

is surely no single answer to this question. An article which leads one individual into a creative research enterprise may be quite unexciting to another. This is, of course, fortunate, for it results in research chemists undertaking problems along many different lines. It is certain that unless a chemist browses through the literature both with regularity and with perception, he has little chance of using this vast storehouse of knowledge in a creative manner. With the tremendous advances in all areas of science now being reported in our chemical periodicals, it seems almost unimaginable that creativity in modern science can have any firm basis except through the theories and experiments which are described in the scientific literature.

Of course, it should always be remembered that individual scientists and groups of scientists create the chemical literature. Creativity based on the literature can only be creativity based on the work of others; the scientific literature represents a medium through which all scientists work together for the advancement of knowledge.

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## Creativity in Organic Chemistry Based on the Literature\*

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When one approaches the subject of creativity in organic chemistry, or for that matter in any science, it seems to me that at least two distinct aspects of the subject must be recognized. One is essentially that based on a chance or purely empirical observation, proper interpretation and exploitation of which results in creativeness of high order. Roughly speaking it can be said the spectacular developments in organic chemistry in the latter half of the nineteenth century for the most part

fall into this class. If the state of evolution of this discipline at about 1850 be considered, the reasons for this situation become abundantly clear. Organic chemistry in 1850 was a relatively new science and its literature was both scanty and frequently of debatable quality. It must be remembered that it was only in 1828 that Wöhler's synthesis of urea without the intervention of a "vital force" disproved the theory held until that time that synthesis of what are regarded as organic compounds without application of such a force was impossible. A few examples of such empirical creativeness may not be out of order.

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When Sir William Henry Perkin prepared the first synthetic dyestuff, mauveine, he in reality was attempting the synthesis of quinine, the structure of which was unknown at the time, by oxidation of aniline. It developed that the aniline used by Perkin was highly impure and it is a tribute to his perspicacity and scientific curiosity that he continued investigation of the highly colored reaction mixture rather than pouring it down the drain as I am afraid many of our contemporaries would be strongly tempted to do. Thus was born the synthetic dyestuff industry as we know it today.

James Mason Crafts working in the laboratory of Friedel added aluminum chloride to amylene and instead of discarding the resultant intractable tar (as it would now be called) continued his investigation of the product. From this emerged what is now known as the Friedel and Crafts reaction and ultimately the huge industry based on acid catalyzed polymerization of various monomers.<sup>1</sup>

As a corollary it follows that those responsible for the development of such products as polystyrene, polyisobutylene, and polymers based on acid catalyzed polymerization of a number of other unsaturated monomers must at some time have been aware of the work of Friedel and Crafts as recorded in the literature. This is not to say that the observations of Friedel and Crafts are the only ones underlying this vast industry. They are used only for illustrative purposes.

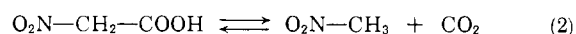
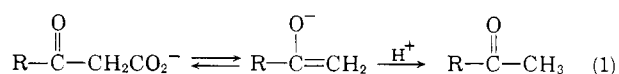
Beginning approximately in 1860 a rather respectable body of empirical observations had come to be recorded in the literature. For the most part these were exactly what the term implies and substantially no efforts had been made to correlate them in terms of common theoretical considerations. From then on advances in creativeness in the area of providing a cohesive theory of organic chemistry were rapid. Probably the first of these strides forward was the advancement of his theory of the structure of benzene by August Kekulé in 1865. Obviously Kekulé could not have developed his ideas which, despite the introduction of such modern refinements as resonance and electron distribution, still provide the basis for all of the chemistry of aromatic compounds, unless he had a profound knowledge of the isolated recorded facts available to him at the time.

To the example of Kekulé may be added the development of the theory of the tetrahedral carbon atom independently by Le Bel and van't Hoff based for the most part on a thorough knowledge of the sound experimental observations of Louis Pasteur. On this foundation rest all of our current ideas of stereochemistry. In recent years the original concepts of Le Bel and van't Hoff combined with the pioneering ideas of von Baeyer on strain in alicyclic compounds have been extended and refined through the introduction of the concepts of molecular conformation, relief of steric strain, transannular reactions and, to mention a few, through the efforts of Barton, Prelog, Roberts, Brown, Cope, Winstein and many others. In all of these it must be assumed that a sound knowledge of recorded fact pointed the way to the spectacular advances which have characterized the development of organic chemistry during the last two decades.

It thus becomes apparent that at about 1860 a second period in the broad subject of creativeness in organic

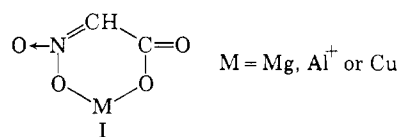
chemistry began. This is almost self-explanatory since from this date the literature in the field became sufficiently voluminous to provide a sound basis for further advances. A few relatively recent developments may be cited based either on personal experience or experience of colleagues.

It has long been known that organic acids carrying so-called negative substituents on the carbon atom beta to the carboxyl group readily undergo loss of carbon dioxide from the carboxyl group. Among others the familiar decarboxylation of acetoacetic acid and its derivatives to ketones and the decarboxylation of nitroacetic acid to nitromethane may be cited. In principle, at least, these may be formulated as reversible reactions as shown in equations (1) and (2)



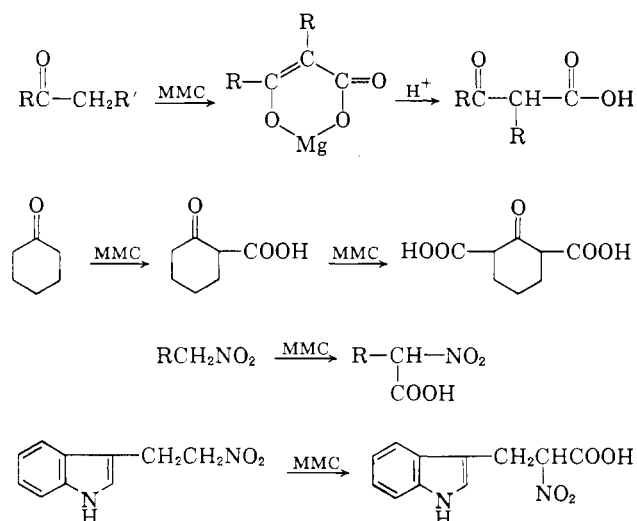
Yet, until about two years ago, it had been impossible to accomplish reversal of these reactions, i.e., to produce, for example, acetoacetic acid from acetone and carbon dioxide or nitroacetic acid from nitromethane and carbon dioxide. As a result of keen analysis of the literature it has now become possible to reverse the above reactions by a relatively simple technique. This has made possible the synthetic preparation of a number of hitherto comparatively inaccessible substances as well as a number of such important compounds as  $\alpha$ -aminoacids.<sup>2</sup>

It had long been known that nitroacetic acid decarboxylates completely to nitromethane (Equation 2) and no evidence had been offered that the reaction ever proceeded in the opposite direction.<sup>3</sup> However Pedersen<sup>4</sup> had noted that nitroacetic acid apparently forms chelate salts with certain metals and from spectrographic data the structure I was proposed for these compounds.<sup>5</sup>



Pedersen made the further observation that decarboxylation of nitroacetic acid was retarded in the presence of these ions. Stiles, impressed by Pedersen's observation, proceeded to a more detailed study of this phenomenon with the result that it became possible not only to reverse equation(2) but to provide a new and apparently widely applicable method for the carboxylation of substances capable of forming enolates.

Reaction of nitroacetic acid with magnesium methoxide in methanol gives a solution of the chelate (I) which, in contrast to a solution prepared from sodium methoxide and nitroacetic acid, is relatively stable to loss of carbon dioxide. Further study resulted in the development of the magnesium methyl carbonate (MMC) reagent by use of which in aprotic solvents, preferably dimethylformamide, carboxylation of a wide range of substances has become possible in acceptable yields.<sup>5,6</sup>



Representative examples are shown in the equations. Thus, by knowledge of Pedersen's observation of the inhibition of the decarboxylation of nitroacetic acid by bivalent chelating metal ions development of a new and valuable synthetic method was possible.

My second example of creativity through knowledge of the literature is taken from the realm of technology and serves to emphasize the desirability of reading in areas of chemistry not too closely associated with one's own field of specialization, although it must be admitted that this practice is becoming more difficult as the volume of literature increases. In earlier days of the petroleum industry the problem of estimating wax in oil stocks was serious. A method developed in 1898 involving use of mixtures of ethanol and ether as extractive solvents offered serious disadvantages. Use of low temperatures ( $-20^\circ$  or lower) was necessary since at higher temperatures the solvent dissolves appreciable amounts of paraffin waxes. In 1918 there appeared a paper<sup>7</sup> in a relatively obscure journal which was abstracted in due course by *Chemical Abstracts*. Schwarz pointed out that, whereas anhydrous methyl ethyl ketone also dissolves significant amounts of waxes present in oil stocks, addition of 1.3 per cent. of water resulted in an excellent precipitating agent for the waxes at convenient temperatures. The abstract came to the attention of a young chemist in the laboratories of one of the major American oil companies who proceeded to prepare a batch of the ketone by the laborious bench methods available at the time and use of it did indeed provide an effective method for estimation of paraffin waxes in oils. Meanwhile demand for paraffin waxes was increasing and the problem of dewaxing lubricating oil stocks was becoming more serious to the petroleum refiners. What was more natural than to adapt this analytical method to plant procedure? The adaptation was entirely successful<sup>8</sup> and methyl ethyl ketone has been widely used since as a dewaxing solvent. As a corollary it should be pointed out that the demand for the ketone provided strong impetus to the development of cheap manufacturing processes not only for it but for other ketones by hydration of olefins and subsequent catalytic oxidation of the resulting alcohols.

Numerous other examples of the adaptation of analytical procedures to larger scale operations can be cited. The point to be emphasized is the value to be gained

by the organic chemist and chemical engineer in reading in areas beyond his immediate field of specialization.

As a final example of dividends to be gained from knowledge of the literature I would cite the development of a rather good laboratory trick which we have found to be extremely useful in connection with reactions involving solutions of ammonia in such solvents as ether or benzene. Ammonia is not too soluble in such solvents and, particularly in large scale operations, this fact necessitates handling rather large amounts of solutions. A few years ago we were in need of substantial amounts of derivatives of  $\beta$ -aminocrotonic esters.<sup>9</sup> A published method for the preparation of ethyl  $\beta$ -aminocrotonate<sup>10</sup> involved saturating a mixture of ethyl acetoacetate and ammonium nitrate in ether with ammonia followed by subsequent heating of the mixture at moderate temperatures in sealed tubes. The role of the ammonium nitrate was not clear from Conrad and Epstein's paper beyond a rather vague statement that it aided the reaction. Dr. Tracy's curiosity was not satisfied by such a generalization and she proceeded to see whether a more satisfactory explanation might not be available. It developed that in 1873 an English chemist, J. W. Diver, had published on the behavior of mixtures of ammonia and ammonium nitrate and had noted that ammonium nitrate at low temperatures forms liquid complexes with ammonia containing ammonia up to a ratio of approximately 3:1 with respect to ammonium nitrate and that at somewhat higher temperatures the complex gives up its ammonia.<sup>11</sup> A convenient method for handling large amounts of ammonia in such solvents without use of excessive volumes is thus provided. All one does is to prepare Diver's liquid at about  $-10^\circ$ , seal the reaction mixture in a vessel such as a citrate of magnesia bottle and heat to a temperature of about  $60^\circ$ . Ammonia then is released slowly from the complex and becomes available for reaction.

Again the moral is obvious. Diver's original paper appeared in a publication with which most practicing organic chemists would not be familiar. Yet Dr. Tracy's inquisitiveness to find a logical answer to a vague statement resulted in the development of an exceedingly useful laboratory method for the organic chemist.

I would venture to guess that any number of similar observations have escaped the attention of organic chemists primarily because their identity has been lost, or at best obscured, by incorporation in a paper the title of which is directed to the main end in view. In Dr. Tracy's case the title of the paper was "Synthesis of the Pyridine Analog of Thiamine." It is therefore with great satisfaction that I recently learned of plans for a new publication which will be devoted primarily to descriptions of instances such as this which may quite properly be called "laboratory tricks" to aid the organic chemist but which only too frequently are not readily called to his attention in the course of his reading.

In conclusion, perhaps a few comments on the sheer volume of current literature may not be out of place. In 1960 *Chemical Abstracts* abstracted approximately 132,000 papers which contained information of interest to chemists of one persuasion or another. I believe that the organic section of *Chemical Abstracts* is the largest in terms of abstracts specifically devoted to the subject. It hardly seems possible for the average chemist to find

the time necessary to read *Chemical Abstracts* in his chosen field to say nothing of the primary references pertaining thereto.

The chemist employed by industry, for the most part, enjoys the advantages of specialized library aid in calling to his attention papers of direct interest to him. The university professor can depend (in general) on graduate students to keep him abreast of the literature amidst his multitudinous distractions such as proliferating committee assignments within his own institution and increasing demands on his time invoked by service on a multitude of advisory committees. I presume these situations are unavoidable. Parkinson's Law seems to have afflicted the universities. The alternative to service on advisory committees is allocation of grants for research subsidized by the government based on recommendations from professional civil servants and bureaucrats who, with the best of intentions, may not only be incapable of proper evaluation of the merits of a particular proposal but only too frequently because of their undoubtedly very excellent capacity for administration are far removed from the current life stream of research.

We are thus on the horns of a dilemma. Time devoted to advisory panels, committees, etc., is time taken from that which should be available for current contact with contemporary literature. On the other side of the argument is the problem of awarding increasing dollar amounts for research without adequate review by those most competent to evaluate research proposals in their respective areas. You just can't have your cake and eat it too.

What is the solution? In my opinion (which is most assuredly open to argument) the answer to this dilemma lies in the publication of *critical* reviews of various aspects of organic chemistry. I intentionally emphasize the term "critical." A review prepared by a company librarian encompassing all references to a given topic without critical evaluation of the relative merits of the cited references will most assuredly cause more trouble than can be compensated for the good will it generates. Similarly an uncritical compilation of data by a graduate student or a post-doctoral assistant will fall into the same pit.

What is needed are *critical* (again emphasized) reviews by experts in given areas in which the relative scientific merits of all papers dealing with these topics are assessed. This applies particularly to the patent literature in which, unfortunately, too much graphite and cellulose chemistry is found. In compiling such critical reviews obviously some sensitive toes will be trodden on. It is sincerely to be hoped that, when this stage is reached, authors will not be bound by personal bias but, rather, will give the subject under discussion completely objective treatment.

This, then, is my closing plea: That either through the established mechanism of *Chemical Reviews* or some presently unestablished publication provision be made for *critical* surveys of appropriate areas not only of organic chemistry but of all areas of chemistry. I predict that the dividends will be enormous and that the burden of keeping *en courant* with current literature in general (rather than in isolated specialties) will be greatly lightened.

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## The Relation of the Industrial Technical Literature to Creativity\*

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In recent article, Jacques Barzun<sup>1</sup> made the important point that the same word—creativity—should not be applied to the chimpanzee's daub, or the four-year old's smear, and also to the Mona Lisa. Creativity should be concerned with the significant.

**Definition.**—The writer's definition of creativity is this: it is the ability to formulate new combinations of social worth. This definition covers the arts as well as the sciences, a symphony or a novel as well as a chemical

investigation. For every creation is a new combination. Creativity formulates the absolutely new as sum from old.

A philosopher will be quick to point out that there is nothing new under the sun, to which I should reply, nay, rather, there is nothing old under the sun, nothing the same this minute as it was last. The philosopher will also have a comment to make on the term, social worth. This means, in simple terms, the creation must be given form, and the resulting formulation must be accepted as valuable by a social group. The larger this group is, and the longer the formulation holds the stage as a valuable

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