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A Quantum−Chemical Study on Water−Mediated Base Pairs in RNA

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Introduction

Water−mediated base pairs have been found in helical regions of RNA structures, Fig.1 [1−3]. In the WUC, WUU, WUA and WGA complexes water (W) is both donor and acceptor of hydrogen bonds, whereas it is double donor or double acceptor in the WUG and WGG mismatches. Very detailed information is available for base pairs linked by two or more direct hydrogen bonds [4], but little is known about the intrinsic properties of water−mediated base pairs. In particular, it is not clear, whether these complexes are enforced by a specific environment or whether they can be expected to occur in other structures as well. In a first step to clarify those questions, we have studied the geometries and interaction energies of the isolated water−mediated complexes and of the related direct base pairs by quantum−chemical ab initio methods.

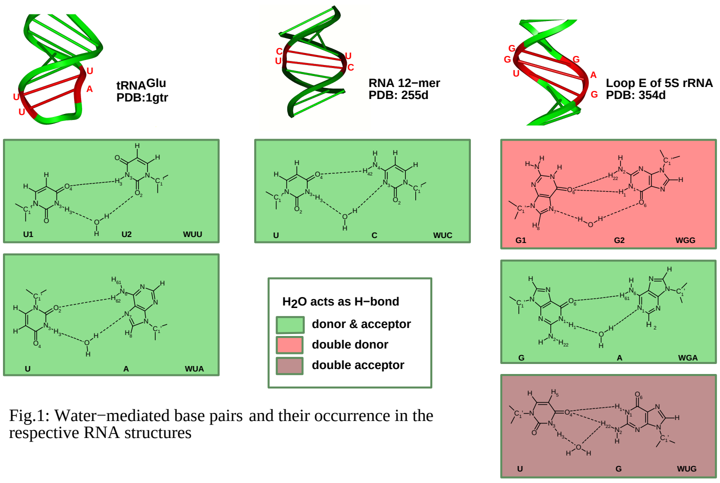


Fig.1: Water−mediated base pairs and their occurrence in the respective RNA structures

Geometries and Interaction Energies

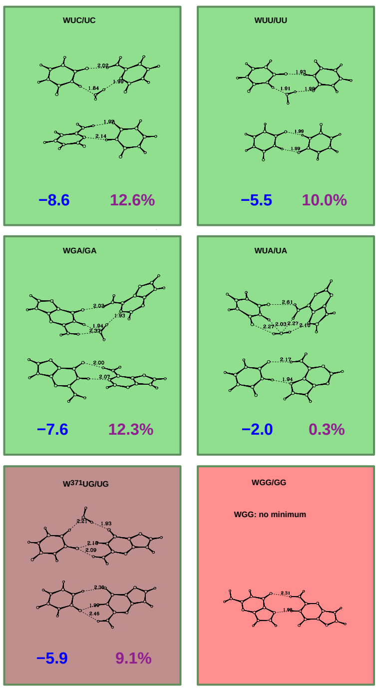


Fig.2: Geometries, differences in interaction energies between water−mediated and related direct base pairs, and cooperativity contributions to the interaction energy of water−mediated pairs

The water−mediated WUC, WUU and WGA base pairs in which water is both donor and acceptor of hydrogen bonds yielded mimima in the quantum−chemical calculations which resemble closely the experimental geometries found in the nucleic acid structures.

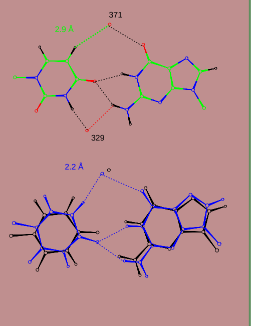
WUA is an intermediate case because in the optimized structure water still links the two bases, yet the H−bond pattern deviates somewhat from the one in the crystal structure and is not cooperative.

The water−mediated UG pair identified in the X−ray study (Fig.1) is not stable. In this case another water molecule (371) has been found which is both donor and acceptor and links C5−H5 of U to O6 of G. Taking into account this water leads to a stable structure with a geometry similar to the experimental one (Fig. 3). Consequently, the WUU, WUC, WUA, WGA and alternative $W^{371}UG$ base pairs can be regarded as structurally autonomous building blocks of RNA. Except for WUA the interaction energy between the water−mediated and direct base pairs is by 6−9 kcal/mol (Fig.2, blue numbers [kcal/mol]) more negative than the interaction energy of the corresponding direct base pair and cooperative effects (Fig.2, purple numbers: $\Delta E^3/\Delta E$]) contribute substantially to its value. The water−mediated base pairs are buckled. The direct pairs are either planer (UU,UA) or non−planar (UC, UG, GA, GG). For WUC and WUU the inclusion of water leads to a C1’−C1’ distance that is closer to the Watson−Crick value, whereas the opposite is true for WGA, WUG and WGG.

Role of C−H...O Interactions

WUG BASE PAIR

- In the experimental structure the standard hydrogen bond between N2[G] and H_2O^{329} has an unusual geometry.
- C5−H5[U] forms a C−H...O contact to H_2O^{371}.
- The calculated structure of $W^{371}UG$ is in good agreement with the **experimental geometry**.
- The $W^{371}UG$ pair is an example for the structural role of C−H...O contacts in biopolymers.



WGG BASE PAIR

- In the experimental structure H_2O is coordinated to H_2O^{330} and to a backbone C5’−H5’ group.
- Due to its size and due to backbone flexibility this system could not be analysed by high−level quantum−chemical methods.

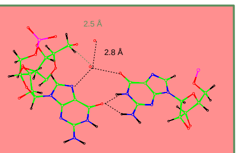


Fig.3: C−H...O interactions in WUG and WGG base pairs

Biological Implications

Our analysis has shown that the water−mediated UC, UU, UA and GA base pairs and their direct counterparts are structurally autonomous and need not be enforced by a particular environment. They extend the alphabet of known base pairs and can play similar roles in biological structures and processes as other canonical and non−canonical base pairs.
The WUG and WGG complexes are not stable and require additional interactions for maintaining the experimental geometry.
The most favourable water−mediated base pair is the WUC complex. Both our quantum−chemical [6] and experimental data [7] support the hypothesis that this base pair can occur in various nucleic acid environments and does not break the helix (Fig.4).
Finally, inclusion of water changes the base pair properties and creates a new motif which may be important for recognition by nucleic acids and proteins.

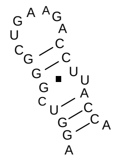


Fig.4: Secondary structure model of 16S rRNA of *Archaeoglobus fulgidus* [5]

Quantum−Chemical Analysis

The structures of the six water−mediated base pairs and of the related direct base pairs have been optimized at the HF/6−31G(d,p) level. Calculations of interaction energies included electron correlation according to second order Møller−Plesset perturbational theory. For the water−mediated complexes the cooperativity term has been calculated as the difference between the total interaction energy and the sum of pairwise interaction energies.

$$\Delta E^3 = \Delta E - \Delta E^{AB} - \Delta E^{BC} - \Delta E^{AC}$$

Interaction energies have been corrected for the basis set superposition error, for deformation energies and for zero point energy changes. All quantum−chemical calculations have been performed with GAUSSIAN 94.

Acknowledgement

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