The First Century of Physical Organic Chemistry : A Prologue

Thomas T. Tidwell

Department of Chemistry, University of Toronto
Toronto, Ontario, Canada M5S 3H6

In order to imagine where this field is going it is useful to realize where it has been, and a view backwards over the past century is informative. The history of physical organic chemistry fits almost completely in the 20th Century. Its emergence as a separate discipline can be traced to the beginning of the century, when many aspects of the subject were beginning to be actively studied. Thus in 1899 Stieglitz (1) published a proposal for the intermediacy of carbocation intermediates, although without experimental support, and in 1901 Norris (2a,b) and Kehrmann (2c) independently observed stable solutions of triphenylmethyl cations in solution, and Baeyer recognized the salt-like nature of these materials (3). In 1900 Gomberg reported convincing studies of the stable triphenylmethyl radical (4), and although his report aroused considerable skepticism, this species attracted wide attention, and the results were reproduced in many laboratories. Carbanions also were becoming clearly understood, and Clarke and Lapworth (5) proposed a mechanism for the critical step in the benzoin reaction as an aldol type process involving a carbanion (Scheme 1), and this is essentially the mechanism accepted today.

Scheme 1
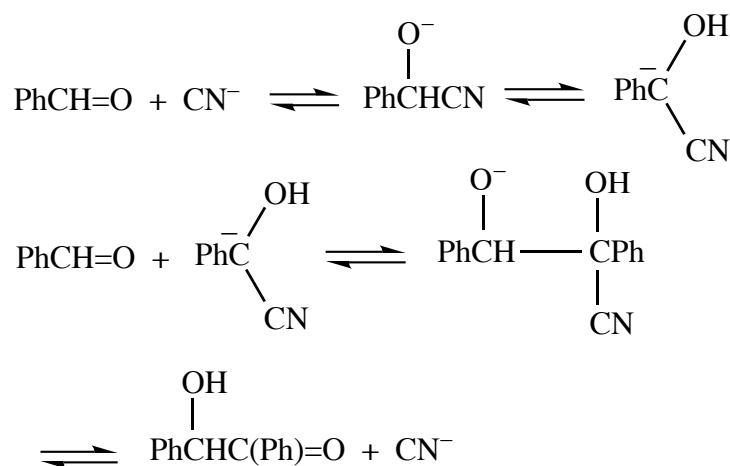
In 1914 Schlenk and Marcus (6) reported that triarylmethyl radicals could be reduced to carbanions by alkali metals, and demonstrated their ionic character by their conductivity, and clearly depicted the negatively charged intermediates. Carbanions were however not named as such until 1933 (7).

The carbene $:CHCO_2Et$ was proposed in 1903 by Buchner and Hediger (8) as a discrete intermediate in the reaction of benzene with diazoacetic ester N_2CHCO_2Et leading to cyclopropane intermediates (8). Staudinger and Kupfer (9) further showed in 1912 that diazomethane formed CH_2, which could react with alkenes to form cyclopropanes, or with carbon monoxide to form ketene $CH_2=C=O$.

Reaction mechanisms based on kinetic studies were beginning to be described at this time, including the study of the mechanism of acid-catalyzed enolization of ketones (10) and HCN addition to carbonyls (11) by Lapworth. Stereochemical studies provided the second pillar for the elucidation of reaction mechanisms, beginning with the study of the stereochemistry of nucleophilic substitution by Walden in 1895 (12).

Key concepts in physical organic chemistry had been formulated by 1900, including the ideas of electronic substituent effects, and the proposals by Kehrmann (13a) and Victor Meyer (13b,c) of steric hindrance. The first linear free energy equation, the Brønsted relationship, appeared in 1923 (14).

Thus by 1925 the experimental basis of the subject existed in a form very recognizable today: the major reactive intermediates, namely carbocations, free radicals, carbanions, and carbenes had been formulated, and the first three were even known as long-lived species; kinetic investigations of reaction mechanisms were being applied; and key factors influencing structure-reactivity relationships were being considered such as stereochemistry, steric effects, and electronic substituent effects.

Despite this strong foundation the development of physical organic chemistry in the first third of the century was somewhat uneven, and this may be attributed to the lag in the development of theories of chemical bonding, and the lack of good explanations of resonance, rearrangements, aromaticity, and the existence of electron deficient intermediates. Mechanistic discussions of the time seem primitive by the standards of elementary textbooks of modern organic chemistry, and the seemingly inordinate time it took for this understanding to develop is a measure of the great advances that would follow in the middle third of the century. This was also a period marked by many bitter disputes, perhaps because the subject was so new and connections between different studies were not apparent, and no consensus had appeared on many subjects or on a basic mechanistic framework. Many theories now widely accepted were regarded with outright disbelief, and carbocations and free radicals were regarded as heresy by many, despite excellent experimental evidence for their existence which is still highly regarded today.

Progress was made by the depiction of nucleophilic displacement in molecular terms by Le Bel (15) and Lewis (16), and the ideas of chemical bonding put forward by the latter (16) provide much of the basis of instruction in the field today. The ideas of electronic displacements to explain organic structure and reaction mechanisms

were introduced in the 1920's by Lowry, Ingold, and Robinson in Great Britain (17). Beginning in the 1920's the development of quantum mechanics laid the fundamental basis for the understanding of organic structure and reactivity, and E. Hückel led the way in this development.

Around 1930 some further major developments were the reinvigoration of free radical chemistry by Paneth (18) and of the role of carbocations by Whitmore (19). Also in 1932 Conant and Wheland published work on the relative acidities of carbon acids (20), and this area is still pursued today. Morris Kharasch and K. Ziegler continued the development of free radicals. In the U.S. in the 1920's J. B. Conant and H. J. Lucas began studies that were continued by Paul Bartlett, Saul Winstein, and Frank Westheimer. Westheimer became a leader in the application of mechanistic principles to the elucidation of biochemical processes. Emil Fischer was the founder of this field, with his theory of enzyme action. Wallace Carothers in the U.S., Hermann Staudinger in Germany, and Hermann Mark, who worked in Germany, Austria, Canada, and the U.S., were pioneers in the development of polymer chemistry, which led to the current emphasis on materials chemistry.   In 1940 the appearance of the influential book *Physical Organic Chemistry* by Louis Hammett named the field and testified to its maturity.

Organometallic chemistry for a long time did not fit into mechanistic analysis, with a major exception of its pivotal role in the understanding of free radical chemistry. However work by Henry Gilman, Wilhelm Schlenk and others on stable carbanions was an integral part of this field. The elucidation of the structure of ferrocene in 1952 (21) was a major turning point, and this was based on sound, physical organic principles, with the participation by a master of this field (and of others), R. B. Woodward.

New techniques were introduced for studying reactive intermediates, such as flash photolysis by Norrish and Porter in 1949 (22), and matrix isolation by Pimentel in 1956 (23). The period 1945-1960 may be seen as the Golden Age of physical organic chemistry, with success following success, and the attitude developed that no goal was beyond reach.

However, by the early 1960's the idea surfaced that physical organic chemistry was past its prime, or even "dead", and that all the major discoveries had been made, and now it could be left to pedants who could catalogue various obscure reaction mechanisms, or improve the precision of physical measurements.

Interestingly the 1960's saw the birth of some of the greatest triumphs of the field, such as the development by Woodward, Hoffmann, and Fukui of the principles of orbital symmetry (Nobel Prize, 1981), host-guest chemistry by Pedersen, Cram, and Lehn (Nobel Prize, 1987), stable carbocations by Olah (Nobel Prize, 1994), and theories of electron transfer by Marcus (Nobel Prize, 1992). It is clear that those who foresaw in the 1960's the relegation of the field to the backwaters had suffered a failure of imagination, but that there were many others, sometimes very youthful, but always youthful in mind and spirit, who saw new challenges.

As the 21st Century approaches the prospects for the field have never been brighter. There are major challenges to be explored, such as the mechanisms of biochemical processes, the chemistry of disease, the design and

understanding of molecular materials, the preservation of the environment on earth, and the understanding of chemistry in the Solar System and beyond, much of which involves organic chemistry. To meet this challenge the chemist has available an unprecedented array of experimental methodology, theoretical insights, and instrumentation, and these are developing at a rapid rate. The economic and political world is changing at a dizzying pace and the chemist must now be aware of these factors. Many talented individuals continue to enter this field, and now is a wonderful time for others to join in, as physical organic chemistry enters a new century that promises to be even greater than the first.

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