



# Increasing occurrences and functional roles for high energy purine-pyrimidine base-pairs in nucleic acids

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There are a growing number of studies reporting the observation of purine-pyrimidine base-pairs that are seldom observed in unmodified nucleic acids because they entail the loss of energetically favorable interactions or require energetically costly base ionization or tautomerization. These high energy purine-pyrimidine base-pairs include G•C<sup>+</sup> and A•T Hoogsteen base-pairs, which entail ~180° rotation of the purine base in a Watson-Crick base-pair, protonation of cytosine N3, and constriction of the C1'–C1' distance by ~2.5 Å. Other high energy pure-pyrimidine base-pairs include G•T, G•U, and A•C mispairs that adopt Watson-Crick like geometry through either base ionization or tautomerization. Although difficult to detect and characterize using biophysical methods, high energy purine-pyrimidine base-pairs appear to be more common than once thought. They further expand the structural and functional diversity of canonical and non-canonical nucleic acid base-pairs.

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## Introduction

In naked unmodified nucleic acid duplexes, purines (guanine and adenine) pair up with pyrimidines (cytosine, thymine, and uracil) through complementary hydrogen bonds to form canonical G•C, A•T, and A•U Watson-Crick (WC) base-pairs (Figure 1a). Due to steric clashes involving imino and amino protons, and energetically unfavorable hydrogen bonding, the purine-pyrimidine (pur-pyr) mispairs G•T/U and A•C do not typically adopt a WC-like geometry when the bases are in their energetically dominant neutral tautomeric form. Rather they typically form G•T, G•U, and A<sup>+</sup>•C wobbles that deviate from the WC geometry (Figure 1b). This geometrical distinction between canonical WC base-pairs and non-canonical wobbles is exploited by

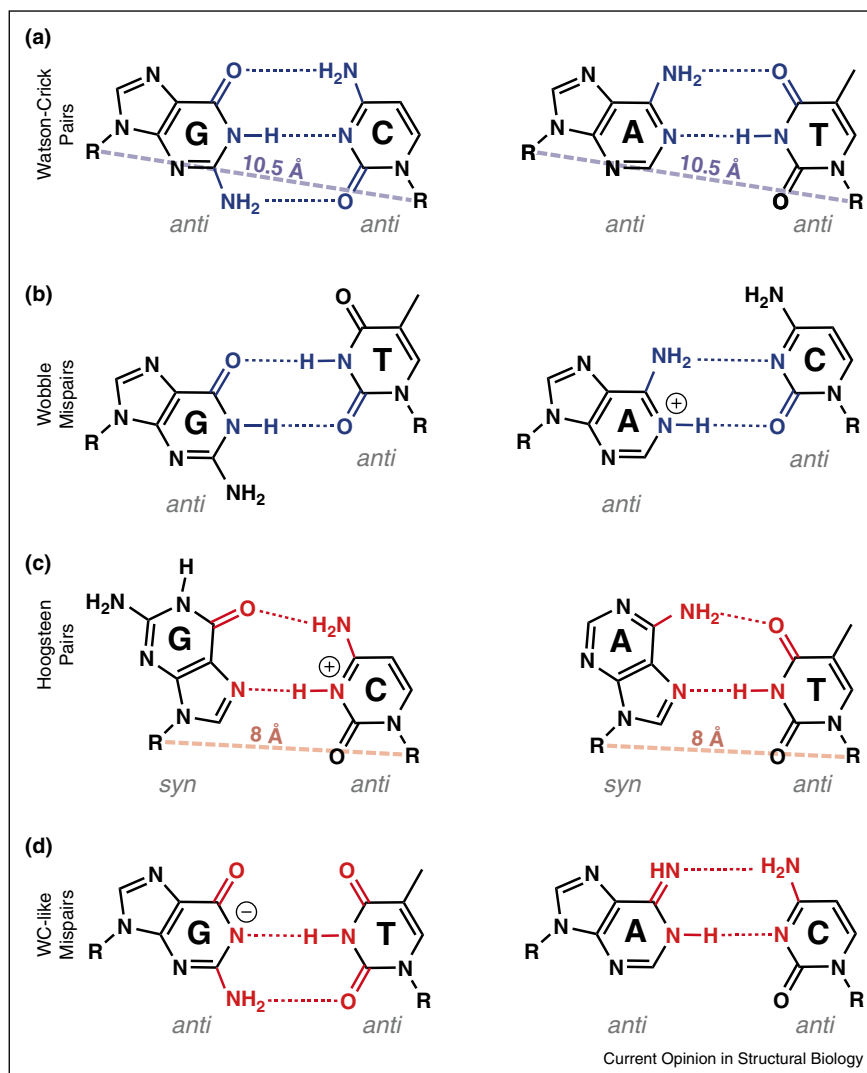
polymerases, repair enzymes, and ribosomes to replicate, transcribe, and translate genetic information with high fidelity.

There are other types of pur-pyr base-pairs that expand on the simple picture depicted above. These base-pairs are seldom observed in unmodified nucleic acids because they entail the loss of energetically favorable interactions or require energetically costly base ionization or tautomerization. We will therefore refer to these base-pairs as ‘high energy’ pur-pyr base-pairs. High energy pur-pyr base-pairs include A•T and G•C<sup>+</sup> Hoogsteen (HG) base-pairs [1–3], in which the purine base in a WC base-pair rotates roughly 180° about the N-glycosidic bond to adopt a *syn* rather than *anti* conformation (Figure 1c). Although A•T HG base-pairs preserve two hydrogen-bonds, as in WC base-pairs, formation of HG G•C<sup>+</sup> base-pairs is accompanied by a net loss of one hydrogen bond and require protonation of C(N3) (Figure 1c). The HG base-pairs also require the translation of the complementary bases into closer proximity, causing constriction of the C1'–C1' distance by ~2.5 Å (Figure 1c).

Other high energy pur-pyr base-pairs include G•T, G•U, and A•C mispairs that adopt a WC-like geometry through movement of otherwise sterically clashing imino (G•T and G•U) and amino (A•C) protons. For G•T and G•U mispairs, this can be accomplished by having either purine or pyrimidine adopt minor O6 or O4 enol tautomers, respectively, or through deprotonation of G(H1) or T/U(H3) (Figure 1d). On the other hand, WC-like A•C base-pairs can only arise by having either the A or C nucleobase adopt its rare imino tautomeric form (Figure 1d) [4<sup>\*\*</sup>,5<sup>\*\*</sup>].

Although the existence and functional importance of such high energy pur-pyr base-pairs was hypothesized soon after the discovery of the double helix [1,6,7], there have been very few reports documenting their experimental observation. Recent studies suggest that such base-pairs can exist ubiquitously but transiently and in low abundance, and that they can be stabilized through intermolecular interactions or functionally important chemical modifications. Thus, there is good reason to believe that high energy pur-pyr base-pairs and base-mispairs exist in greater abundance than previously thought, and that they expand the structural and functional diversity of both canonical and non-canonical base-pairs.

Figure 1



Low and high energy pur-pyr pairing schemes. Hydrogen bonding partners for low energy WC and WB pairs are shaded blue, while high energy HG and WC-like mispairs' hydrogen bonding partners are shaded red. **(a)** Canonical Watson-Crick G•C and A•T pairs. A rough average WC C1'-C1' distance is shown as a dashed blue line for comparison with Hoogsteen pairs. **(b)** Neutral G•T wobble and ionized A<sup>+</sup>•C wobble. **(c)** G•C<sup>+</sup> and A•T Hoogsteen pairing geometry, where purines are shown in the *syn* conformation. A rough average HG C1'-C1' distance is shown as a dashed red line, reflecting the constriction of the C1'-C1' distance by ~2.5 Å. **(d)** Deprotonated guanine in a WC-like G•T mispair is shown alongside an imino adenosine in a WC-like A•C mispair. Although different tautomers and ionization states can explain the WC-like geometry, only two were shown for brevity. Possible ionized & tautomeric states that can explain the WC-like geometry for G•T mispairs include: G(enol), T(enol), G(N1-) and T(N3-). For A•C mispairs they include: A(lmino) and C(lmino).

### Methods for characterizing transient base-pairs and base ionization and tautomerization

There are several challenges in characterizing high energy pur-pyr base-pairs in nucleic acids. First, their energetic instability relative to other competing base-pairs in naked duplexes means that if they exist, they do so only transiently for short periods of time and in low abundance. Second, even when stabilized appreciably, characterizing such pur-pyr base-pairs can prove challenging by conventional spectroscopic techniques. For example, it can be difficult to distinguish HG from

WC base-pairs by X-ray crystallography because the *syn* purine in a HG base-pair often entails small geometrical differences as compared to an *anti* purine in a WC base-pair, particularly for A•T base-pairs (Figure 2a) [8,9]. On the other hand, base ionization and tautomerization involves movement or loss of protons, which are not directly observed by X-ray crystallography. As a result, such base-pairs have to be inferred based on heavy atom positions, taking into account potential hydrogen bonding schemes and the local steric and electrostatic environment. Although solution nuclear magnetic resonance

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