# Derek H. R. Barton – Fifty Years in Pursuit of Inventions

The world of science became poorer with the sudden demise (16 March 1998) of one of the great chemists of this century, Sir Derek Barton, Dow Distinguished Professor of Chemical Invention, Texas A&M University, at the age of 79. Amongst the multitude of contributions of Barton spanning over fifty years, perhaps the best known one is on conformational analysis by which it became possible to explain the difference in the reactivity of certain isomers of steroids, based on the spatial arrangements of the functional groups. Subsequently, this concept had profound impact in organic chemistry and more recently in molecular biology and biochemistry for the understanding of biological processes.

Derek Harold Richard Barton was born on 8 September 1918 in Gravesend, to parents (William Thomas and M. Henrietta Barton) of modest means. Barton himself stated that 'Anyone who knew my family background would never have predicted that one day I would go to Stockholm to receive the Nobel Prize'. His father and grandfather were carpenters. At school, the headmaster–priest left a deep impression on young Barton and during his adolescence, he contemplated joining the priesthood. Later, Barton's father shifted him to a bigger school at Tonebridge. However, due to the sudden death of his father, he had to discontinue his studies and join the family carpentry business. Soon he realized that there 'must be something more interesting in life' and chose chemistry as a career, because, 'its much more related to life'. Indeed most of the contributions of Barton over five decades had relevance to bioorganic chemistry. He joined the Imperial College and graduated in Chemistry in 1940. He continued at the Imperial College and obtained the Ph D degree in 1942 with Professor Ian Heilbron. He worked on the synthesis of vinyl chloride, a subject of national importance in war time Britain. After his Ph D, Barton worked for military intelligence on the development of secret inks. He did not find this work intellectually stimulating and initiated investigation on the secretion of the flour-beetle (*Tribolium castaneum*), while working during late evenings and holidays. From the defensive secretions of 5000 'angry' beetles he isolated and characterized *p*-ethyl benzoquinone and *p*-toluquinone. This was the first scientific paper by Barton and thus his contributions to Bioorganic Chemistry started. After a brief stint in industry, Barton preferred to accept a position of assistant lecturer (inorganic chemistry) at the Imperial College even at half the salary he was getting in industry. At the suggestion of Sir Ewart Jones (E. R. H. Jones at that time),

Barton critically analysed the data on triterpenoids and steroids and could correlate the molecular rotation differences with the structures. Through the precise analysis of the published data on molecular rotation, he revised the structures of some of the naturally-occurring steroids and triterpenoids.

At the invitation of Louis Feiser, Barton spent one year (1949–50) at the Harvard University to teach natural product chemistry while Woodward was on sabbatical leave. It was here that Barton wrote the famous paper on conformation analysis. Barton's physical chemistry background was very useful in the understanding of the implication of the pioneering work of Hassel on isomers of decalins and Pitzer's statistical mechanical calculations on rotational barrier in ethane. Barton himself made force field calculations on conformations of cyclohexane rings but found them to be *too laborious*. Instead, he started to apply conformational arguments to compounds with rigid framework such as steroids. A discussion at a seminar in Feiser's, group at Harvard University on the reactivity of steroids prompted Barton to explain the observed phenomenon on the basis of conformational analysis. Though Barton's explanation was different from that of Feiser's the latter encouraged him to write the paper. Barton has mentioned that 'the paper was short because I had to type it myself'. Thus Barton wrote the paper entitled, 'The conformation of the steroid nucleus' which appeared in *Experientia* in 1950. The background of physical and organic chemistry and intuition helped Barton to *jump the gap between steroids and chemical physics*. As a consequence of this discovery, a vast number of unexplained observations in organic chemistry could be understood by taking 3-D structures into consideration. The concept of conformation has subsequently had a great impact in the understanding of biological processes. Nineteen years later, in 1969, Barton shared the Nobel Prize with the Norwegian chemist, O. Hassel.

Back home in 1950, Barton joined Birkbeck College as a Reader and soon became a Professor. In 1954, he was elected as a Fellow of the Royal Society, London. In 1955, he was appointed Regius Professor Chemistry at Glasgow. During this period, Barton made outstanding contributions in the chemistry of natural products and elaborated the complex structures of many important compounds such as lanosterol, cycloartenol (the key intermediates in steroid biosynthesis), limonin, caryophyllene, etc. In collaboration with Woodward, the total synthesis of lanosterol was accomplished. This era provides some of the finest examples of classical work of carefully-chosen chemical degradation of molecules, generating structural information through the ingenious interpretation of the data. During the course of structure elucidation of terpenoids, Barton's attention was drawn towards photochemical reactions. Remarkable molecular acrobatics of $\alpha$-santonin in the presence of light rekindled his interest in photochemistry and many reactions of synthetic importance were discovered.

In 1957, he returned to his Alma Mater, Imperial College, as Hoffmann

Professor of Chemistry and continued to work on the various facets of bioorganic chemistry. He revised the structure of Pummerer's ketone – one electron oxidation product of *p*-cresol.

Based on the phenolate coupling routes, a short and elegant synthesis of usnic acid was devised. The concepts of *ortho–para* phenolate couplings thus developed were used in the elaboration (and correction) of the biosynthetic pathways of papaver alkaloids (e.g. morphine), erythrina alkaloids and other phenolics (e.g. lignans). In a novel approach to biosynthesis, nyastatin-resistant blocked mutants were used to unravel the biosynthesis of ergosterol in yeast. Since meaningful chemical degradations of complex molecules are often difficult, Barton used NMR spectroscopy to trace the isotopic labels directly. For example, using judiciously chosen substrates labelled with stable isotopes ($^{13}C$, $^{2}H$) and in conjunction with NMR spectroscopy, the complete biosynthesis of the complex fungal metabolite, fusicoccin, was elaborated without recourse to a single degradation.

Driven by the demand of the pharmaceutical industry for a good synthesis of steroid hormones, Barton invented photolysis of nitrites (Barton Reaction) for the preparation of aldosterone acetate in three steps. Corticosterone acetate was converted into the nitrite which on photolysis and isomerization gave the oxime. Treatment of the oxime with nitrous acid gave aldosterone acetate. Using this methodology, 60 g of the hormone was prepared when the total world supply was only a few milligrams. This work was carried out at the Research Institute for Medicine and Chemistry, Cambridge, USA. The Institute was funded by the Schering Corporation. The Barton Reaction was extended to the preparation of many biologically-active molecules.

For Barton, the discovery of new reactions went on unabated. He recognized the advantages of free radicals over ionic reactions. Though conventional reactions involving carbon-free radicals are not known for high yields, Barton designed procedures to discipline free radicals and could direct reactions to the desired goal. This led to the invention of several free-radical based reactions of preparative importance. Realizing the importance of deoxygenation of alcohols for the preparation of biologically important molecules such as aminoglycoside antibiotics, a radical based reaction (Barton–McCombie reaction) was invented. Subsequently in the 1980s, many new radical based reactions of preparative importance were discovered (deamination, decarboxylation, deoxygenation).

In the 1960s, Barton had some problems in his personal life. His first wife Jeanne left him. In order to fill the vacuum created by the unfortunate incidence, he enrolled in the evening class of Lycee Francais de Londeres to improve his French. Here he met Christiane Chaline, a French Professor and eventually married her. In 1977 at the age of 59, he went to France to accept the position of Director, Institut de Chimie des Substances Naturrelles at Gif-sur-Yvette – a picturesque suburb of Paris. He continued his work on radical chemistry. Barton was fascinated by the challenging problem of selective substitution of saturated hydrocarbons. With generous funds from British Petroleum under the blue-sky projects, Barton initiated work on the application of iron chemistry for the selective substitution of saturated hydrocarbons. Taking cues from Nature ($P_{450}$ enzymatic mechanism) and through a systematic and rational approach, he soon introduced several reagents ($Gif^{III}$, $Gif^{IV}$, etc.) which showed dramatic results in the oxidation of the hydrocarbons. He said, 'Gif chemistry turned into an extraordinary and bizarre chapter of original chemistry'. In a symposium held on 6 February 1998 at La Jolla in his honour, Barton presented his latest discoveries and felt that he was on the verge of solving the difficult problem. But sadly he died a few days later. As usual, he held a group meeting on 16 March 1998. Later he went to his lab with one of his post-docs to do an experiment. He was excited by the outcome of the experiment. But shortly after, at 6.30 p.m., he suffered a massive heart-attack and passed away before he could be admitted to the hospital. Sir Derek is survived by his third wife, Judy and a son from his first wife.

In addition to the Nobel Prize, Barton amassed about 200 honours including the 1995 Priestley Medal, the highest honour of the American Chemical Society. He had more than 1000 publications. Barton always acknowledged the contributions made by his students and research fellows (about 300, many of them Indians). I had the privilege to be associated with Barton as a Research Associate at Imperial College and was in touch with him ever since. While advising researchers from developing countries, he said, 'You don't have to spend your money on grandiose projects but on more practical things like examining the fauna and flora and marine natural products for useful drugs'.

Barton's dedication to chemistry was complete. He said, 'Chemistry to me is rather like a religion. I have to do it to express myself'. In addition to research, Barton brought about many revolutionary changes in the teaching of chemistry. He was a masterly teacher. Sir Derek was always accessible to students and colleagues for scientific discussions. He was kind, considerate, gracious and a gentleman. Though known for brevity, Sir Derek showed subtle, typically British sense of humour. GOOD BYE PROFESSOR. Barton will always be remembered as one the most outstanding chemists of this century.

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