pair. Thus, if a protein locks in a RNA helix through the 2-amino group of a GoU pair, the replacement of the GoU pair with a UoG pair will lead to a deviation of the helix, mostly marked a couple of base pairs away (Masquida et al., 1999). A

FIGURE 8. Isostericity matrices for wobble (in tandem) and bifurcated GoU pairs based on sequence analysis of 288 eubacterial 5S rRNAs (Szymanski et al., 1998). The sizes of the black circles are proportional to the number of occurrences in the phylogeny (three sizes, (1) 1<20 instances; (2) >30; (3) >100). From Leontis & Westhof (1998, 1998a).

FIGURE 9. Observed cleavage sites around isolated GoU bases in natural systems (group I introns and hepatitis delta virus, HDV) and in artificial systems (light-induced cleavage in presence of isoalloxazine derivatives and UV-induced cleavage in presence of tris(4,7-1,10-phenanthroline rhodium (III)). Interestingly, in some group I introns (Michel & Westhof, 1990), the GoU pair forms in some instances the rare tandem 5'UoG3'/5'UoG3'. Tandem of GoU pairs are not cleaved by light-induced cleavage in presence of isoalloxazine derivatives (Burgstaller et al., 1997).

recent article (Chang et al., 1999) provides data suggesting that GoU pairs also constitute points of deformability allowing the necessary conformational adaption for promoting catalytic efficiency in aminoacyl tRNA synthetases (Rould et al., 1989; Cavarelli et al., 1994).

Thus, geometrically and dynamically, it appears that wobble pairs present several assets for specific recognition. They introduce a polar pocket and thus a slight asymmetry in an otherwise rather regular helix with a dependence on strand polarity so that a GoU pair is not equivalent to a UoG pair. At the same time, the alternation of low and high twist values propagates differently in the 5' or 3' directions away from a GoU pair.

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