Photo courtesy: Official website of Noble Prize Association

2023 Nobel Prizes in Sciences

Physics, Chemistry and Physiology & Medicine

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Nobel Prize in Physics: Peering into the Microcosmos - Attosecond Science


Photos courtesy: Official website of Noble Prize Association

Anne L'Huillier Pierre Agostini Ferenc Krausz

The 2023 Nobel Prize in Physics has been awarded to three scientists for groundbreaking work in "experimental methods that generate attosecond (as) pulses of light for the study of electron dynamics in matter". These attosecond pulses serve as a potent tool, functioning like a powerful microscope on a time scale, enabling the study of electron dynamics in matter.

The time scales associated with various ultra-fast processes

Fig.1 depicts the time scales involved in different ultra-fast processes. Mechanical shutters and "microwave electronics" equipped with fast transistors are capable of probing processes up to ~ns, while delving into smaller time scales requires "ultra-fast optics" and "light-wave electronics" facilitated by laser technology.

Fig. 2 showcases the evolution of laser technology with respect to pulse duration and peak power. In 1960, the continuous wave laser was invented. Shortly thereafter, short-duration pulses with high power were generated for applications like laser ablation, laser cutting, and drilling. The discovery of the Q-switching technique in 1962 allowed the generation of pulses of ~ns with peak power reaching ~GW/cm^2. In 1964, the development of the mode-locking technique enabled the generation of ~ps pulses with peak power ~TW/cm^2. After a hiatus of 20 years, in 1985, the advancement to the Chirped Pulse Amplification (CPA) technique allowed the generation of femtosecond (fs) pulses with power generation of PW/cm^2 without causing damage to the gain medium. Ahmed Zewail received the Nobel Prize in 1999 for utilizing fs lasers to study the motion of atoms in molecules. This set the stage for the production of attosecond (as) pulses using the peta watt fs laser.

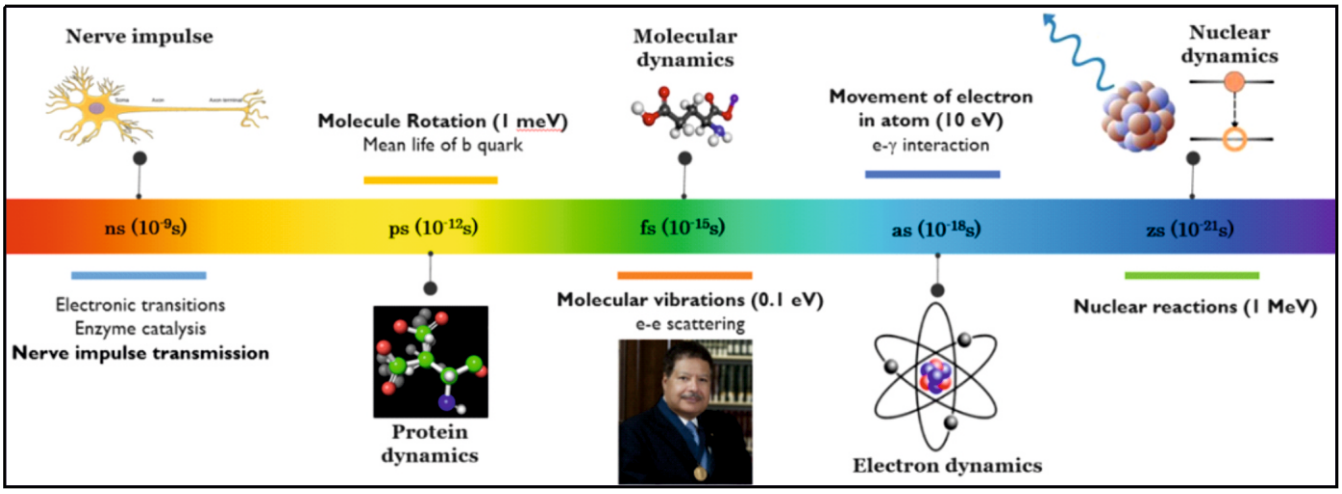

Fig.1: Time scales involved in various processes.

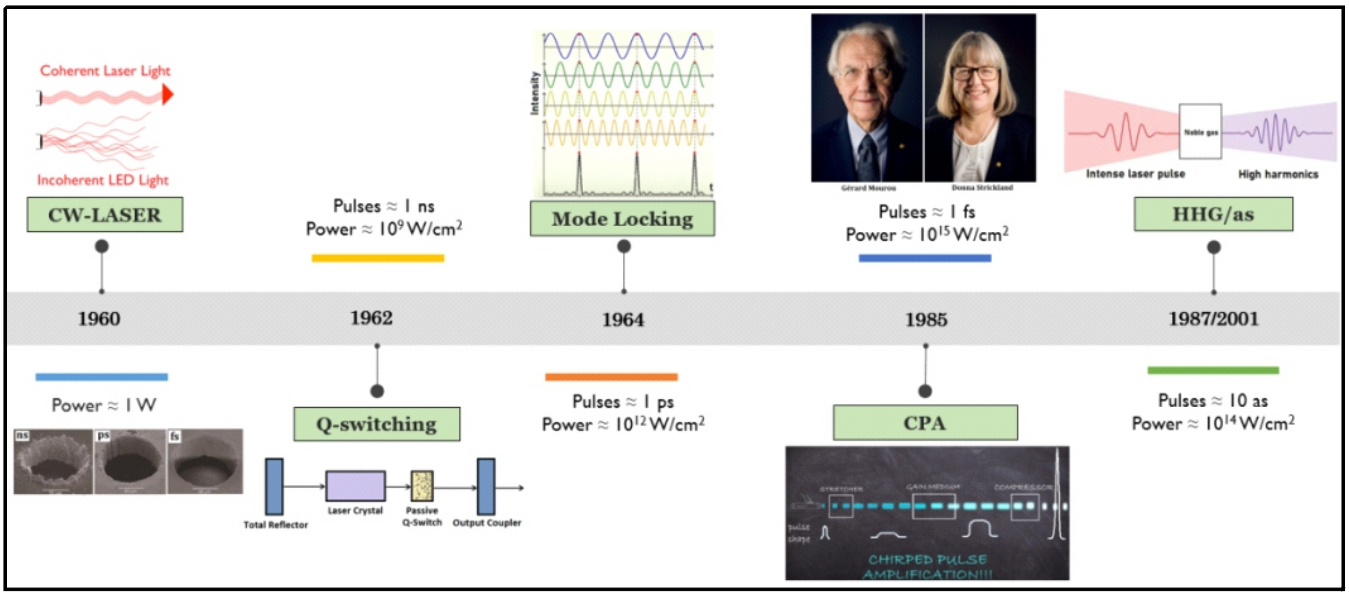

Fig.2: Evolution of laser technology.

Challenges to produce as pulses

The primary limitation lies in the optical time period of light, restricting the pulse duration. Use of a Ti-sapphire laser directly (λ ~ 800 nm, T ~ 2.7 fs), will lead to generation of pulses of only about 3 fs. Thus, the initial step in generating an *as* pulse involves producing coherent XUV (extreme ultraviolet) radiation (λ ~ 30 nm, T ~ 100 as). One method for generating XUV radiation is through Free Electron Lasers (FEL). However, the drawback is that FELs necessitate kilometer-long accelerators, making them impractical for conventional laboratory work. In the 1980s, Anne L'Hullier and her research group conducted experiments and directed a high-power infrared (Ti-Sapphire) laser onto Argon gas. They observed that the output not only included the original light, but also photons of higher frequencies, that were odd integer multiples of the incoming photon frequency. Thus, exposing noble gases to a high-power red laser with a photon energy of about 1eV, photons of higher energies, reaching up to hundreds of eV, were generated. This phenomenon is referred to as High Harmonic Generation (HHG).

Mechanism behind HHG

Paul Corkum from Canada, a significant contributor to theoretical attosecond physics, proposed a three-step classical process to explain HHG. Despite his notable contributions, he has not been included in the Nobel list. Fig. 3 (a) illustrates the Coulomb potential experienced by an electron in a noble gas. The electron is initially trapped within the atom due to the barrier height of the Coulomb potential.

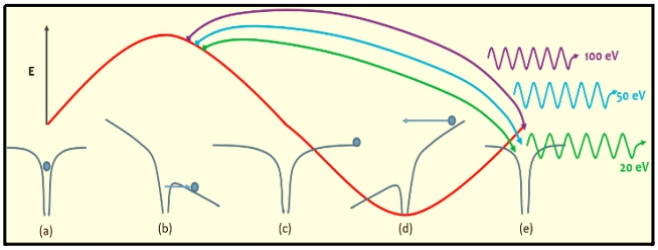

Fig.3: Mechanism to explain HHG (a) potential experienced by an electron in noble gas atom (b) distortion of the Coulomb potential due to high power driving laser, which leads to tunneling of the electron (c) acceleration of the electron away from the parent atom (d) the electric field of the driving laser reverses pulling the electrons back. (e) re-collision of the electron giving rise to emission of photons extending up to XUV region.

When a laser field, ~peta W/cm^2, is applied to the noble gas, the laser electric field becomes comparable to the Coulomb field, distorting the latter entirely (Fig.3 (b)). This distortion reduces the height of the Coulomb barrier, enabling the electron to tunnel through the barrier quantum mechanically (Fig. 3 (c)). This constitutes the first step of the process. In the second step, the electron undergoes acceleration (by absorbing multiple photons), moving away from the ion to a distance of up to tens of angstroms, gaining significant kinetic energy (Fig. 3 (d)). Subsequently, as the last step, the electric field of the laser reverses, prompting the electron to travel back towards the ion and undergo a re-collision, thus releasing the kinetic energy gained in the second step by emitting a photon. The energy of the emitted photon depends on the phase of the driving laser at the time of electron tunneling and can be as high as a few 100 eV (Fig. 3 (e)). It is to be noted that these photons are produced only during a fraction of time period of the driving laser, when the electric field is high enough.

Fig.3. Mechanism to explain HHG (a) potential experienced by an electron in noble gas atom (b) distortion of the Coulomb potential due to high power driving laser, which leads to tunneling of the electron (c) acceleration of the electron away from the parent atom (d) the electric field of the driving laser reverses pulling the electrons back. (e) re-collision of the electron giving rise to emission of photons extending up to XUV region. In effect, when a high-power laser with a pulse width of approximately 3 fs and a photon energy of around 1.5 eV is incident on noble gas, high harmonic generation allows generation of photon pulses lasting approximately 100s of as, with a photon energy of approximately 100 eV (Fig. (4)).

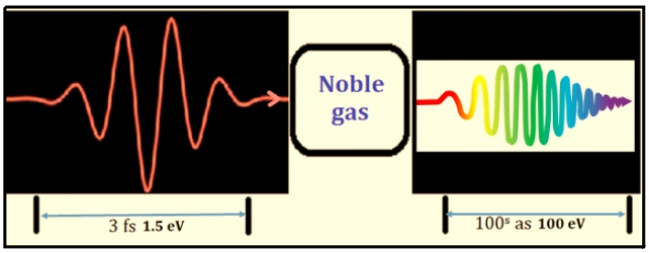

Fig.4: Ti-sapphire laser (λ ~ 800 nm, T ~ 3 fs), when directed on noble gas, produces photons with energies up to 100 s of eV. These photons are produced only during a fraction of the time period of the driving laser, when the electric field is high enough. Thus, the burst of high energy photon lasts only up to 100s of as.

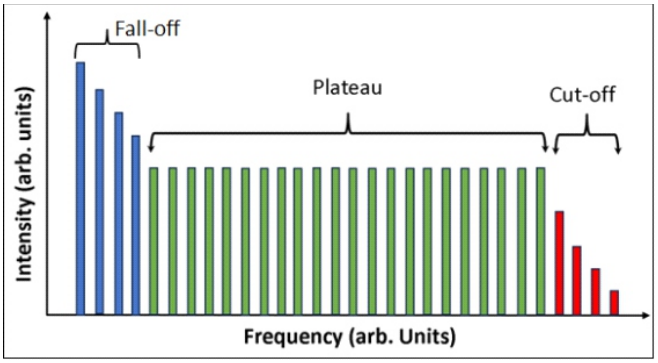

Fig.5: A generic HHG spectrum with its characteristic features:initial intensity fall-off, plateau and the cut-off.

From quantum mechanical perspective, the electron tunnelling can be conceptualised as a beam splitter for the wave function. It divides a bound-state electron wave packet into two: one remains in the bound potential, and the other propagates in the ionization continuum. The coherently re-colliding electron wave packet interferes with the bound-state electron wave function, resulting in a dipole that produces coherent light in a short burst of radiation extending into the XUV (extreme ultraviolet). This technique is truly unique in nature, offering a time scale resolution of approximately 100 as and a spatial resolution of around 1Å.

Contributions of each Nobel laureate

In the 1980s, Anne L'Huillier studied phenomenon of HHG and in 1991,presented the shape of the HHG spectrum through numerical solution of the time-dependent Schrödinger equation (Fig.5). It was realised that HHG is a single electron effect, providing the first ever discussion of macroscopic phase matching, which required solving Maxwell's equations. In 2001, Pierre Agostini created a train of pulses, each of 250 as duration and invented the Reconstruction of Attosecond Beating by Interference of Two-photon Transitions (RABBITT) technique to characterize the as pulses. To address the requirement of isolated pulses, such as in pump-probe method, FerencKrausz, in 2001, successfully separated individual ultrashort pulses from a pulse train. These isolated pulses, with a duration of 650 at to seconds, became instrumental in the study of electron dynamics.

Applications of *as* physics

Electrons are in the heart of most of the processes in physics, chemistry, biology and electronics, and hence knowing the motion of electrons enables a better insight into its applications and control. For example, as pulses allow to study ultrafast processes within molecules, such as electron dynamics during chemical reactions. They enable the investigation of electronic structure and dynamics in matter, providing a tool for attosecond spectroscopy. Inpump-probe experiments, *as* pulses are used in to investigate processes like electron tunneling and ionization on extremely short timescales that has applications in time-resolved imaging, and capturing snapshots of ultrafast processes in materials. When applied to study the ultrafast dynamics of biomolecules, *as* techniques can provide insights into biological processes. This is useful for understanding the working principle of medicines in human body, with a possibility of tweaking the medicines for enhancing their potential.

Nobel Prize in Chemistry: Discovery and Synthesis of Quantum Dots

Photos courtesy: Official website of Noble Prize Association

Alexei I. Ekimov Louis E. Brus Moungi G. Bawendi

The 2023 Nobel Prize in Chemistry was awarded to three scientists, Alexi I. Eklimov (Nanocrystals Technology Inc., New York, NY, USA), Louis E. Brus (Columbia University, New York, NY, USA) and Moungi G. Bawendi (Massachusetts Institute of Technology (MIT), Cambridge, MA, USA) for the "Discovery and Synthesis of Quantum Dots".

Quantum Confinement

Quantum Dots (QDs) are semiconductor nanocrystals which show "quantum confinement effect", which manifests when the size of the particle becomes comparable or smaller to the natural length scale of electron and hole. This natural length scale is known as Bohr radius. When the particle size is less than the Bohr radius, the color changes with change in the dimensions and is given by the equation 1:

$$E_g(QD) = E_{g,0} + \frac{h^2}{8m_{eh}R^2} \quad (1)$$

where, $E_{g,0}$ is the band gap of bulk semiconductor. $E_g(QD)$ is the band gap of QDs having radius R. m_{eh} is the reduced mass. It is interesting to observe from eq. 1 that band gap of a material increases with decrease in size. Although, this relationship was known in 1980s, it had not been practically demonstrated. On the other hand, the utilization of this effect was very well done by our ancestors in Lycurgus cup, Abbasid tiles and Medieval church windows.

With the development of molecular beam epitaxy, researchers have shown that the formation of a thin film of nanomaterials over a surface, changes color with change in size, thus practically verifying the size - band gap relationship.

Quantum Confinement Effect in Glasses

Alexi I. Eklimov was not very satisfied with the molecular beam epitaxy approach on quantum confinement is explanation, since it needed extremely low temperatures and ultrahigh vacuum, both of which were unlikely in ancient times. Thus he started reinventing the mystery and initiated work in this direction. He was a semiconductor scientist working in Russia and was familiar with the power of optical techniques in understanding material properties. He began investigating glass formation process for which he doped 1% CuCl in fused silica and heated it at different temperatures for different times. He monitored that the CuCl crystals were formed inside the glass, the size of which was determined using small angle X-ray scattering. He then observed that the optical absorption spectra of the glass changes with change in size of the particles. This was the first experiment that practically showed that the size of particle is related with its size. He then carried out systematic studies and showed that at high temperatures and for longer heating durations, particles size increases, thus unfolding the mystery behind the colored glasses. However, his research was not very well documented in open literature and here comes the contribution of other Nobel laureate Louis E. Brus.

Demonstration of Size Quantization in Solutions

Louis E. Brus was working in Bell laboratories as a catalyst scientist. He was the first scientist to demonstrate that the size quantization effect can also occur in free flowing solutions. His research was focused on harvesting solar radiation for chemical reactions, for which he was using CdS nanomaterials as a catalyst. In one instance, he observed that the color of the CdS nanomaterials solution changed when left overnight. He was fascinated by this behavior and then started exploring it much deeply. He measured the absorption spectra and size of both fresh and aged particles and observed that the spectra shifted towards red in aged particles as compared to fresh ones and also the size was larger in aged particles as compared to fresh ones. He then carried out more systematic studies and synthesized different size particles in two different solvents, water and acetonitrile to study the effect of solvent on size and aging. It was observed that the large size particles have red shifted absorption spectra as compared to small size particles and the average size is less in acetonitrile as compared to water. The results were found to correlate with size quantization effect. Brus was the first scientist in the world to show that the size quantization effect in particles is practically possible.

Synthesis of High Quality Quantum Dots

Moungi G. Bawendi was the third Nobel laureate in the series. He developed a method to synthesize high quality, reproducible and monodisperse QDs. He was the post doctoral student of Louis E. Brus at Bell laboratories, where he was working on the synthesis of monodisperse quantum dots. However, he did not succeed until he moved to Massachusetts Institute of Technology (MIT). Here he developed a method to synthesize high luminescent QDs by hot injection route. For the synthesis, he employed organometallic Cd precursor in TOPO as a solvent and TOPX (X- S, Se, Te) as chalcogenide source. The reaction was carried out at 280-300 °C and depending on injection temperature, reaction time, and concentration of precursor different size particles were synthesized. The particle size was measured by TEM and corresponding absorption spectra were recorded. It was observed that the absorption spectra of the particles shifted towards red wavelength as the particle size increases. This procedure of high quality QDs synthesis has opened many areas of application of QDs such as in LEDs, solar energy harvesting, sensing and in diagnosis for which Bawendi was awarded the Nobel prize.

Nobel Prize in Physiology and Medicine

For development of mRNA vaccine against COVID-19

Photos courtesy: University of Pennsylvania, Philadelphia, USA & Official website of Noble Prize Association

Dr. Katalin Kariko (Hungary)
(RNA Biochemist)

Dr. Drew Weissman (USA)
(Immunologist)

The 2023 Nobel Prize in Physiology or Medicine was jointly awarded to Katalin Karikó and Drew Weissman for their groundbreaking discoveries in nucleoside base modifications, which catalyzed the development of highly effective mRNA vaccines against COVID-19. This article explores how conventional vaccines are usually made, the difficulties in traditional vaccine development, the exciting beginning of mRNA vaccines, and how Karikó and Weissman changed medicine with their great ideas.

The Evolution of Vaccines

To understand why Karikó and Weissman's work is important, it is important to understand the conventional methods of developing vaccines. In the past, vaccines were created using either the weakened or whole viruses or bacteria that were responsible for causing a given disease. Examples of such vaccines include those for polio, measles, and yellow fever. As science advanced, researchers started making

vaccines by using specific parts of the viruses instead of the whole virus. This approach paved the way for vaccines against diseases like hepatitis B and human papillomavirus. Some vaccines even use harmless viruses to carry parts of the harmful ones, like in the case of Ebola.

The work of Karikó and Weissman added a new dimension to the story by using mRNA to make vaccines. This is like a set of instructions that helps human cells create proteins. Before their discovery, using mRNA was tricky because it caused inflammation and was not stable. But, Karikó and Weissman figured out how to modify the mRNA so as to eliminate these issues.

In simple terms, they made a breakthrough in finding a better and faster way to make vaccines using the instructions in our cells, and this has been a big deal, especially during the COVID-19 pandemic.

Modus-operandi of vaccines

Vaccines work by leveraging the body's immune response mechanisms, particularly the adaptive immune system. They typically contain weakened or inactivated forms of pathogens, their proteins, or genetic material. When a vaccine is administered, these components mimic the presence of the actual pathogen, prompting the immune system to mount a defensive response. Following steps takes place after administration of vaccine inside the human body.

The immune system recognizes the foreign elements in the vaccine as antigens. Antigens are substances that provoke an immune response. This recognition triggers the activation of immune cells, such as macrophages and dendritic cells.

Immune cells present the antigens to specialized cells called T cells and B cells. This process educates these cells about the specific characteristics of the pathogen, enabling them to respond effectively.

T cells play a crucial role in coordinating the immune response. They can stimulate other immune cells, like B cells, and directly attack infected cells. Activated T cells multiply to form an army of cells primed to combat the pathogen.

B cells, upon activation, differentiate into plasma cells that produce antibodies. Antibodies are proteins that can recognize and neutralize specific pathogens. These antibodies circulate in the bloodstream, ready to target and neutralize the actual pathogen, if encountered.

A crucial aspect of vaccination is the formation of memory cells. These cells "remember" the characteristics of the pathogen, providing long-lasting immunity. If the individual is later exposed to the real pathogen, memory cells can quickly mount a robust and targeted immune response, preventing or reducing the severity of the infection.

Challenges in Traditional Vaccine Development

Traditional vaccine production relies on large-scale cell culture, limiting rapid response capabilities during outbreaks. Efforts to develop vaccines independent of cell culture related hurdles, prompted the researchers to explore alternatives to meet the demands of emerging infectious diseases.

The Promise of mRNA Vaccines

In the early 1990s, Hungarian biochemist KatalinKarikó faced challenges in developing mRNA therapies but stayed dedicated. Despite funding difficulties, she worked persistently on her vision. Partnering with immunologist Drew Weissman, they studied how different RNA types interact with the immune system. This teamwork not only paved the way to overcome challenges but also pushed the development of mRNA technology for clinical use. Karikó and Weissman made important contributions to the scientific understanding and use of mRNA, marking a crucial step forward in this groundbreaking therapeutic approach.

The Breakthrough

Karikó and Weissman studied dendritic cells and found that *in-vitro* transcribed mRNA caused inflammatory reactions upon cell entry. Recognizing the significance of modifying nucleoside bases, especially substituting uridine with pseudouridine, they successfully made mRNA non-immunogenic. Their groundbreaking work, documented in key studies in 2005, set the stage for additional findings in 2008 and 2010. These discoveries highlighted the potential of base modifications to reduce inflammation and improve protein production.

Realization of mRNA Vaccines

As the interest in mRNA technology grew, different companies started using it. They initially looked at the Zika virus and MERS-CoV. But the big challenge came when COVID-19 hit the masses. The quick development of base-modified mRNA vaccines for SARS-CoV-2 during the pandemic showed how well the method can be adapted effectively. These vaccines, with reported protection of about 95%, got approval in December 2020. This was a huge step in the history of vaccines, showing that mRNA technology can be fast and successful in responding to urgent health threats.

Global Impact and Future Prospects

mRNA vaccines have made a global impact, with over 13 billion doses given worldwide. They didn't just save lives and stop severe sickness; they helped societies to get back to normalcy. In the future, it is envisaged that this potent mRNA technology can do much more than fighting infections; it may be capable of delivering important proteins and treating serious conditions like cancer and HIV.

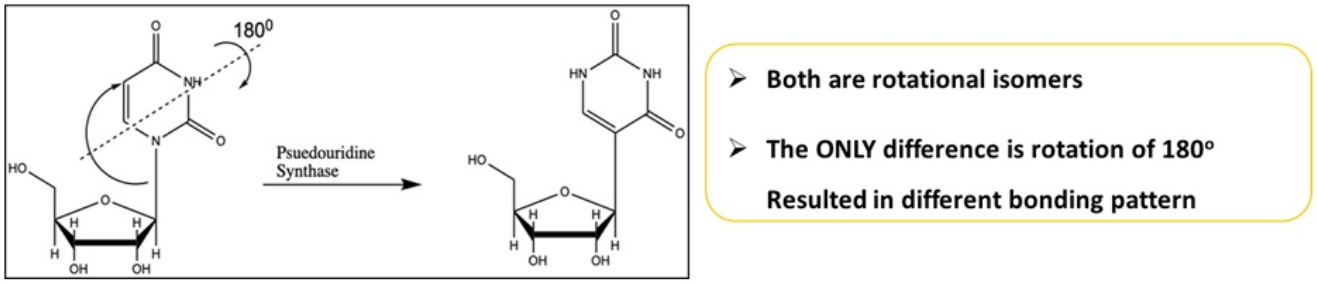

Fig.: Conversion of Uridine to Pseudouridine by enzyme Pseudouridine Synthase; rotation of bond by 180° changes their hydrogen-bonding ability with their partner nitrogenous bases.