

## FROM SMALL MISUNDERSTANDINGS MIGHTY DISPUTES GROW

E.D. Hughes' American Paper

Martin D. Saltzman, Providence College

In the well over 200 papers that Edward David Hughes (1906–1963) published there is a single short paper that appeared in the *Journal of the American Chemical Society* in 1935 (1). Why did Hughes choose to publish this paper entitled "Hydrolysis of Secondary and Tertiary Halides" in an American journal when all the rest of his publications appeared in British journals?

An attempt will be made in this paper to produce a scenario that led to the publication of this 1935 paper in an American journal. In doing this some of the problems American chemists had with the assimilation of the principles developed by the "English school" will be illustrated.



There are several reasons that can be advanced for the difficulty American organic chemists had with applying electronic theory to organic reaction mechanisms. Though Gilbert Newton Lewis (1875–1946) and Irving Langmuir (1881–1957) had, between 1916 and 1920, produced a comprehensive theory of bonding involving the electron pair and the octet theory, they unfortunately produced few if any examples relating to organic compounds. Neither Lewis nor Langmuir was particularly interested in organic chemistry so there was little momentum generated to apply their ideas to organic reaction mechanisms. Applications by American chemists in the 1920's were few and far between. Among those who attempted to use Lewis-Langmuir theory were James Bryant Conant (1893–1978) of Harvard University in his 1921 study of addition to carbonyl compounds and Howard J. Lucas (1885–1963) of Cal. Tech., who published a series of papers on electron displacements in organic compounds from 1924 to 1926 (2,3). Morris Kharasch (1895–1957) of the University of Chicago published two papers in the *Journal of Chemical Education* in 1928 and 1931 on the electron in organic chemistry. Except for these scattered examples there was unfortunately not a single example of a research program dedicated to the application of Lewis-Langmuir theory to the process of organic reaction mechanism by any American chemist until the late 1930's. By way of contrast in Britain, both Robert Robinson (1886–1973) and Christopher K. Ingold (1893–1970) had adopted Lewis-Langmuir theory in the 1920's. They had produced an extensive set of papers dealing with applications to a group of very diverse types of organic reactions.

American chemists had also been traumatized to some extent about the use of electronic theory as applied

to organic reactions by the overly enthusiastic application of the ideas of John Joseph (J.J.) Thomson (1856–1940) by a group of American chemists in the period between 1904–1920. In 1904 Thomson had presented a model of bonding which in essence was a modern revival of the dualistic ideas of Berzelius. This led to the presumption of an ionic type of bonding in organic molecules which of course led to problems. Practioners of this electropolar conception principally were Harry Shipley Fry (1879–1949) of the University of Cincinnati, George Falk (1886–1953) and Charles Nelson (1876–1965) of Columbia University, Julius Steiglitz (1867–1937) of the University of Chicago, and William Albert Noyes (1857–1941) of the University of Illinois. Their theories were quickly shown to be unworkable and this may have caused organic chemists who followed the controversy to be put off by electron theory.

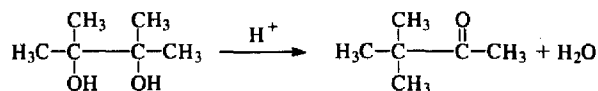
C.K. Ingold has written of the scientific work of Hughes the following (5):

It can certainly be said that this work has changed the aspect of organic chemistry, by progressively replacing empiricism by rationality and understanding. . . . This revolution of approach has been completed . . . essentially because his particular combination of scientific and human insight enabled him . . . not only to provide the required scientific concepts, but also to achieve their general acceptance, even though this task in communications involved a campaign to break through a sustained opposition.

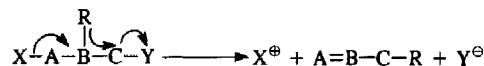


I hope to show that it was just this sort of opposition and misunderstanding in the United States that led to the publication of Hughes' 1935 paper in an American journal. The chief protagonists in this drama on the American side were Frank C. Whitmore (1887–1947) and Everett S. Wallis (1899–1965) and on the British side Hughes and Ingold.

The series of events began in 1928 when C.K. Ingold, acting as one of the reporters for the *Annual Reports on the Progress of Chemistry*, made the following comments in reviewing studies related to molecular rearrangements (6)

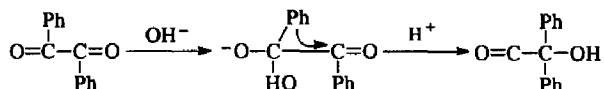


A general expression, involving what is called the "pinacolic electron displacement," and embracing the pinacol-pinacolin, Wagner-Meerwein and related transformations, has been given in the following form:



in which the tendency of X to part from, and of Y to retain, electrons during ionization or combination with a reagent supplies the driving force of the mechanism.

In the changes mentioned, X is usually an ionizable hydrogen atom and Y a potential anion such as hydroxy or halogen, but in certain cases a preliminary reaction is necessary to provide the complete system; for instance, in the benzil-benzilic acid change the effect of X is provided by a negative pole formed by the preliminary addition of hydroxide.



In 1932 there appeared one of the landmark papers in the history of American physical organic chemistry "The Common Basis of Intramolecular Rearrangements" (7) by Frank C. Whitmore. In this paper Whitmore presents a rationale for the benzil-benzilic acid rearrangement as follows (7):

Although rearrangement of compounds containing carbonyl groups and a group corresponding to the X in the systems discussed so far might be expected to follow a very different course, such may not be the case. The only difference is that an atom with an open sextet may be formed by the addition of a positive ion instead of the removal of a negative ion. Thus the first step in the benzilic acid rearrangement becomes:



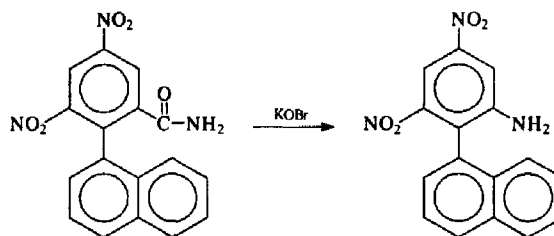
Whitmore in his paper on the Hofmann rearrangement stated that by means of a private communication from E.S. Wallis they both had agreed upon the negative nature of the migrating group. Thus E.S. Wallis became a participant in the unfolding controversy with Hughes and Ingold.

The next stage occurred when George A. R. Kon (1892–1951), as the reporter for the homocyclic division of the 1933 *Annual Reports*, commented upon the work of Whitmore and Wallis concerning molecular rearrangements which had appeared in 1932 (13). Kon was a close associate of C.K. Ingold as both had been at Imperial College during the period that Ingold had been a student and later a junior member of the staff (1913–1924). In his report Kon first summarized the crux of Whitmore's hypothesis concerning the common basis for intramolecular rearrangements. He paid particular attention to points in the original paper and subsequent papers of Whitmore's which presented ambiguities. In particular, Kon pointed to the paper on the Hofmann rearrangement where the neopentyl group was said to be negative yet in the formation of halide from neopentyl alcohol it was viewed as positive because re-

arrangement occurred. In addition, Kon pointed out the problem in the Whitmore interpretation of the benzil-benzilic acid rearrangement previously cited. In a footnote concerning this rearrangement Kon stated "The reporter wishes to thank Prof. C.K. Ingold for drawing his attention to this point." It appears obvious that Ingold was very familiar with Whitmore's work, and the mechanism that Whitmore had proposed was the just the inverse of that described by Ingold in 1928. The following statement by Kon most likely triggered the events which followed (13):

There appears to be some danger that hypotheses of this kind, helpful though they are in interpreting the course of numerous reactions, may be too widely generalised and it is well to recognize their limitations. For instance, there are changes which cannot be satisfactorily reconciled with an ionic mechanism, and of these the Hofmann rearrangement of the optically active amide to an active amine constitutes an important example.

Kon then went on to criticize the interpretation that Wallis had given to the retention of optical activity in the rearrangement of 3,5-dinitro-2- $\alpha$ -naphthylbenzamide to the corresponding amine:



The activity of the original compound is due to the restricted rotation, owing to the steric effect of the carbamyl and the nitro-group in the o-positions: the blocking effect never ceases, as would doubtless be the case if the migrating group were to leave the system as an ion prior to its transfer to a nitrogen atom.

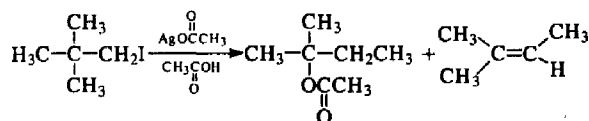
In essence Kon attributed an ionic mechanism to the Hofmann rearrangement even though Wallis very firmly stated in his summary to the paper where this reaction was reported, "These results preclude the possibility of migration of the optically active group in any free form, either positive, negative or neutral free radical." (12) Either Kon had not understood what Wallis had written or was wedded to the idea of intramolecular rearrangements being ionic in nature. He went on in his report to present other evidence in papers that had appeared in 1933 that could lead to the interpretation of the Lossen, Beckmann, and benzidine rearrangement in terms of an ionic mechanism.



E.S. Wallis

We cannot with any certainty know how much of what Kon wrote was the result of the input of C.K. Ingold, but certainly he must have seen the manuscript in advance and would certainly have called Kon's attention to any gross errors in his report. One can only surmise this from Kon's acknowledgment of Ingold's contribution concerning the benzoic acid rearrangement.

Whitmore and Wallis reacted to the comments of Kon in the *Annual Reports* very quickly because there followed in 1934 two short papers, the first from Whitmore and Flemming in the *Journal of the Chemical Society* entitled "Electronic versus Ionic Mechanisms for Intramolecular Rearrangement" (15), and the second from Whitmore and Wallis in the *Journal of the American Chemical Society* entitled "The Electronic Mechanism of Intramolecular Rearrangement" (16). In essence both of these short papers claimed that the "British school of organic chemists," as Whitmore referred to them, had completely misinterpreted the points that he and Wallis had made regarding the nature of intramolecular rearrangements. These processes do not occur by ionic mechanisms at all, but by transfer of the migrating group with its electrons. The migrating group never leaves the molecule and hence these mechanisms cannot be ionic. In the *Journal of the Chemical Society* paper the authors describe the steps involved in the reaction of neopentyl iodide with silver acetate in glacial acetic acid at 60°C which produced tert-amyl acetate and trimethylethylene:

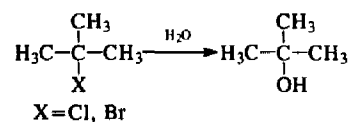


In the *Journal of the American Chemical Society* paper Whitmore and Wallis argued that the work of either of them offered evidence for the correctness of each other's interpretation (16):

We do not agree with this implication; in fact, careful reflection will show that the reaction of Wallis and Moyer, in which an optically active amide of a sterically hindered diphenyl derivative gives an optically active amine, is the strongest existing evidence for the correctness of this modern electronic viewpoint as contrasted with the older ionic mechanisms. A concise electronic explanation of the steps involved in the Hofmann reaction from an electronic standpoint was given to show that the reaction is truly intramolecular and not ionic. In all of this Whitmore never directly addressed the problem of the benzoic acid rearrangement or his use of positive and negative radicals in his paper on the Hofmann rearrangement. He did say that chemists may

not have really understood the implications of his work. They assumed that he was presenting an ionic hypothesis such as ones already available in the literature to explain rearrangement in compounds that can undergo ionization to some extent. He pointed to the work of Meerwein appearing in *Annalen* in 1927 (17).

Whitmore and Wallis submitted their short notes concerning what they perceived as the misinterpretation of their views in April and May of 1934. No doubt when these appeared in print they must have caused great consternation in the Ingold group. At this time there existed a good deal of trans-Atlantic enmity between many of the American chemists of Whitmore's generation and the Ingold school (18). Much of this was probably due to the lack of understanding of the revolutionary insights that Ingold and his collaborators had brought to the understanding of organic reaction mechanism. I believe the Hughes paper was an attempt to show the ignorance of Whitmore with respect to the power of the ideas advanced by Ingold *et al.* The impetus for this paper was the appearance of the first paper in a series on the hydrolysis of tertiary halides by Whitmore in the June, 1934 issue of *Journal of the American Chemical Society* (19). In this paper Whitmore presented a series of observations concerning the hydrolysis of tertiary butyl and amyl halides to the corresponding alcohols.



Whitmore found that tertiary halides were far more resistant to hydrolysis than he had expected. In either cold water or cold aqueous sodium hydroxide the reaction produced some alcohol but mostly alkene, whereas in hot water only alkene was formed. In the same issue as Whitmore's paper there was a publication from A.E. French, W.H. McShan, and W.W. Jöhler of the University of Missouri on the "Action of Inorganic Bases on Secondary and Tertiary Butyl Bromides." (20) In this study the ratio of alkene to alcohol formation was determined by varying the type and concentration of metallic hydroxides. Their results indicated that secondary butyl bromide gave increasing amounts of alkene as the base concentration increased. In the case of tertiary bromides the maximum formation of alkene was only 2%, the rest being the alcohol.

Hughes' paper on secondary and tertiary halides was received on November 30, 1934 and published in April, 1935. In this paper Hughes gave a mechanistic expla-

nation of the results of Whitmore and French *et al.* It should be mentioned that at this time Hughes was a junior member of Ingold's department at University College, London, and was most likely acting as a surrogate for Ingold. Hughes had come to University College in 1930 to do post-doctoral work with Ingold, who himself had just arrived from a previous post at Leeds University. Hughes had just recently received the Ph.D. degree at the University of Wales under the tutelage of Herbert B. Watson (1894–1975). From Watson, Hughes mastered techniques of kinetic analysis which Ingold was to use to such great advantage in the 1930's. Watson himself had been a student of Kennedy J.P. Orton (1872–1930), one of the undisputed masters of kinetic analysis in Britain and head of the department at University College, Bangor (Wales) where Hughes studied. Hughes' life and career were completely dominated by Ingold, and it would seem quite strange why he would have submitted this paper in question to the *Journal of the American Chemical Society* unless asked to do so. Hughes began his paper as follows:

Comment has been recently passed on the relative proportions in which alcohol and olefins are formed by the hydrolysis of secondary and tertiary alkyl halides. We wish to direct attention to some considerations relating to the same. (1)

There followed a discussion of the mechanisms of substitution and elimination using the  $S_N1$ ,  $S_N2$ ,  $E1$ ,  $E2$  notation developed by Ingold. Hughes specifically indicated that the intent of his paper was to report that he had found the changeover point from  $S_N2$  to  $S_N1$  in dilute aqueous alcoholic solution as being between the ethyl and isopropyl group. The work of French *et al.* on secondary halides, Hughes pointed out, is consistent with the operation of a combination of  $S_N1$  and  $E2$  mechanism. Tertiary halides reacted much more rapidly than the secondary halides and produced little olefin because this is consistent with an  $S_N1$  mechanism which predominates over the  $E2$  mechanism. With respect to the work of Whitmore, it was pointed out that in *t*-amyl chloride,  $E1$  now becomes a significant pathway as the halide becomes more highly substituted. Whether dilute aqueous acid, base, or neutral medium is used, it plays no role in the process as it is purely unimolecular. The pathway of this reaction is consistent with  $S_N1$  and  $E1$  mechanisms and experimental evidence for this was offered by Hughes. One wonders how many American chemists reading this paper in 1935 had any idea of what Hughes was writing about!

There is no recorded reply to this paper by Hughes, and curiously this series on tertiary halide hydrolysis

began and ended with paper I. Perhaps Whitmore knew if he published any thing further it would be a subject for further papers pointing to his lack of an understanding of the mechanism of the processes he was studying. Certainly Ingold through Hughes had achieved his purpose!

It should be mentioned that a very short note appeared in the August, 1938 *Journal of the American Chemical Society*, "The Common Basis of Intramolecular Rearrangements. IV A Correction: The Benzilic Acid Rearrangement." (21) Whitmore stated in a face-saving way that "no facts have been found contrary to the assumption of the basis of molecular rearrangements as due to a carbon with an open sextet. However, the extreme extension of the hypothesis to the benzilic acid rearrangement, involving the addition of a proton to benzil to form a positive ion, cannot be supported." (21) Whitmore had no alternative but to publish this retraction a decade later, not because of what Ingold had published in 1928 nor the criticism leveled at this mechanism by Kon in 1934, but because of the work of several American chemists.

Frank Westheimer (22) had shown in 1936 that the benzilic acid rearrangement was second-order and a function of hydroxide concentration. Irving Roberts and Harold Urey (23) in 1938, performing oxygen exchange experiments in alkaline media, showed that there was rapid and reversible addition of hydroxide to form a negative ion intermediate, which was then followed by rearrangement. Roberts and Urey concluded their paper with the following remark. "This mechanism is entirely consistent with the organic evidence and with the theory of reactivity of organic compounds as a function of electron displacements as developed by English workers". (23) Reluctantly, Whitmore admitted his error and that his mechanism was indefensible, in the face of the accumulated evidence.

It is hoped that this curious episode has shown that the radical revolution created by Ingold and other members of the so-called English School in the understanding of organic reaction mechanism was one that proceeded with some difficulty in the United States. Even among chemists such as Whitmore who was interested in applying electronic concepts to reaction mechanisms the transition was difficult. It would remain for the new generation of chemists who were free of many of the restrictions of the past, such as Saul Winstein (1912–1969), Paul Bartlett (1908–), Herbert C. Brown (1912–) and Frank Westheimer (1912–) among others, to facilitate the transition. Through their efforts and those of others, American chemists would become the

leaders in the field of physical organic chemistry in the post-war era.

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#### ABOUT THE AUTHOR

Martin D. Saltzman is Professor of Natural Science at Providence College, Providence, RI. His major interests are in the development of physical organic chemistry in the United States and Great Britain prior to 1950, as well as the dye and petroleum industries.