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Nobel prize for chemistry

This year's Nobel prize for chemistry has been awarded to Rudolph A. Marcus of the California Institute of Technology, Pasadena, California, USA *for his contribution to the theory of electron transfer reaction in chemical systems.*

In the mid-fifties I heard a seminar by Rudolph Marcus on *Molecular Reaction Rates* at the Polytechnic Institute of Brooklyn. At that time much information had been gathered by spectroscopists on the vibrational properties of many kinetically interesting molecules. Marcus tried to ingest this knowledge into the theory of molecular reaction rates. This must have been the beginning of his now renowned work, which resulted in his being awarded this year's Nobel prize.

When two molecules (in a solution) exchange one or more electrons, there is a 'redox' process in which one molecule accepts the electrons (reduction) and the other loses them (oxidation). The possible mechanisms of redox reactions in inorganic systems were first considered by Henry Taube of Stanford—the 1983 chemistry Nobel prize winner. So innovative were his experiments that Taube is considered the godfather of the area of electron transfer reactions.

The approach that Marcus made was different. In his way of thinking, in such reactions no chemical bonds are broken; only changes take place in the structure of the reacting molecules and their nearest neighbours. These molecular changes enable electrons to jump between the molecules. The rate and efficiency of this electron transfer are influenced by various structural and thermodynamic factors. These are the intervening medium, the orientation of the molecules (the parameters that affect such orientation), the reorganization of the energies of the donor and the acceptor, diffusional, collisional and electrostatic factors. At first all these appeared to be vague speculations but they were quantified by Marcus and the theory became a grand unifying theme.

In this theory an important criterion is that changes take place in the structure both in the reacting molecules and those in the solution medium. The

Rudolph Marcus

energy of the molecular system therefore rises temporarily, enabling electrons to transfer between the molecules. Energy must obviously be supplied to the electron to cross the energy barrier. The size of the energy barrier determines the speed of the reaction. Strangely enough although in some cases in which large energy barriers were not at all expected, the rates of reaction turned out to be exceedingly slow.

Between 1956 and 1965 Marcus published a series of papers which led to the solution of this problem of *greatly* varying reaction rates. He made two assumptions about the reacting molecules. Firstly they were bonded very loosely to each other during the course of the reaction. Secondly he assumed that the solvent molecules in the immediate vicinity change their positions, thus increasing the energy in the molecular system. The electron can only jump between two states that have the same energy and this condition is fulfilled by increasing the energy of both the molecules.

Marcus found a simple mathematical formula for calculating the energy change and was also able to estimate the size of the energy barrier. He further developed a model by which the energy barrier could be obtained as a sum of the terms characterizing each of the two components of the reaction. Finally he derived a general connection between the speed of the electron transfer and the free energy changes of the reactions, i.e. its driving force.

The general equation between the driving force and speed of reaction is a parabola. This explained many of the results which were contrary to the intuition of chemists. For example, for very large driving forces instead of the reaction rate increasing, it actually decreased, i.e. larger the driving force, slower is the reaction. This is now called the 'inverted effect'.

Since 1965, chemists have been continually testing Marcus' theory. Statistical mechanical techniques have also been used to explain the quadratic (parabolic) nature of Marcus' free energy versus rate of reaction curve.

J. R. Miller and G. L. Closs of the University of Chicago were the first to establish definitely the prediction of the 'inverted' effect, wherein highly exothermic electron transfer reactions could be slower than less exothermic ones. This has now been verified by many other investigators also. 'The inverted effect', says Marcus, 'has been of great interest because it represents one of the ways in which solar energy system can be constructed either mechanically or synthetically'

This remarkable concept of electron transfer developed by Marcus has grown much more than what its discoverer expected. So many different systems, inorganic and organic, colloids, metal

liquid electrode interfaces, semiconductor–liquid electrodes, liquid–liquid interfaces, proteins, etc.

Marcus' work has greatly stimulated experimental work in chemistry and it makes predictions concerning such widely differing phenomena as the fixation of light energy by green plants, photochemical production of fuel, chemiluminescence, the conduction of electrically conducting polymers, corrosion, the methodology of electrochemical synthesis and analysis, etc.

Editor

Regulatory role of protein phosphorylation recognized

This year's Nobel prize for physiology or medicine was awarded to Prof. Edwin G. Krebs of the Department of Pharmacology, University of Washington, Seattle, USA, and to Prof. Edmond H. Fischer of the Department of Biochemistry of the same university for their pioneering work on 'reversible protein phosphorylation as a biological regulatory mechanism'. The first protein whose function (in this case enzyme activity) was shown to be regulated by reversible phosphorylation was glycogen phosphorylase[1,2] (also known simply as phosphorylase), an enzyme involved in the breakdown of glycogen in muscle and liver. They not only discovered this covalent modification reaction but also identified and purified the enzymes involved in this regulatory process, namely phosphorylase kinase and phosphorylase phosphatase. Their fundamental findings initiated an area of research which is one of the most active and wide-ranging.

Regulation of phosphorylase by reversible phosphorylation was discovered in mid-fifties. Till late sixties it was believed that protein phosphorylation was not widespread. The only enzymes shown to be regulated by reversible protein phosphorylation, till then, were those involved in glycogen metabolism namely phosphorylase, phsophorylase kinase[3] and glycogen synthase[4]. However, the situation changed rapidly after Krebs and his colleagues[5] in 1968 showed that cyclic AMP activates a protein kinase, now known as cyclic AMP-dependent protein kinase. Since then the function of many enzymes and non-enzymatic proteins has been shown to be regulated by reversible protein phosphorylation and this process has emerged as one of the major devices by which eukaryotic cells control their response to extracellular stimuli such as hormones, neurotransmitters, growth factors, etc.

Discovery of the first regulatory protein phosphorylation

When Krebs and Fischer started their work on the regulation of enzyme activity of phosphorylase it was known from the work of Cori[6] in the forties that phosphorylase in muscle exists in two forms. One of the forms called phosphorylase *a* was active in the absence of AMP whereas the other form, phosphorylase *b*, required AMP for its enzyme activity. The work of Krebs and Fischer in the mid-fifties showed that phosphorylase *b* can be converted to phosphorylase *a* in presence of ATP and a divalent metal ion[1]. The requirement for ATP provided the first clue for this conversion from *b* to *a* form to be a phosphorylation reaction. They also isolated the enzyme (phosphorylase kinase) which catalysed the conversion of phosphorylase *b* to phosphorylase *a* Using ^{32}P-labelled ATP they were able to show[2] that during this conversion, the radioactive label was tightly bound to phosphorylase *a* and that this labelled phosphorylase *a* could be converted to the *b* form which did not have the bound ^{32}P. This conversion to the *b* form was catalysed by what was known as PR enzyme[7] (now known as phosphorylase phosphatase). The term PR enzyme (prosthetic group removing enzyme) was originally given because it was thought to remove a prosthetic group from phosphorylase *a*. Interestingly, the presence of phosphate in phosphorylase *a* was shown as early as 1943 (ref. 7).

The regulation of the enzyme activity of phosphorylase is, however, much more complex. The *b* form of this enzyme is active in presence of AMP which is an allosteric regulator. ATP acts as an inhibitor by competing with AMP. Glucose 6-phosphate is also an inhibitor of phosphorylase *b*. Phosphorylase *b* is generally inactive under physiological conditions due to inhibitory effects of ATP and glucose 6-phosphate. Phosphorylase *a* is fully active and is not affected by ATP, AMP or glucose 6-phosphate. The relative rates of phosphorylation and dephosphorylation determine the proportion of the active enzyme, the *a* form. Almost all of the enzyme is in inactive *b* form in resting muscle which gets converted to the active *a* form when the levels of hormone, epinephrine, increase in the blood.

The enzyme phosphorylase kinase was shown to be regulated by phosphorylation[3]. Like phosphorylase it is also activated by phosphorylation; dephosphorylation converts it into the inactive (or less active) form. The phosphorylation

Edmond H Fischer (left) and Edwin G Krebs

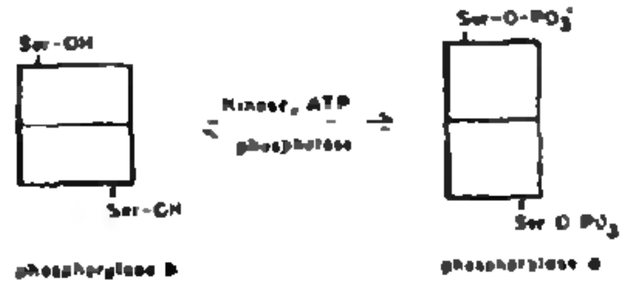

Figure 1. A schematic diagram showing regulation of enzyme activity of phosphorylase by phosphorylation and dephosphorylation at a single serine residue per subunit Phosphorylation of Ser by phosphorylase kinase results in conformational change in the enzyme, converting it to active form