13.3.2 The urea cycle

Ammonia is an important product of nitrogen catabolism. Some is re-used in the biosynthesis of new nitrogen-containing compounds, but the remainder must be excreted. Different organisms use one of three ways to get rid of this excess ammonia:

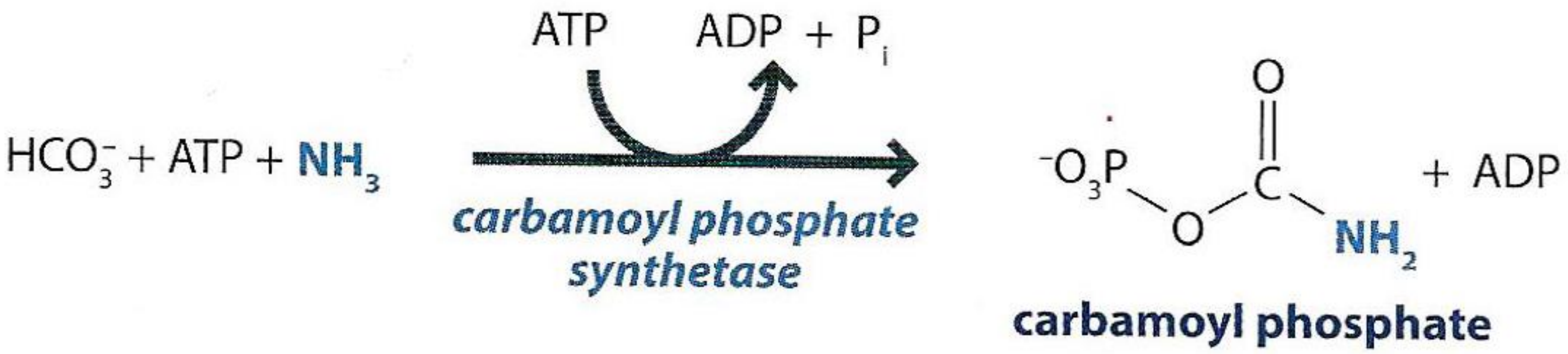
- **Ammonotelic** species include many aquatic invertebrates and these organisms simply excrete the ammonia into the water in which they live.
- **Uricotelic** organisms excrete nitrogen in the form of uric acid. These species include birds, snakes, land-dwelling reptiles, and arthropods such as insects.
- **Ureotelic** organisms include mammals, amphibians and some fish, which convert ammonia into urea, which is excreted in the urine.

The pathway by which humans and other ureotelic organisms convert ammonia to urea is called the urea cycle. We will follow through the steps in the urea cycle and then examine how the cycle is controlled.

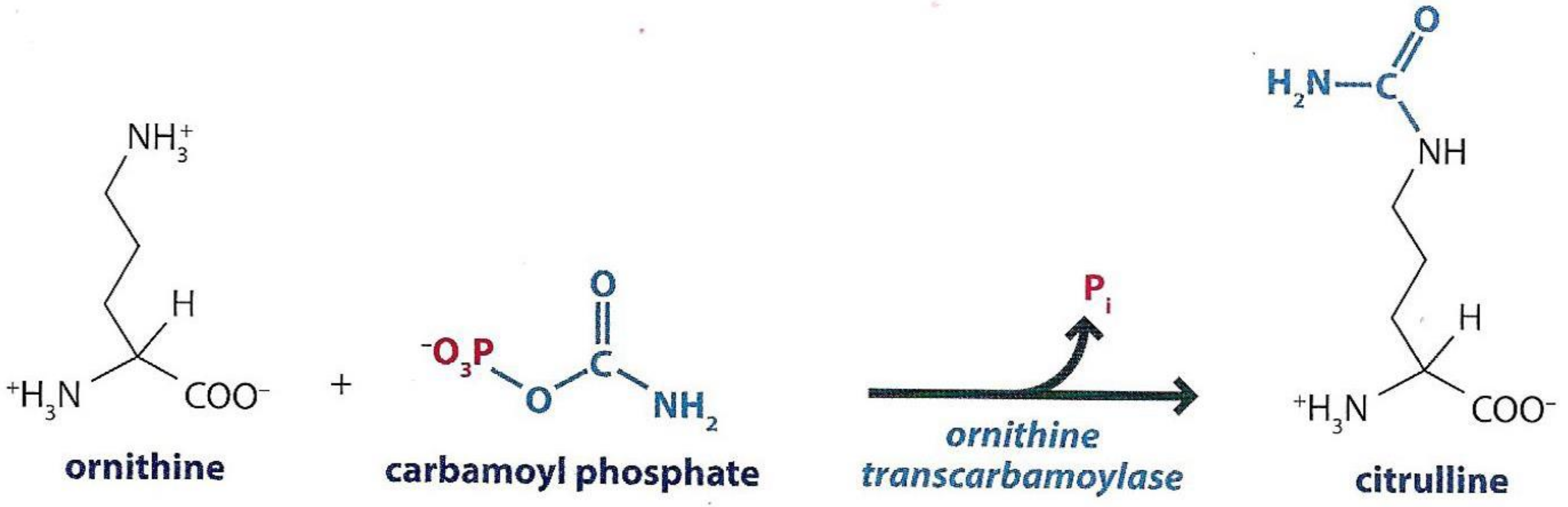
The urea cycle enables excess nitrogen to be excreted as urea

The urea cycle is carried out in the liver, with the resulting urea passed via the bloodstream to the kidneys from where it is excreted in the form of urine. The pathway is shown in outline in *Figure 13.22*. The individual steps are as follows:

Step 1. Ammonia enters the urea cycle after conversion to carbamoyl phosphate, which requires addition of a bicarbonate ion and a phosphate group from ATP. A second ATP is required to provide energy. The enzyme that catalyzes this reaction is **carbamoyl phosphate synthetase**.

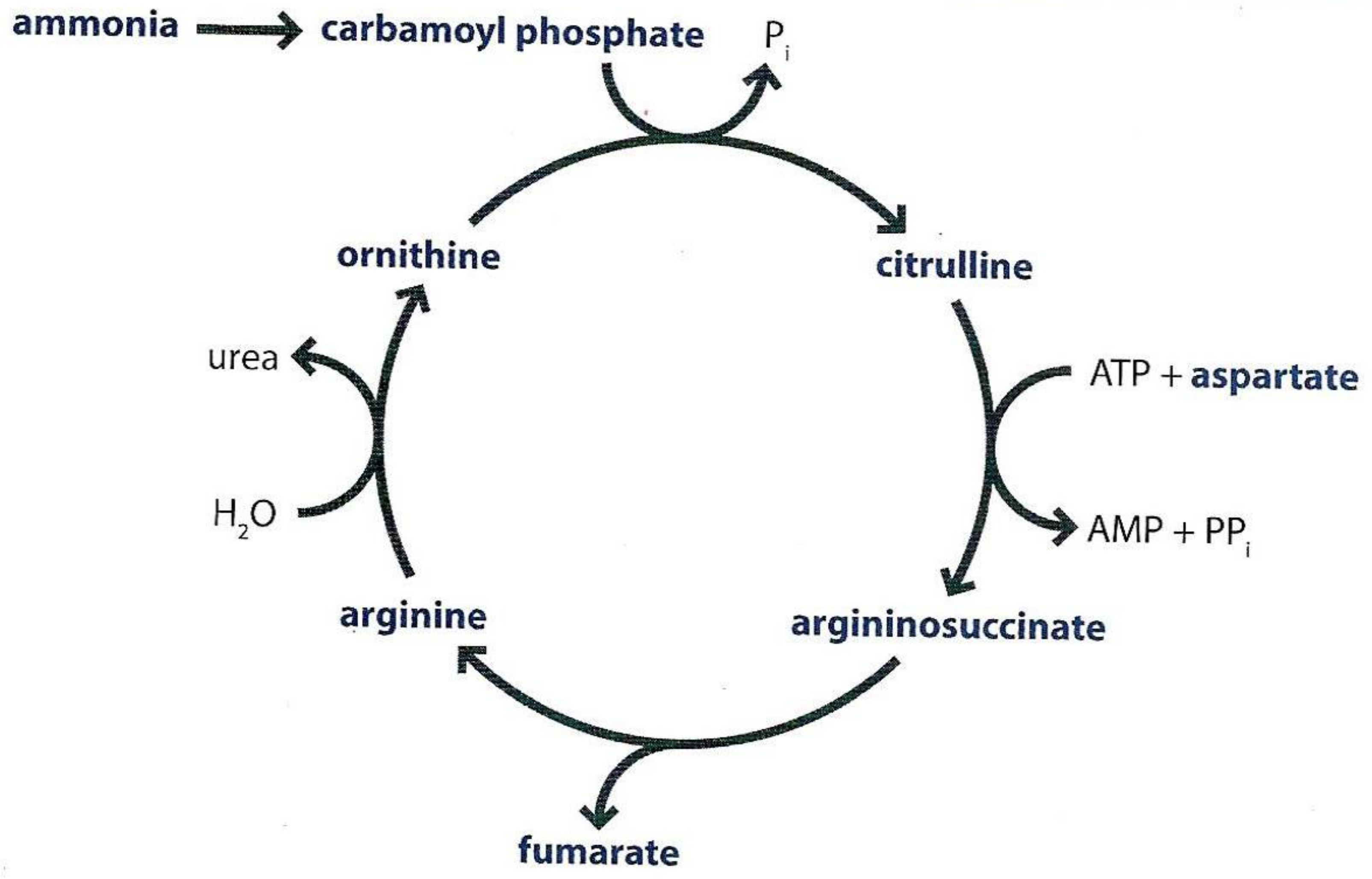


Step 2. The carbamoyl group is now transferred to an ornithine molecule by **ornithine transcarbamoylase**, to give **citrulline**.

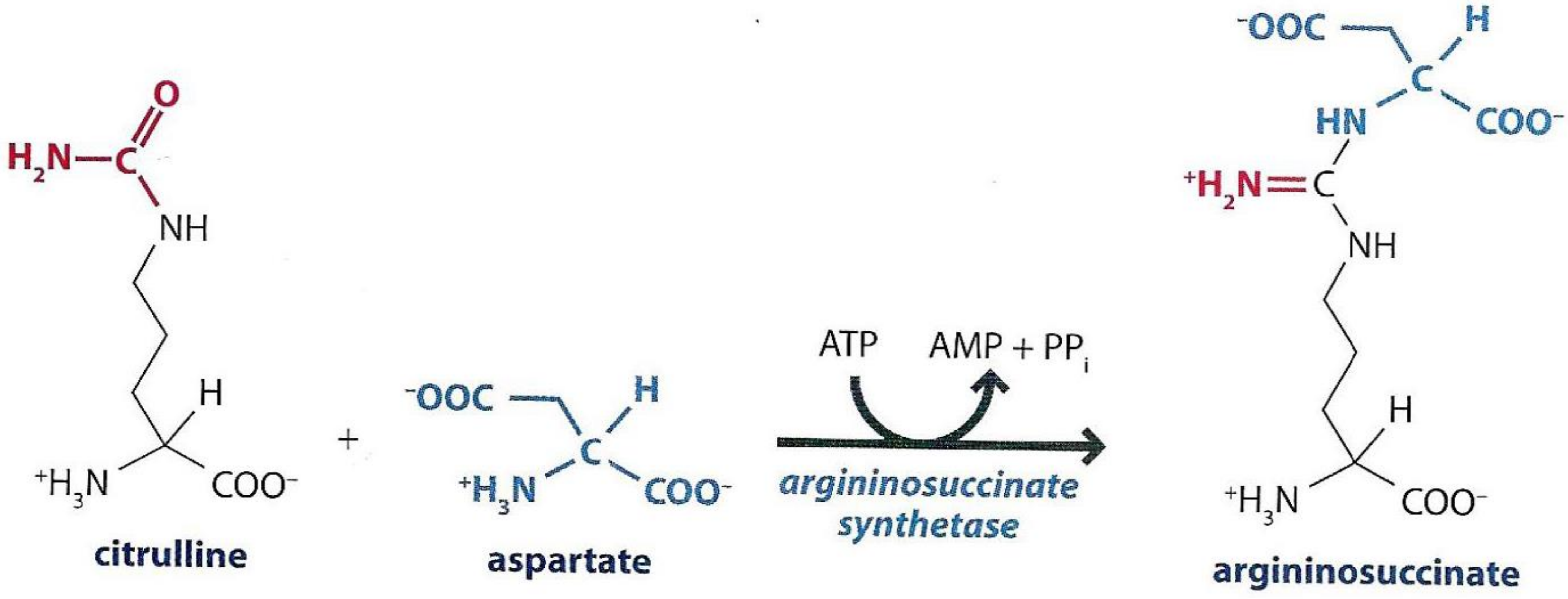


Both ornithine and citrulline are amino acids, but not ones that are used in protein synthesis. **Steps 1** and **2** take place in the mitochondrial matrix, but the remainder of the urea cycle occurs in the cytoplasm. The citrulline is therefore transported out of the mitochondrion.

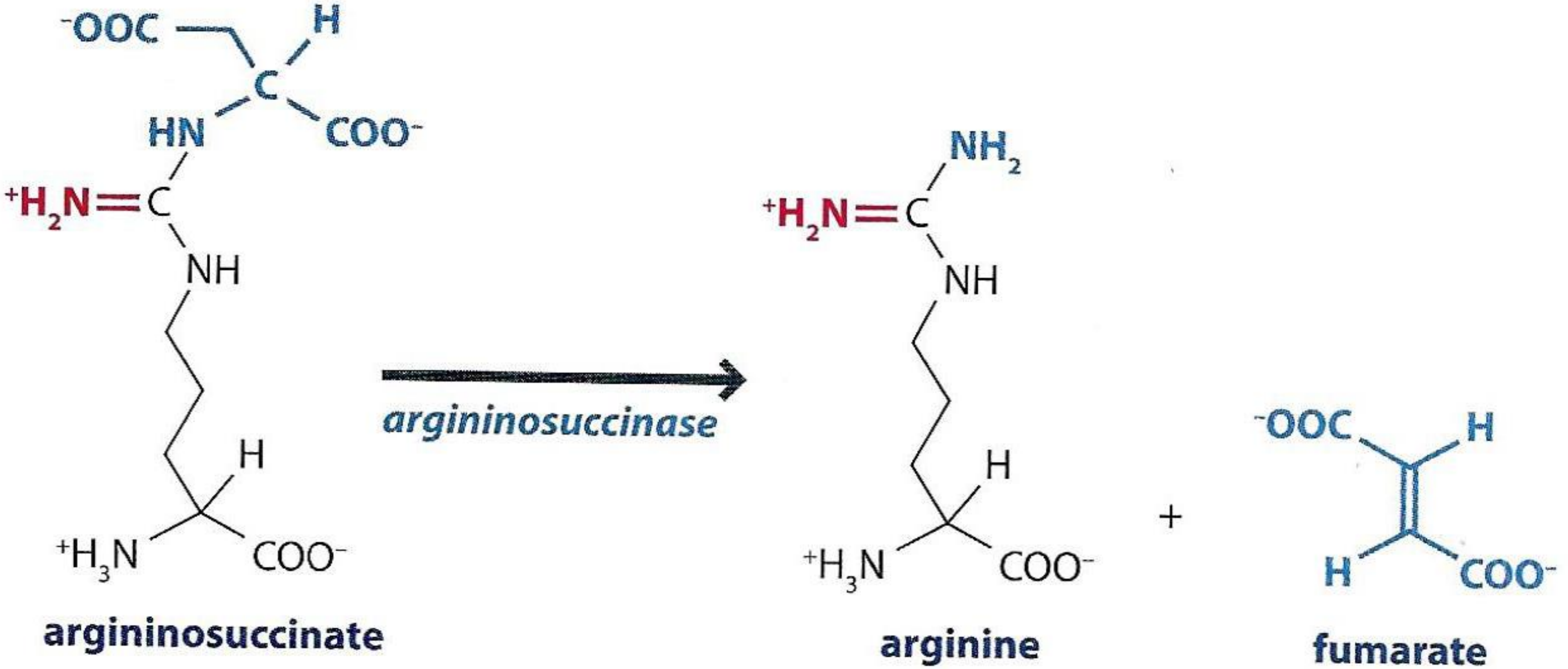
Figure 13.22 Outline of the urea cycle.



Step 3. A condensation reaction between citrulline and aspartate gives argininosuccinate. An ATP is converted to AMP in this reaction catalyzed by **argininosuccinate synthetase**.

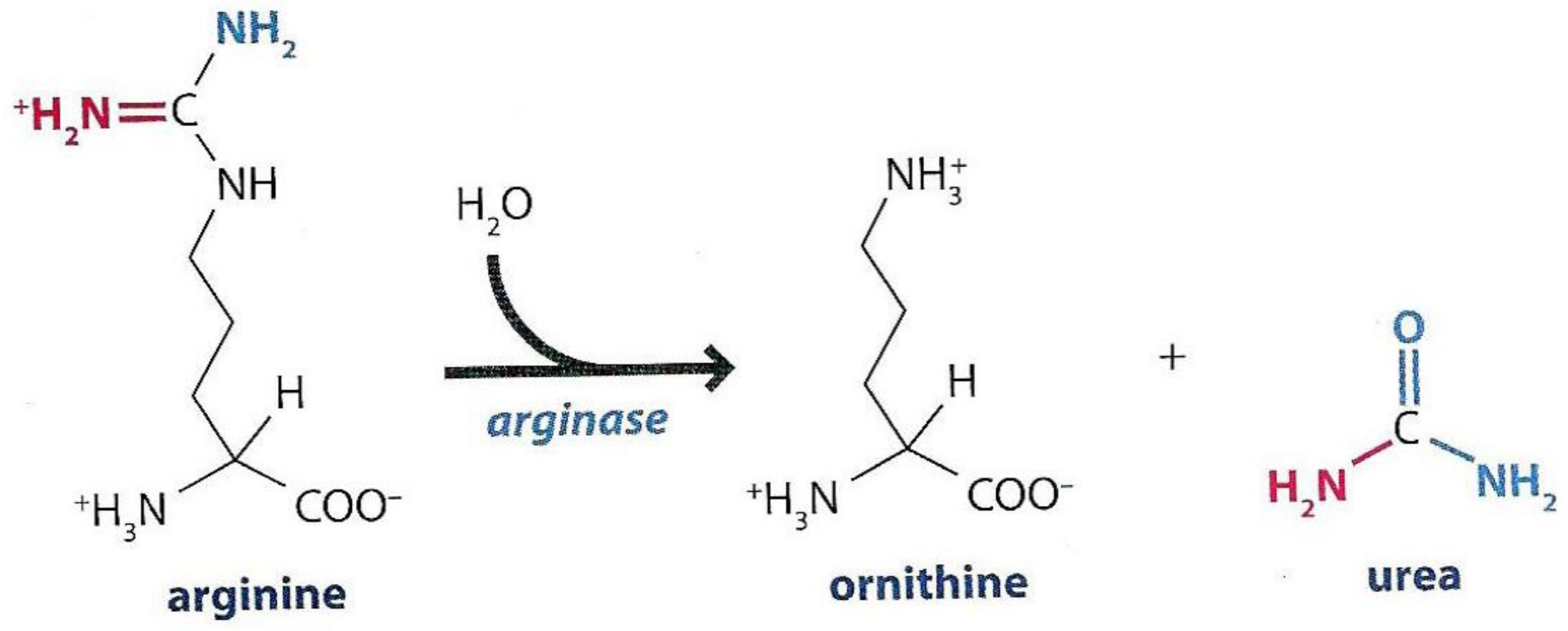


Step 4. The carbon skeleton of aspartate is removed from argininosuccinate by **argininosuccinase**. The products are arginine and fumarate.



The outcome of ***Steps 3*** and ***4*** is to transfer the amino group of the aspartate to citrulline. The aspartate is converted to fumarate, a non-nitrogenous carbohydrate, and citrulline is converted to arginine.

Step 5. **Arginase** cleaves arginine, producing a molecule of urea and regenerating the ornithine used up at the start of the cycle.



The ornithine shuttles back into the mitochondrion so that the cycle can recommence.

Regulation of the urea cycle involves a metabolic dead end

The rate at which the urea cycle needs to operate depends on several factors, including the composition of the diet. A protein-rich diet requires rapid operation of the urea cycle to deal with the excess ammonia that is generated as the amino acids are broken down so that their carbon skeletons can be used for energy.