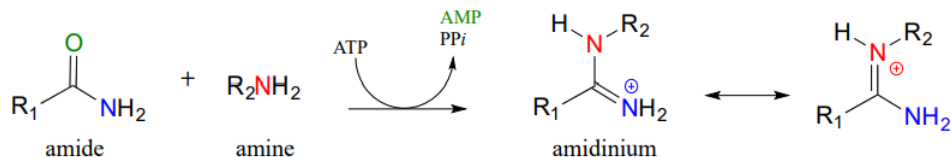


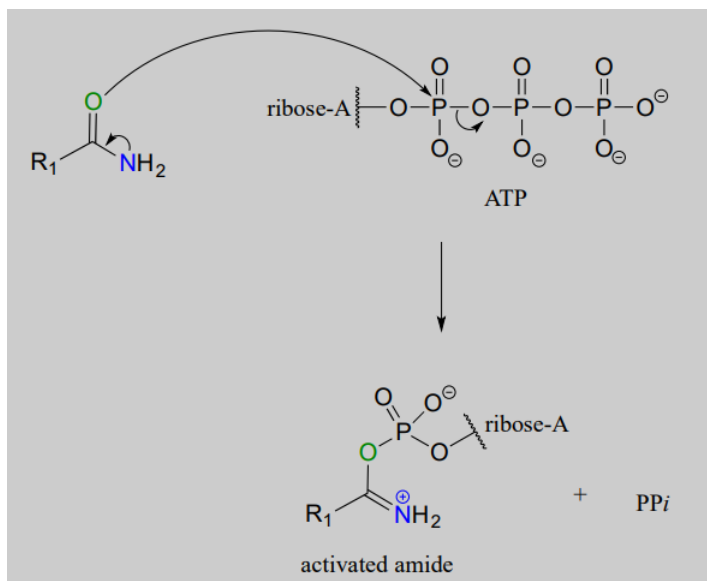
11.9: Nucleophilic Substitution at Activated Amides and Carbamides

In discussing the nucleophilic acyl substitution reactions of acyl phosphates, thioesters, esters, and amides, we have seen many slight variations on one overarching mechanistic theme. Let's now look at a reaction that can be thought of as a 'cousin' of the nucleophilic acyl substitution, one that follows the same general pattern but differs in several details. Below is a generic illustration of this reaction type:



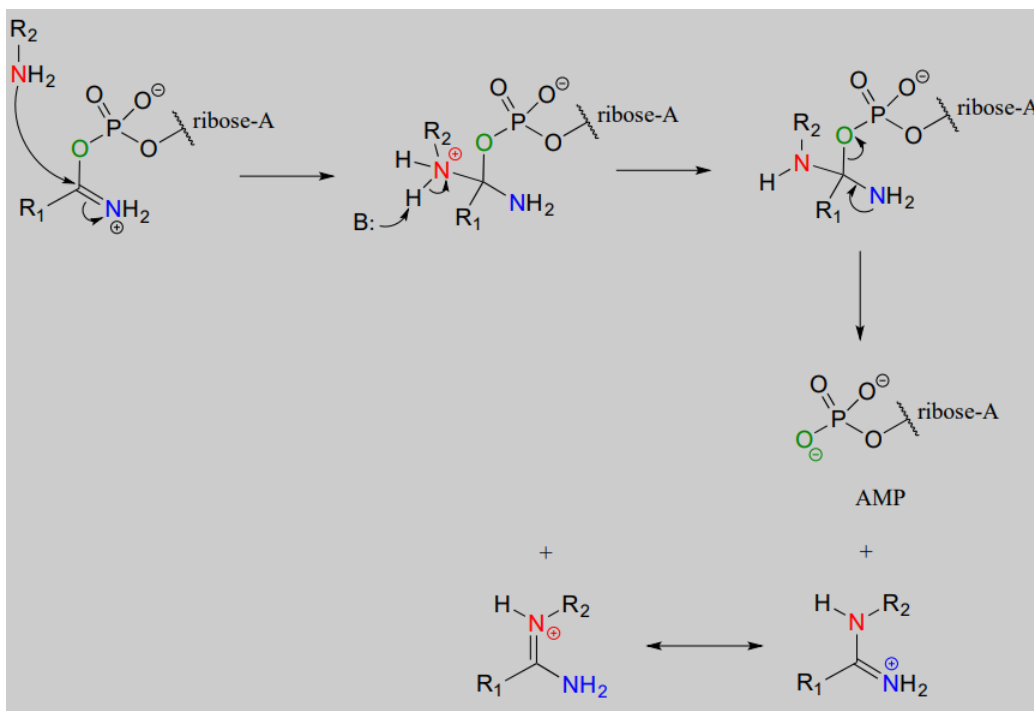
Looking at this reaction, you can see that substitution is occurring at an amide group, but the atom that gets expelled is the amide oxygen rather than the amide nitrogen. Also, we see that the substituting nucleophile is an amine, and the product is a functional group referred to as an amidinium ion (the uncharged conjugate base is called an amidine, and the pKa of the group is close enough to 7 that it can be shown in either protonated or deprotonated form in a biological context). As we learned previously in this chapter, amides are comparatively stable to nucleophilic substitution, and thus it stands to reason that the starting amide must be activated before the reaction can take place. This occurs, as you might predict, through the formation of an acyl phosphate intermediate at the expense of one ATP molecule. The amide oxygen acts as a nucleophile, attacking the α -phosphate of ATP to form the activated acyl-AMP intermediate:

Substitution at an activated amide, phase 1 (activation):

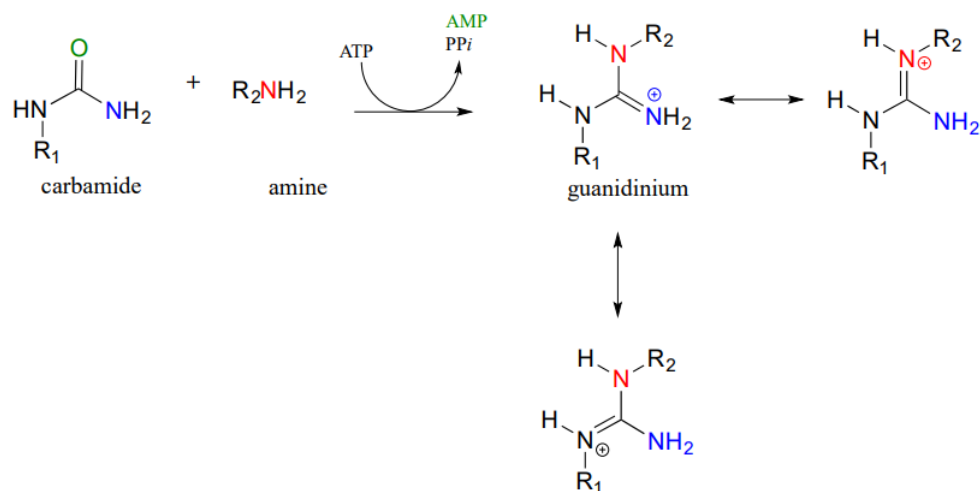


Next, a kind of acyl substitution occurs that we have not yet seen: an amine nitrogen attacks the electrophilic carbon of a carbon-nitrogen double bond, and the reaction proceeds through a tetrahedral intermediate before the AMP group is expelled, taking with it what was originally the carbonyl oxygen of the starting amide.

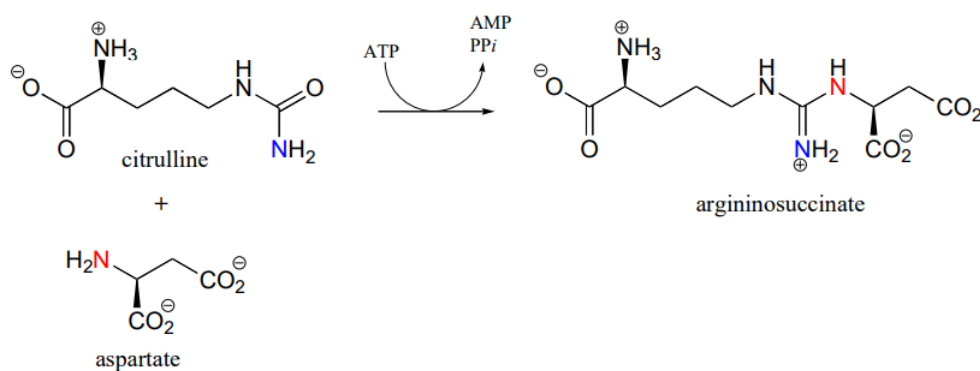
Substitution at an activated amide, phase 2:



Carbamides, a kind of 'double amide' functional group in which a carbonyl oxygen is bonded to two nitrogens, also undergo this type of reaction, leading to the formation of a guanidinium/gaundine functional group (look again at the structure of the amino acid arginine and you will see that it contains a guanidinium group on the side chain).



The reaction catalyzed by argininosuccinate synthetase (EC 6.3.4.5) is the second step in the urea cycle, a four-step series of reactions in which ammonia is converted into urea for elimination in urine. Note that the substitution takes place at the carbamide group of citrulline, the nucleophilic amine is on aspartate, and the product has a guanidinium functional group.



? Exercise 11.9.1

- Draw the structure of the 'activated carbamide' intermediate in the reaction above.
- Draw the structure of the cyclic product of a hypothetical intramolecular substitution reaction of citrulline (ie. aspartate is not involved).

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