INGOLD, ROBINSON, WINSTEIN, WOODWARD, AND I

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The hero of this article, Sir Christopher Ingold, was born in 1893 and died in 1970, nearly 25 years ago (1). Ingold had a profound influence on the development of physical organic chemistry, especially in the seminal work carried out in collaboration with the late Professor E.D. Hughes.

Ingold was the only son of William Kelk Ingold. For family reasons, he took his B.Sc. as an External Student of London University at Southampton in the South of England in 1913. He proceeded promptly to Imperial College and began his collaboration with Jocelyn Field Thorpe (for many years Professor of Organic Chemistry at that institution). After a detour into industry, Ingold returned to Imperial College in 1920 and then left in 1924 at the age of 31 (in the same year as his election to the Royal Society) to become Professor at Leeds. He returned to London in 1930 as Professor at University College and stayed there until his retirement in 1961 and as Emeritus until his death in 1970.

Ingold was clearly a boy genius who could turn his mind to any aspect of chemistry. His early work with Thorpe led to the discovery of the Thorpe-Ingold Effect (2), which still remains an important experimental generalization even though the explanation given by conformational analysis is different from that first offered.

From early days in 1922, Ingold was fascinated by the problem of the structure of benzene (3). From 1925 onwards, he added electrophilic aromatic substitution to his interests (4), as well as alternating effects in carbon chains. Robinson was shown to be in error in some of his arguments (5). It was Leeds versus Manchester, later to become Oxford versus University College, London. In a few years, thirty-two papers appeared in the *J. Chem. Soc.* on these aspects of organic chemistry.

Ingold became interested in the titration curves of dibasic acids and published three papers on the subject (6) in 1928-1929 with R. Gane. These papers eventually led me to my first interview with Ingold. It was 1946 and I was interviewing with a Fellowship Committee at Senate House in London. Ingold was chairman. He asked me what I intended to do. I was planning to apply the results of Gane and Ingold to determine the distance apart of two carboxyl groups (or other acidic functions) in triterpenoids. Ingold brightened up at once and started to talk about his work. However, I detected a misquotation of his own work. I quickly pointed out his error. He seemed surprised, but not impolite. The interview promptly ended and on reflection, I felt that it was I who had made the error in correcting the words of the great master. However, I got the fellowship and published an impressive looking article on the subject (7).

The move to London brought the first meeting between Ingold and E. D. Hughes. This meeting was prolonged from 1930-1944 and renewed (when Hughes returned from his stint in his native Wales) from 1948-1963.

While still at Leeds, Ingold had been interested in elimination reactions. As he put it in his own words, "my purview expanded to embrace the whole of organic chemistry, a process that conceptually was complete by 1927." Robinson had exactly the same confidence in his own universality.

At University College, the interest in elimination reactions was harmoniously interwoven into the famous substitution reactions of the S_N1 and S_N2 classification. The Golden Years of collaboration with Hughes had begun. To S_N1 and S_N2, mechanisms were added in a harmonious paradigm–E1 and E2. Organic chemists rarely made kinetic studies on preparatively significant

organic reactions at that time. Hughes and Ingold opened a new era of precision (8). One of the noteworthy accomplishments was a revelationary clarification of the hitherto mysterious Walden Inversion.

While on sabbatical leave at Stanford in 1932, Ingold decided to write a summary on the principles of an electronic theory of organic reactions. This duly appeared and created a lot of attention. Ingold wrote clearly, using the simplified nomenclature that is still in use today. As Ingold modestly put it (9):

> The new work made it inescapably clear that the old order in organic chemistry was changing, the art of the subject diminishing, its science increasing: no longer could one just mix things: sophistication in physical chemistry was the base from which all chemists, including the organic chemist, must start.

Robinson was infuriated by this article. It was a "clash of the Titans." Ingold in one short review article had replaced the abstruse and sometimes obscure language of Robinson by a much simpler vocabulary. He had also shown the value of the precise kinetic studies carried out in collaboration with Hughes which justified the Ingoldian quote above.

The American organic chemical scene of the time was also not always appreciative. Ingold and Robinson could be put in the same basket and labeled "the English Heresy." Since Hughes was also involved, it would have been more accurate to call it "the Anglo-Welsh Heresy."

However, over the next ten years, American organic chemistry changed and by 1948, University College had become the mecca of American professors on sabbatical leave and of many Fulbright scholars. It was as if Ingold were a reincarnation of Allah. His lectures were indeed like sermons. He spoke with wonderful clarity and precision. He started with the proposition, followed by the evidence sometimes provided by a mysterious Finkelstein (Saul Winstein whispered to me once, "Who is he?"); but all was illuminated as we approached the beautiful revelation of truth. A slight descent to a conclusion that Ingold was indeed a "prophet of science" completed the lecture. Could one ask questions after this? Not an English audience; Robinson never attended. American audiences in later years did.

I remember once at Manchester at a Chemical Society meeting, Hughes, Ingold, Winstein, and I were all on the program. Hughes and Winstein had an interesting discussion. Winstein asked Hughes what he would call a reaction which was neither S_N1 nor S_N2. Hughes thought about this heresy for a few moments and then replied, "A bastard." Everybody within hearing distance laughed.

The Golden Years of Hughes and Ingold were interrupted by the Second World War. University College Chemistry Department was sent off to the wilds of Wales at Aberystwyth. The more prosaic Imperial College never left South Kensington. I was there until the end of 1944. They were exciting, nonchemical times!

At the end of the war. the precise kinetic measurements resumed, especially on elimination reactions (10). In 1946 Hughes and Ingold published a seminal paper on steric effects and the Wagner rearrangement (11). Later, work on the solvolysis of bornyl and isobornyl chlorides led to the postulate of synartetic acceleration involving synartetic ions (12). At the same time, Winstein was studying the same phenomenon under the name of anchimeric acceleration. Hughes and Ingold were probably surprised to realize that they had an American rival worthy of their own genius. The same applied to the relationship between Robinson and Woodward. It was very dificult for Sir Robert to realize that another intelligence, fully the equal of his own, had entered upon the alkaloidal scene. R. B. Woodward liked to tell the following story about the structure of strychnine. In 1947, Woodward and Robinson had dinner together in a New York restaurant, Sir Robert being the host. As the meal progressed, Woodward told Robinson that he had been thinking about the structure of strychnine. Since Robinson had a group of fifteen or so workers concentrated on this subject, he had to admit that the problem was interesting. Woodward asked Robinson what he thought about the true—as later revealed—structure of strychnine and wrote it on the paper table cloth. Robinson looked at it for a while and cried in great excitement, "That's rubbish, absolute rubbish!" So ever after, Woodward called it the rubbish formula and was indeed quite surprised to see, a year later in *Nature*, that this was also the formula deduced eventually by Robinson. Woodward should have sent the table cloth for publication!

Back in London, Hughes and Ingold started to produce a memorable series of papers on the nitronium ion and its role in aromatic nitration. All the available physical tools were brought to bear upon the identification of the nitronium ion. This work, which undoubtedly had its inception in the wartime fabrication of explosives, is presented in one of the many papers published in 1950(13).

Hughes and Ingold were also the first to systematize the mechanisms of hydrolysis of esters. Six different mechanisms involving acyl-oxygen and alkyl-oxygen cleavage were presented. The first pioneer-

ing paper was in 1939 (14), while a more general discussion was given in the memorable year of 1950 (15).

Ingold showed, in general, a fine perception of the importance of the reactions on which he worked. A reaction which was not quite in that category was the benzidine rearrangement, a fascinating problem by the standards of the day. Earlier work by Ingold in 1933 had established that the rearrangement of hydrazobenzene to benzidine was intramolecular. A short note in 1941 correlated the benzidine rearrangement with electrophilic aromatic substitution (16). A deeper analysis in 1950 (17) gave rise to a general understanding in 1964 (18). Sadly, the last paper tells us that Ted Hughes had already left the scene, slain by a cancer.

Ingold never forgot his love for the structure of benzene. He returned to the problem when deuterated benzenes became available in the 1930's. Suitable deuterium substitution destroys the symmetry of the molecule and allows a much more profound analysis of the first excited UV band. To present all his post-war work on this subject, Ingold filled a complete monthly issue of the *J. Chem Soc.*–a feat never equaled by any other author. Winstein, who was very impressed by this work, once asked me whether Ingold really understood the theory of what he was doing. I assured him that Ingold was a superior brain and that he did. The work was summarized in Ingold's second Presidential Address to the Chemical Society (19).

When in 1961 Ingold changed from the status of Professor to that of Emeritus Professor, he did not loosen his grip on the frontiers of chemistry. His last twelve publications demonstrate well the majesty of the man. In 1965 there appeared his fourth paper on octahedral substitution in cobalt complexes (20)–a contribution to inorganic chemistry. In the following year, we see the monumental proposals (21), still in general use today, on the specification of molecular chirality. In 1967 and 1968, Ingold returned to the benzidine rearrangement with four papers of his usual high quality. He summarized it all in an Israeli publication (22).

Then in 1968, he also published a paper on electrophilic substitution in organomercury compounds which was followed a year later by two additional papers, the last with M. D. Johnson (23). His final publication was a true monument to his genius. It was the second edition (first edition in 1953) of his book *Structure and Mechanism in Organic Chemistry*. It seems that he then laid down his pen for the last time.

C. W. Shoppee has paid a well-merited tribute to Ingold (1):

> If we stand back from the detail and look down a vista of some 50 years, the conclusion is inescapable that Ingold had extraordinary imagination, insight, initiative and ingenuity, that he possessed one of the greatest intellects in chemistry in the 20th century, and that he added a new dimension to organic chemistry. *Amplius alteris providebat*.

I fully concur with these words and so one can return to the rumors current in the late fifties and in the sixties. One heard the question, "Why has Ingold not received a Nobel Prize?" Another question, more American this time, was posed, "Why have Ingold and Winstein not shared a Nobel Prize?"

Winstein was born in 1912. His *Biographical Memoir* (24) shows that, like Ingold, he was a boy genius. Before he started his Ph.D. at Cal. Tech., he had taken an A.B. and then an M.A. at UCLA. This produced eight publications in collaboration with the late Professor W. G. Young *before* he became a graduate student. After the Ph.D. with Professor H. J. Lucas and a year at Harvard as National Research Fellow, he started his academic life as an Instructor at Illinois Institute of Technology. R. B. Woodward told me once that Winstein, who was nominally collaborating with P. D. Bartlett at Harvard, in fact, spent most of his time discussing chemistry with R. B. The discussion was surely mutually beneficial. Winstein was a much better practical chemist than R. B. After one year in Chicago, Winstein was appointed Instructor at UCLA. He rapidly climbed the academic ranks and six years later, in 1947, he became a Full Professor. He gained rapid fame for his work on neighboring group participation, on intimate and solvent-separated ion pairs, on anchimeric assistance, and on aromaticity. He died in 1969, one year before Ingold, from a heart attack. Neither man spared himself in his personal crusades for truth. So why was the Nobel Prize not awarded in time?

The answer surely lies in the machinations of Sir Robert Robinson, for whom there is an excellent biography (25). Sir Robert, as will be realized from remarks already made, was strongly opposed to any recognition of Ingold. Robinson had a brilliant career and spent 25 years in Oxford (1930-1955) as Waynflete Professor. He received the Nobel Prize in 1947 "for his investigations on plant products of biological importance, especially the alkaloids." Sir Robert had a special friend in Stockholm, Holger Erdtman, Professor at the Royal Institute of Technology. One can surmise that Sir Robert's candidature was discretely aided and perhaps Sir Christopher's was not.

In any case, Sir Robert's autobiography (26) says it all. In Chapter XI (p. 184) under "Development of an Electronic Theory," Sir Robert modestly wrote about himself, "The development of these ideas constituted, in the writer's opinion, his most important contribution to knowledge."

About myself, all has already been written (27). After the four Titans I have described, I was the lesser being who knew both some chemical physics and a reasonable amount of natural product chemistry. At the right moment in time, this produced a seminal article (28) and nineteen years later in 1969 a Nobel Prize shared with Odd Hassel. I was fortunate, for Sir Robert gave it his reserved approval. I plan to be alive in the year 2000 to celebrate 50 years of conformational analysis!

REFERENCES AND NOTES

1. The factual information in this article is taken from the excellent paper by C. W. Shoppee, F.R.S., "Christopher Kelk Ingold, 1893-1970," *Biogr. Mem. Fellows R. Soc.*, **1972**, *18*, 349-411.
2. R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **1915**, *107*, 1080-1106; C.K. Ingold, *ibid*, **1921**, *119*, 305-329.
3. C. K. Ingold, "The Structure of the Benzene Nucleus. Part 1. Intra-nuclear Tautomerism," *J. Chem. Soc. Trans.*, **1922**, *121*, 1133-1143.
4. C. K. Ingold, "The Nature of the Alternating Effect in Carbon Chains. Part I. The Directive Influence of the Nitroso-group," *J. Chem. Soc.*, **1925**, *127*, 513-518.
5. E. L. Holmes and C.K. Ingold, "The Nature of the Alternating Effect in Carbon Chains. Part III. A Comparative Study of the Directive Efficiencies of Oxygen and Nitrogen Atoms in Aromatic Substitution," *J. Chem. Soc.*, **1925**, *127*, 1800-1821.
6. R. Gane and C. K. Ingold, "Electrometric Titration Curves of Dibasic Acids. Parts I-III," *J. Chem. Soc.*, **1928**, 1594-1600 and 2267-2272; *ibid.*, **1929**, 1961-1700.
7. D. H. R. Barton and (in part) G.A. Schmeidler, "The Application of the Method of Electrostatic Energy Differences. Part I. Stereochemistry of the Diterpenoid Resin Acids," *J. Chem. Soc.*, **1948**, 1197-1203.
8. E. D. Hughes and C. K. Ingold, "Dynamics and Mechanism of Aliphatic Substitutions," *Nature*, **1933**, *132*, 933-934.
9. C. K. Ingold, "Principles of an Electronic Theory of Organic Reactions," *Chem. Rev.*, **1934**, *15*, 225-274.
10. M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw, and L. I. Woolf, "Mechanism of Elimination Reactions. Part XVI. Constitutional Influences in Elimination. A General Discussion," *J. Chem. Soc.*, **1948**, 2093-2119.
11. I. Dostrovsky, E. D. Hughes, and C. K. Ingold, "Mechanism of Substitution at a Saturated Carbon Atom. Part XXXII. The Role of Steric Hindrance. Magnitude of Steric Effects, Range of Occurrence of Steric and Polar Effects and Place of the Wagner Rearrangement in Nucleophilic Substitution and Elimination," *J. Chem. Soc.*, **1946**, 173-194.
12. F. Brown, E. D. Hughes, C. K. Ingold, and J. F. Smith, "Wagner Changes, Synartetic Acceleration, and Synartetic Ions," *Nature*, **1951**, *168*, 65-67; C. K. Ingold, "Old and New Ideas on Saturated Rearrangements" *J. Chem. Soc.*, **1953**, 2845-2852. [Presidential Address]
13. E. D. Hughes, C. K. Ingold, and R. I. Reed, "Kinetics and Mechanism of Aromatic Nitration. Part II. Nitration by the Nitronium Ion, NO_2, Derived from Nitric Acid," *J. Chem. Soc.*, **1950**, 2400-2440.
14. S. C. Datta, J. N. E. Day, and C. K. Ingold, "Mechanism of Hydrolysis of Carboxylic Esters and Esterification of Carboxylic Acids. Acid Hydrolysis of an Ester with Heavy Oxygen as Isotopic Indicator," *J. Chem. Soc.* **1939**, 838-840.
15. C. A. Burton, E. D. Hughes, C. K.Ingold, and D. F. Meigh, "Walden Inversion and Reaction Mechanism. Walden Inversion in the Acid Hydrolysis of Carboxylic Esters by Unimolecular Alkyl Fission," *Nature*, **1950**, *166*, 680.
16. E. D. Hughes and C. K. Ingold, "Note on the Theory of Aromatic Substitution and Rearrangement with Special Reference to the Benzidine Change," *J. Chem. Soc.*, **1941**, 608-613.
17. E. D. Hughes and C. K. Ingold, "Mechanism of the Benzidine Rearrangement," *J. Chem. Soc.*, **1950**, 1638-1639.
18. D. V. Banthorpe, (the late) E. D. Hughes, and C. K. Ingold, "Mechanism of Benzidine and Semidine Rearrangements. Part XV. A Collective Discussion," *J. Chem. Soc.*, **1964**, 2864-2901.
19. C. K. Ingold, "Signs of a New Pathway in Reaction Mechanism and Stereochemistry," *J. Chem. Soc.*, **1954**, 2991-2998. [Presidential Address to the Chemical Society, April 2, 1954, Manchester]
20. B. Bosnich, C. K. Ingold, and M. L. Tobe, "Mechanism of Octahedral Substitution Reactions in Non-aqueous Solutions. Part IV. The Kinetics and Steric Course of Chloride Exchange in the

cis-Dichlorobis (ethylenediamine) Cobalt III cation in Methanol," *J. Chem. Soc.*, **1965**, 4074-4084.
21. R. S. Cahn, C. K. Ingold, and V. Prelog, "Specification of Molecular Chirality," *Angew. Chem.*, **1966**, *78*, 413-447.
22. C. K. Ingold, "The Benzidine Rearrangement," *Proc. Israel Acad. Sci. and Humanities*, **1968**, No. 10.
23. D. Dodd, C. K. Ingold, and M. D. Johnson, "Mechanism of Electrophilic Substitution at a Saturated Carbon Atom. Part XIII. Concurrent Unimolecular and Bimolecular Mercury-exchange with Anion Catalysis in Water," *J. Chem. Soc. B*, **1969**, 1076-1079.
24. W. G. Young and D. J. Cram, "Saul Winstein. 1912-1969," *Biogr. Mem. Natl. Acad. Sci. USA*, **1973**, *43*, 321-353.
25. Lord Todd and J. W. Cornforth, "Robert Robinson, 1886-1975," *Biogr. Mem. Fellows R. Soc.*, **1976**, *22*, 415-527.
26. Sir Robert Robinson, *Memoirs of a Minor Prophet, 70 Years of Organic Chemistry*, Elsevier, Oxford, 1976. (The title was suggested by the late Holger Erdtman.)
27. Sir Derek H. R. Barton, *Some Recollections of Gap Jumping*, in the series, *Profiles, Pathways, and Dreams*, J. I. Seeman, Ed., American Chemical Society, Washington, DC, 1991.
28. D. H. R. Barton, "The Conformation of the Steroid Nucleus," *Experientia*, **1950**, *6*, 316-320.

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