Ronald Breslow (1931–2017)

A Versatile Physical Organic Chemist

Ronald Breslow, a giant among chemists, passed away in New York on 25th October 2017 at the age of 86 [1] [2].

Breslow was born on 14th March 1931 in Rahway, New Jersey, and had his undergraduate training at Harvard University. He pursued PhD at Harvard with R B Woodward (a Nobel Laureate known for his elegant synthesis of several complex organic molecules), followed by a postdoctoral stay at Cambridge University with Alexander Todd (a Nobel Laureate who worked on the chemistry of a variety of biomolecules including several vitamins). Breslow started his independent career at Columbia University at the young age of 25, and had an amazing research and teaching career, spanning over six decades. He made immense contributions in a variety of areas, some of which are briefly highlighted below [3] [4].

Breslow's first contribution was on the mechanism of action of thiamine, commonly known as Vitamin B1, which acts as a cofactor in enzyme catalysed processes. Through elegant deuterium exchange experiments and other mechanistic studies, he showed that the thiazolium ring essentially acts as the biological equivalent of a cyanide ion (which promotes Cannizzaro reactions). Formally, the purpose of this cofactor is to generate a stabilised acyl anion equivalent (*Box* 1). Another area that he initiated around the same time was the exploration of aromatic and antiaromatic compounds. While many aromatic compounds with 6, 10 or more pi-electrons were known, 2-electron aromatic compounds (allowed by the 4n+2 Hückel rule, with n = 0) were not known. Breslow synthesised the triphenylcyclopropenium cation for the first time and continued working in this area extensively for more than a decade. In the late sixties, Breslow also realised that chemists should be able to mimic the way nature carries out chemical transformations, using the natural chemical principles (but not necessarily the reaction conditions). He coined the term 'Biomimetic Chemistry'

Prof. Breslow at the Indian Institute of Science (IISc), Bangalore, in January 2009 to give a Centenary Lecture.

and in the subsequent decades became a champion in developing a number of biomimetic transformations. Through clever use of nature's principles, his group designed a variety of enzyme mimics, some on cyclodextrin platforms (e.g. phosphate ester hydrolysis, transamination), and some involving photochemistry and radical reaction processes (e.g. remote functionalization). Another area in which Breslow made significant advances is understanding how hydrophobic effects can accelerate certain classes of reactions (e.g. the Diels–Alder reaction). These studies encouraged a number of synthetic chemists to use water as a solvent for carrying out organic reactions [5]. Additionally, Breslow, along with a research group in Memorial Sloan Kettering Cancer Center in New York City, developed an anticancer drug – Vorinostat – which received FDA approval in 2006 (the first approved HDAC6 inhibitor) (*Box* 2). During the past decade, his team has explored the origin of homochirality in nature and has imitated prebiotic homochirality in laboratory reactions.

Apart from his research activities, Breslow was also a highly respected teacher. Even though he was not required to teach once he became a University Professor in 1992, he continued to teach freshman chemistry and was an extremely popular instructor. He was also a great promoter of gender equality, and primarily through his efforts, Columbia College became coeducational in 1983 [6].

Ronald Breslow was an intellectual giant, and the breadth of his knowledge was phenomenal. His creative work in diverse fields, and deep understanding of how reactions work were just unbelievable. He always believed and presented chemistry as the 'Central Science', and wrote a book highlighting this theme for students, non-chemists, and the public [7]. For his outstanding work, Breslow received many honours and awards, a few of which are: the Arthur C. Cope Award (1987), the National Medal of Science (1991), the Othmer Gold Medal (2006), the Priestley Medal (1999), and the Perkin Medal (2010). He served as the President of the ACS in 1996. In 1997, he was named one of the top 75 contributors to the chemical enterprise of the past 75 years by *Chemical & Engineering News*. The Ronald Breslow Award for Achievement in Biomimetic Chemistry, which is awarded annually by the ACS, is named in his honour. In recognition of his teaching, he received both the Mark Van Doren Award and the Great Teacher Award from Columbia University. He was also a Foreign Fellow of the Indian National Science Academy (1992) and has visited India several times [8].

He is survived by his wife Esther, Emeritus Professor of Biochemistry at Weill Cornell Medical College, and their daughters Karen and Stephanie (*Boxes* 3, 4) [9].

Box 1. Classic Breslow Paper: Mechanism of Thiamine Action

A manuscript of one of his early publications on this work is reprinted in this issue. One of the proposed intermediates is known as the 'Breslow intermediate', now recognised as a member of the family of N-heterocyclic carbenes (NHC).

Box 2. Remembering Breslow

A blog written by Derek Lowe (http://blogs.sciencemag.org/pipeline/archives/2017/10/27/ron-breslow-1931-2017) states: "The number of people who have discovered a marketed drug and also had a mechanistic intermediate named after them is very, very small. In fact, that list might narrow down to just one: Ron Breslow."

Box 3. My 2017 Birthday Wishes to Breslow

I was the 72nd PhD student from the Breslow group, and had greatly enjoyed the highly academically stimulating environment in the group. Breslow was very kind to his students. He had an exceedingly fine sense of humour! On his 86th birthday, I emailed him, and he responded: "Thank you. The snow here on my birthday was quite a bit higher than yours on the same day. Do I really want a return of that day? – Ron", to which I replied, "I am predicting a snow-free, sunny day on 14th March 2018." Unfortunately, he passed away before my prediction could be verified.

Box 4. Breslow's Message to Chemistry Students

The undergraduate students at IISc asked me to give a talk on a Physical Organic Chemistry theme on RB's 86th Birthday. I requested him to send a message to the students. This is what he wrote: "Chemistry Students: Physical Organic Chemistry is a wonderful field. We can make new compounds with exciting properties, but also understand how reactions occur so we can predict new reactions that are both useful and intellectually exciting. It has the creative part so special to organic chemistry, and also the mechanistic part that lets us understand existing and future compounds and reactions. It also gives us tools to understand biochemistry and biology. And there is no limit yet to how far it can go."

Suggested Reading

[1] https://cen.acs.org/articles/95/web/2017/10/Ronald-Breslow-dies-86.html

[2] https://www.nature.com/articles/d41586-017-08461-5

[3] https://en.wikipedia.org/wiki/Ronald_Breslow

[4] For a video interview with Ronald Breslow, please visit: https://www.organicdivision.org/eminentorganicchemists/ronald-breslow/

[5] This paper, entitled Hydrophobic Acceleration of Diels–Alder Reactions, *J. Am. Chem. Soc*., 1980, has received over 1000 citations and is RB's third highest cited paper.

[6] https://www.college.columbia.edu/news/columbia-college-mourns-loss-university-professor-ronald-breslow

[7] *Chemistry Today and Tomorrow: The Central, Useful, and Creative Science*, Ronald Breslow, ACS and Jones and Bartlett Publishers, USA, first published 1997.

[8] Prof. Breslow visited the Indian Institute of Science as the Centenary Lecturer in early 2009.

[9] An obituary published in *Angew. Chem. Int. Ed. Engl*., by three of RB's former associates (Alanna Schepartz, Robert Bergman and Robert H Grubbs) can be found here: http://onlinelibrary.wiley.com/doi/10.1002/anie.201711641/epdf.

Uday Maitra
Department of Organic Chemistry
Indian Institute of Science
Bengaluru 560 012, India
Email: maitra@iisc.ac.in