

Fundamentals and Applications of Supramolecular Chemistry
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Week 08
Lecture 40

W8L40_Ion transport processes

So, let us continue the further discussion. Hello everybody. So, in the previous lecture, we were looking at the processes of transport. I told you about the uniport mechanism, where you have movement of the ion in a particular direction; you can have the symport mechanism, where the cation and the anion can move in the same direction, and you can have the cation and the anion moving in opposite directions, referred to as an antiport process.

Now, these are extremely important processes in biological systems. For example, we are aware of the fact that we need to maintain the sodium and potassium concentrations in our body at the optimal level so that the body functions in an optimal way.

And what is the most important requirement in the body? To do work; and when we do work, the system burns energy, and the energy is released by the conversion of ATP to adenosine diphosphate and then to adenosine monophosphate.

So, there is a stepwise process because ultimately, we need to convert glucose to carbon dioxide and water. So, in this process, what happens is that the energy is stored in the body. Now this energy has to be released; for example, when muscle contraction takes place, these reactions start, where ATP has to be converted to ADP.

This process of energy release is catalyzed by a class of enzymes called ATPases, of which the sodium and potassium ion ATPase is the most important example. Also, we need to keep in mind that one mole of ATP releases 35 kJ/mol of energy.

So, we essentially now have the ribose part, along with the adenine part, and then this is covalently connected here. So, this is covalently connected to $\text{CH}_2\text{-O-(P=O)-O-}$, -O-(P=O)-O- , -O-(P=O)-O- , -O- . So, we have this adenosine triphosphate, and now there is a cleavage of this particular bond, and this happens in the presence of a magnesium ion, and the ΔG of this process is -35 kJ/mole .

And it gives you the $[\text{H}_2\text{PO}_4]^-$ ion, plus the ribose, adenine, and ADP, and this is the inorganic phosphate that is released, and magnesium acts as a catalyst for this particular process.

So, it is a very important process because the P-O bonds are the strongest bonds, and when they break, the maximum amount of energy is released when it converts into the inorganic phosphate and adenosine diphosphate.

And now, coming to the application of this, you first need to know the biochemical concentrations of potassium ions and sodium ions in millimoles per kg of the body. So, this is the human intracellular fluid. The potassium ion concentration is 92, the sodium ion concentration is 11, whereas in the human extracellular fluid, which we also call blood plasma, the potassium ion concentration is 5 and the sodium ion concentration is 152.

Now, if you look at this process here, we can show it in the form of a box. So, what happens is that now the potassium concentration inside is greater than that outside, and the sodium concentration outside is greater than that inside.

So, because of this, what happens is that the natural concentration gradient operates in a way that the potassium ion flows from a higher concentration to a lower concentration. So, it goes from inside the cell to outside the cell, where the concentration is lower, whereas for the sodium ion, it goes from the outside to the inside of the cell. But what we actually need to do in these biochemical processes is to uptake potassium ions.

So, potassium ions have to be taken inside now. Potassium ions have to be taken in, potassium ions have to go inside, and this is against the concentration gradient, and sodium ions have to come outside.

So, this has to be excluded (sodium ion from inside), and this has to be included inside (potassium ion). This is against the concentration gradient, and the process of pumping potassium ions from the outside to the inside of the cell, and sodium ions from the inside to the outside of the cell, is done using this Na^+/K^+ - ATPase enzyme.

Because this is not a natural process, it is occurring against the concentration gradient, and what this enzyme does is that it essentially scavenges the sodium ion from inside and puts it outside, and the potassium ion it takes from outside and puts it inside, and this is against the concentration gradient, and this is done by this ATPase enzyme.

In the biological system, specifically in the human system, this process of transporting potassium ions against the concentration gradient, as well as sodium ions, is carried out by a class of molecules referred to as ionophores, and this is accomplished using a carrier mechanism.

So, there are different types of mechanisms that can transport the ions; one is the carrier mechanism, and the other is the channel mechanism, where there exist channel-like structures in the bilayer across which the ions can be transported.

In a carrier mechanism, the ions, which are actually hydrophilic, must be transported across the bilayer, which is of a lipophilic nature, and because it is of a lipophilic nature, we will have to modify the environment around the cation so that the cation can be transported effectively across the bilayer.

So, in this regard, the carrier mechanism has to operate, and the species that will be able to carry the potassium ions across the bilayers are referred to as ionophores. The traditional examples of these naturally occurring ionophores are nonactin and valinomycin.

Just to look at the structures, these are pretty large structures; actually, I can draw this for you. The structures are as follows: this is three times. So, here we have DHYI; this is called D-valine, this is lactic acid, and that is L-lactic acid, which we call L-lac; this we call D-val, and this is D-hydroxy isovaleric acid, which is DHYI. We have D-valine as well, and then this becomes L-valine. So, we have DHYI, D-valine, L-lactic acid, and L-valine now.

These essentially make up the valinomycin structure, and here you can see that you have got the polar parts, and you also have got the non-polar parts. So, when you have this kind of arrangement, this kind of very specific spherical arrangement, we see that the ionophore is also pre-organized because this is the cyclic structure, and now what happens when it interacts with the potassium cation?

Now, because the ionophore has to capture the potassium cation, it will interact with these oxophilic or hydrophilic carbonyl groups. And now, when these oxygen atoms point towards the potassium cation, they will encapsulate it, and the isopropyl groups shall be present as a lipophilic exterior.

They will now present a lipophilic exterior, and because of this, what will happen is that the potassium ions can be effectively transported across the bilayers. Let us see how this takes place.

So, to understand this ion-transport mechanism, chemists have actually started making synthetic ionophores, and in this regard, the 18-crown-6, which we have already discussed, functions as a very efficient ionophore.

So, in this regard, we would like to understand the ion-transport mechanism. So, let us look at this process. So, we now have the chambers here. We have this as the lipophilic membrane; this is the hydrophobic part.

And we know that the hydrophilic part is always solvated by the water molecules, which are in the extracellular space or in the intracellular space. So, this is the extracellular space; this is the intracellular space.

We now have the potassium ions, and these are actually first captured by the organic ligand, which we call the ionophore. And where will they be captured essentially? When they are captured by the ionophore, only then will they be able to be transported across this lipophilic membrane. So, before we go there, let us first take the metal ions, which are actually solvated by the water molecules.

So, this is the aqueous layer. Now what happens? The desolvation has to take place; you see the solvent loss, and now the metal ions will be captured here. Effectively, you will have the oxygen sites here, and so the ionophore comes and picks up the metal ion, forming a particular complex.

Then this particular complex will be transported from the outside to the inside of the cell, and it will now present the lipophilic sheet towards the interior of the cell, and it will present the metal ion to the hydrophilic part, and will now be released into the intracellular space. So, we have the metal ion, which will be transported by the ionophore that exists in a particular conformation.

Upon encapsulation, it has this particular arrangement; it is now being transported and then released into the intracellular space, where you now have the solvent molecules that will pick up the metal ion and get solvated. So, this is how the metal ions have been transported across the bilayer.

This is to show you that synthetic equivalents of the naturally occurring ionophores have been designed that can transport the potassium ion very effectively, and this is referred to as a carrier mechanism. And so naturally, as I told you, this particular process is being carried out by the Na^+/K^+ - ATPase enzyme. This is the enzyme that catalyzes this process.

As we have now realized that in the case of the natural system, what is happening is that the potassium ions are being taken inside from the outside against the concentration gradient.

And the sodium ions have to be taken from the inside to the outside, against the concentration gradient, and the overall reaction that takes place in the natural system is as follows.

So, we have three Na^+ intracellular, plus two K^+ extracellular, plus ATP^{4-} , plus water in the presence of magnesium, taking 3 sodium ions to the extracellular, plus 2 potassium ions to the intracellular, plus now releasing ADP^{3-} , plus $[\text{HPO}_4]^{2-}$, plus H^+ . Ok. So we have a net charge of plus 1 here, a net charge of plus 1 here.

So, we have the conversion from ATP to ADP, and we also have the ion-pump mechanism, which operates where the potassium ion is taken from the outside to the inside against the concentration gradient, and the sodium ion is taken from the inside to the outside against the concentration gradient.

So, we have this movement of these ions across this particular bilayer, which is actually facilitated by the Na^+/K^+ - ATPase enzyme, and this enzyme, I should tell you, is a membrane protein. So, this is a membrane protein that has a molecular weight of 294 kilodaltons, and the active site actually consists of 2 peptides, which we call alpha-beta, and overall, this alpha-beta dimer makes up the active site. And this is what this enzyme looks like. The structure facilitates the transportation of the potassium ion.

Overall, this particular transport process has also been explained in the form of a pump storage model. So, you have a process where if you plot the energy as a function of the spatial coordinate, you will see that we are actually pumping the ions—potassium ions and sodium ions—against the concentration gradient.

So, this is the pumping mechanism, which is actually the active process, and we also have the passive process, the gating mechanism, which is the passive process. So, the natural mechanism, as we saw, was that the concentration of potassium ions inside is greater than that outside. So, the natural mechanism is to go from inside to outside, but we actually need the reverse process.

We need potassium ions to go inside, and this is done using a pump mechanism, and in this case, we will say that the metal ions are pumped from low concentration to high concentration, against the concentration gradient, until a dynamic non-equilibrium state is reached, in which active pumping is balanced by diffusion.

And in order to activate the gating process, a certain hormone or chemical messenger, for example, acetylcholine, can selectively activate and open up the gated ion channels, allowing the passive and therefore rapid flow of ions back to equilibrium, resulting in the flow of current.

So, this is the overall explanation: metal ions are being pumped from low to high concentration, against the concentration gradient, because you have a dynamic non-equilibrium state in which active pumping has to be balanced by diffusion.

The process of diffusion will start only when there is a stress to the system, an impulse, or a chemical messenger or hormone that can activate or open up these gated ion channels, which allows the rapid diffusion of the ions back to equilibrium. This process creates a flow of current and plays an important role in nerve transduction.

That is how the nerves carry the electrical current and why this process occurs. So, this signal nerve transduction in the nervous system is done in this particular process, and we also realize that overall, this is relevant in the biological system.

This is how the sodium ion and potassium ion together operate as a pump mechanism to maintain equilibrium in the body. So, we will just take up another example, where we will be looking at another very important application of these cations. So, we have looked at the sodium-potassium pump.

We can also look at another example, where just as you have these naturally occurring ionophores, people were also interested in looking at other species in which cations have to be taken up to perform the necessary biological processes at the cellular level. Another very important class of molecules is referred to as siderophores.

In the case of siderophores, what has been observed is that the essential element that has to be taken up is iron. And iron, as we know, has enormous applications because it plays a very important role in oxygen uptake and, hence, is relevant in cellular processes. And the problem with iron is that Fe^{3+} is insoluble.

For example, it exists as rust in aqueous solution, and at a physiological pH of about 7.4, the solubility of the iron hexa-aqua $3+$ is around 10^{-18} dm mole per dm cube. Whereas in the case of microorganisms, the optimal concentration is 10^{-7} mole dm cubed. So, how do we achieve this required concentration of Fe^{3+} inside the microorganisms?

So, we need a certain ligand in the biological system that will capture Fe^{3+} and deliver it to the cell. These highly effective iron complexing agents are called siderophores.

They come from the Greek word meaning "iron bearer." The siderophores were discovered as early as 1911, but it was only in 1951 that the first natural siderophore was discovered, which was called Mycobactin. Mycobactin was the first natural siderophore discovered, and after that, another siderophore called Enterobactin was discovered as well.

And what is essential in these particular complexes is a pretty large-sized ligand, but what they have is that they have got the catechol moiety. In this catechol moiety, they have the dihydroxylated groups, and these dihydroxylated groups get deprotonated at slightly alkaline pH.

And then this is because they are O minus; they are now able to interact with the Fe³⁺ and capture it very effectively. So, what essentially happens here is you have now got, in the case of entrobactin, this CO₂ N-H backbone, which is here, and then what will happen if I give you a skeleton view of this. The most important part is that you will now have this O⁻, O⁻, O⁻, and O⁻, and then you will have the third one from here.

So, you will have O⁻, O⁻. This is how they will come out, and this entire set of 6 oxygens will now capture Fe³⁺, forming a trigonal prismatic geometry. And so, we have these deprotonated hydroxyl groups, and these catecholate moieties are there. The overall charge on the ligand is 6⁻, and then it interacts with Fe³⁺, forming [Fe-L]₃⁻.

The overall charge on the ligand now is 3⁻, and the binding constant, which is very high at 10 to the power of 52, indicates that these are extremely stable chelating agents for iron.

And this is what makes them very efficient siderophore, because they can capture Fe³⁺; now the binding is extremely efficient, and it is able to form the trigonal prismatic geometry, where Fe³⁺ coordinates with these deprotonated hydroxyl groups, to form the [FeO₆]₃⁻ species.

So, thus we see that nature has developed, you know, very facile and very robust mechanisms, so that these processes, go on in a very efficient manner, over millions of times. And supramolecular chemists, have tried to design ligands, that can actually mimic the active site of the naturally occurring substances.

And this is what also constitutes an important application of supramolecular chemistry, in biology: people have now started designing better and better molecules that can actually mimic the natural processes occurring in nature.

For example, people want to now develop oxygen uptake models, or make models that mimic the plant photosynthesis processes, and so on and so forth. So, with this, I hope you have been able to appreciate the role of ion transport in biological systems, and in the next set of lectures, we will now switch to the other systems, that particularly involve self-assembly processes.

Thank you.