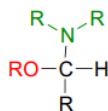
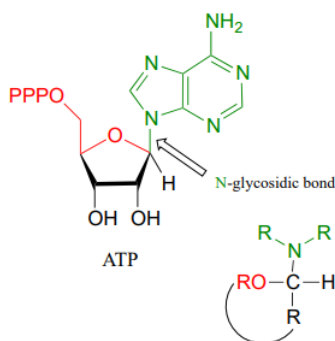


10.5: N-glycosidic Bonds

We have just seen that when a second alcohol attacks a hemiacetal or hemiketal, the result is an acetal or ketal, with the glycosidic bonds in carbohydrates providing a biochemical example. But if a hemiacetal is attacked not by a second alcohol but by an amine, what results is a kind of ‘mixed acetal’ in which the anomeric carbon is bonded to one oxygen and one nitrogen.

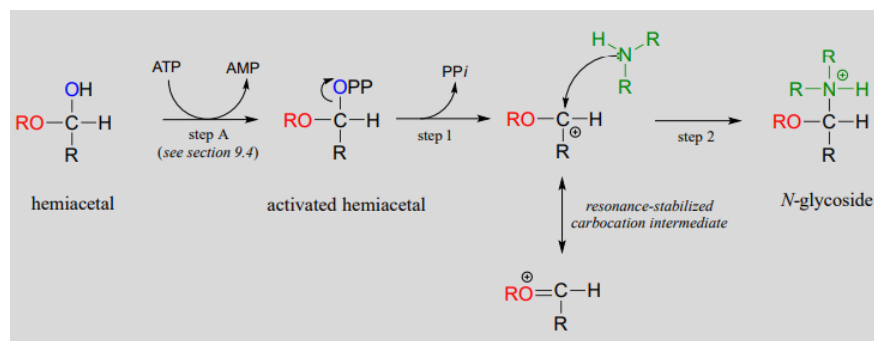


This arrangement is referred to by biochemists as an *N*-glycosidic bond. You may recognize these as the bonds in nucleosides and nucleotides that link the G, C, A, T, or U base to the sugar.

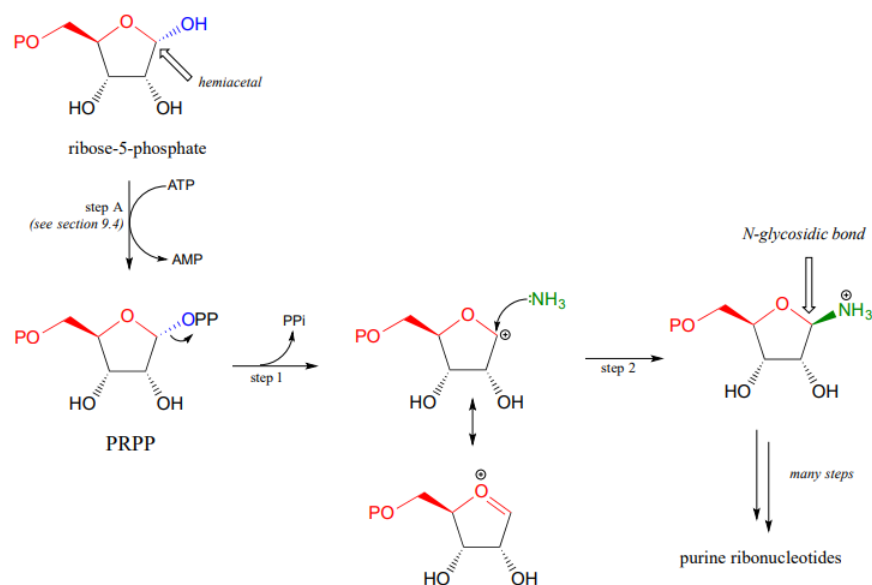


The formation of *N*-glycosidic bonds in ribonucleotides is closely analogous to the formation of glycosidic bonds in carbohydrates – again, it is an S_N1 -like process with an activated water leaving group. Typically, the hemiacetal is activated by diphosphorylation, as illustrated in step A of the general mechanism below.

Mechanism for formation of an *N*-glycosidic bond:



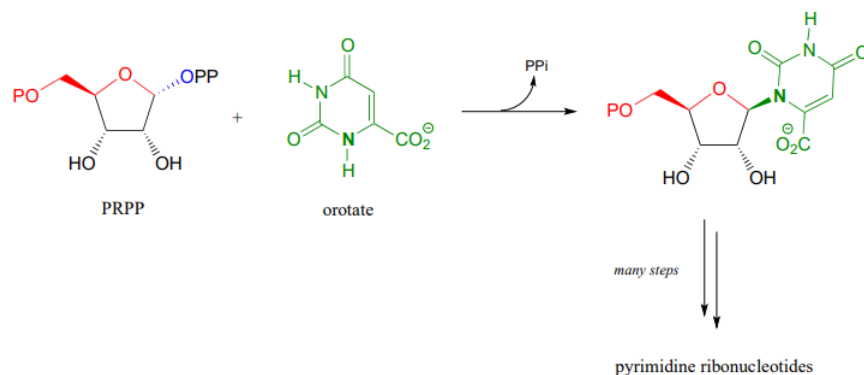
The starting point for the biosynthesis of purine (G and A) ribonucleotides is a five-carbon sugar called ribose-5-phosphate, which in solution takes the form of a cyclic hemiacetal. The critical *N*-glycosidic bond is established through substitution of NH_3 for OH at the anomeric carbon of the ribose. The anomeric OH group is first activated (step A below) to form an activated intermediate called phosphoribosylpyrophosphate (PRPP). The inorganic pyrophosphate then leaves to generate a resonance-stabilized carbocation (step 1) which is attacked by a nucleophilic ammonia in step 2 to establish the *N*-glycosidic bond.



With the *N*-glycosidic bond in place, the rest of the purine base is assembled piece by piece by other biosynthetic enzymes.

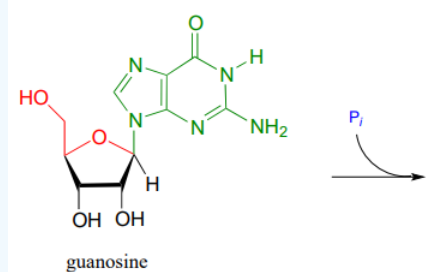
(The mechanism above should look familiar - we saw step A in chapter 9 as an example of alcohol diphosphorylation, and steps 1 and 2 in chapter 8 as an example of a biochemical S_N1 reaction).

Establishment of the *N*-glycosidic bond in biosynthesis of the pyrimidine ribonucleotides (U, C and T) also begins with PRPP, but here the ring structure of the nucleotide base part of the biomolecule has already been 'pre-fabricated' in the form of orotate:



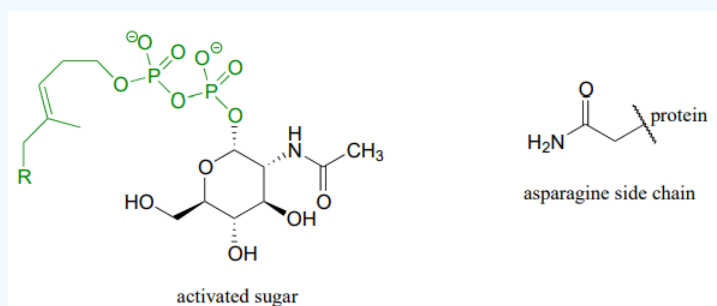
? Exercise 10.5.1

We have just seen an illustration of the formation of an *N*-glycosidic bond in a biosynthetic pathway. In the catabolic (degradative) direction, an *N*-glycosidic bond must be broken, in a process which is analogous to the hydrolysis of a glycosidic bond (illustrated earlier). In the catabolism of guanosine nucleoside, the *N*-glycosidic bond is broken by inorganic phosphate (not water!) apparently in a concerted (S_N2 -like) displacement reaction (Biochemistry 2011, 50, 9158). Predict the products of this reaction, and draw a likely mechanism.



? Exercise 10.5.2

Glycoproteins are proteins that are linked, by glycosidic or *N*-glycosidic bonds, to sugars or carbohydrates through an asparagine, serine, or threonine side chain on the protein. As in other glycosylation and *N*-glycosylation reactions, the hemiacetal of the sugar must be activated prior to glycosidic bond formation. Below is the structure of the *activated* sugar hemiacetal substrate in an asparagine glycosylation reaction



Draw the product of the asparagine glycosylation reaction, assuming inversion of configuration of the anomeric carbon.

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