NATIONAL ACADEMY OF SCIENCES

JOHN ULRIC NEF

1862—1915

A Biographical Memoir by

MELVILLE L. WOLFROM

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Biographical Memoir

John Ulric Nef

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June 14, 1862–August 13, 1915

BY MELVILLE L. WOLFROM

JOHN ULRIC NEF was a great pioneer in American chemistry. It was he, along with Arthur Michael and Ira Remsen, who was mainly responsible for the transfer to the universities of the United States of the tenets of the actively growing science of organic chemistry from the laboratories of the great European universities of the time. Nef was a pioneer in theoretical organic chemistry, a great experimentalist, and an inspiring trainer of men. His advanced students, the Ph.D. trainees, went into positions in the American universities, and especially in the Middle West, determined to carry on the tradition of research. In the words of one: "We were determined to keep some research going if it were only to boil water." This establishment of chemical research in the American universities was carried out under the most difficult of conditions and with little support or understanding on the part of the administrators of these growing institutions, who mainly considered the science departments, in the liberal arts colleges, as units which cost a lot of money and produced results of doubtful cultural value. In the agricultural and engineering schools, on the other hand, the fundamental science departments were frequently looked upon as of insufficient practical significance. The intensity of training in the true research spirit received by the students of Nef enabled them to overcome these difficulties and, in turn, to train others in the same tradition. Nef was therefore one of the

[1] Dedicated to the memory of my two teachers, William Lloyd Evans and W. Lee Lewis, both of whom were loyal and devoted students of John Ulric Nef.

greatest teachers of all times, albeit he was a notoriously poor classroom lecturer.

John Ulric Nef was born on June 14, 1862, at Herisau, Kantonli Ausser Appenzell, Switzerland. This small section of Switzerland is composed largely of German-speaking Protestants. John Ulric was the eldest of two sons of Johann Ulrich Nef (1834–1884) and Anna Katherina Mock Nef (1842–1910). The father, employed as a young foreman in one of the textile plants for which this Swiss canton was famous, became interested in the possibilities of the textile industry in America and emigrated there in 1864. After he became established as a foreman in a textile mill at Housatonic, in southwestern Massachusetts, he brought his family to this country in 1866 and established them in a small farmhouse four miles from Housatonic. The son was then four years old and here he remained until he was sixteen. He first attended school at Housatonic but his father considered the school so poor that he sent him after one year to that at Great Barrington, likewise four miles from his home. Every school day, rain or shine, for eight years (1869–1877), he would walk along the railroad tracks to Great Barrington, carrying his books and lunch, to return in the afternoon. At the same time he had his regular chores to perform at home. His father inculcated in him a love of books, of music, of sport, and of work; and the boy had inherited the energy to maintain an intense program in these spheres. It was to this early training that the son ascribed his lifelong belief in the balance between strenuous intellectual work and equally strenuous physical exercise, as the foundation of a well-rounded life. He became a strong swimmer, and it was while swimming underwater as a youth that he broke an eardrum, as a result of which he became practically deaf in his right ear. He was always a vigorous walker and stepped along at a hiker's pace. In later years he played an excellent game of tennis and especially enjoyed having A. A. Michelson as a partner in this sport.

When John Ulric was sixteen, it was settled that he should go to college, preferably Harvard; after spending two years in a New York

City college preparatory school, he entered Harvard University at the age of eighteen with the class of 1884. He had planned to prepare for the medical profession but from the time he took his first course in chemistry he was fascinated by the tremendous opportunities for research and discovery presented by this discipline. In his junior year he was elected to Phi Beta Kappa. He far outdistanced all of his fellow students in his senior year and was awarded the Kirkland Traveling Fellowship, which enabled him to study in Europe; he held this from 1884 to 1887. Throughout his life Nef always maintained cordial relations with the Chemistry Faculty at Harvard and especially kept up a correspondence, over many years, with Professor C. Loring Jackson. In a letter to Nef written in 1892, Jackson advises that an applicant for the Ph.D. at Harvard must have had either Latin or Greek, and preferably both. He then goes on to state: "I have 4 good advanced men who give me all I want to do and 130 elementary students who give me a great deal more."

John Ulric had been confirmed in the orthodox German (Evangelische) Lutheran Church to which his parents belonged at Housatonic. During his college years his religious views became more liberal and he particularly enjoyed the sermons of that eminent divine, the Reverend Phillips Brooks. He maintained an interest as a listener to, rather than a performer of, music and regularly attended concerts in Boston. Throughout his life he delighted in music and the arts and developed a predilection, especially, for the musical compositions of Beethoven and Wagner.

Nef left for Europe in the summer of 1884 and was accompanied by his father, who unfortunately had contracted tuberculosis. They spent the summer together in the vicinity of the Vierwaldstätter See and then his father returned to the United States, where a few months later he died at the age of fifty. This left the son with the responsibility of caring for his mother, who later became an invalid and died in 1910 at Herisau, where she had been brought by her son.

Arriving in Munich, he threw himself into his work and into the cultural life of that great German city. After two years he received

the Ph.D. *summa cum laude,* in 1886, under Adolf von Baeyer, with a thesis entitled "Ueber Benzochinoncarbonsäuren," and concerned with aspects of tautomerism, which phenomenon had been discovered by Baeyer in the isatin series. After receiving his degree, Nef remained in the Baeyer laboratory for an additional year. Professor Baeyer was very fond of this intense young man and frequently entertained him as a guest in his home. Professor R. Willstätter has stated that Professor Baeyer had remarked to him that Nef was the most brilliant of all the students he had had during his tenure of the chair of chemistry at Munich. Throughout the long life of Baeyer, Nef maintained a cordial correspondence with him.

In 1887 Nef accepted an appointment at Purdue University, Lafayette, Indiana, at a salary of $1200, payable quarterly. In making this offer, President J. H. Smart wrote as follows:

"We have a laboratory at Purdue University in which are 48 individual desks with closets, drawers and individual reagents each. We have room for 16 desks more. The amount of time a man will have for private research will depend on his power of organization. He will be occupied in class and laboratory work about 4 hours a day."

John Ulric Nef demonstrated this "power of organization" and plunged into an intense period of research activity in which he exhibited an experimental skill probably unequaled in the history of organic chemistry. The lights of his laboratory burned far into the night. He had no assistance, all had to be done with his own hands. Largely as a result of this work, he published three papers in Ira Remsen's *American Chemical Journal,* one of which was republished in German in *Liebigs Annalen.* In this he established a precedent for his future work, all of which was incorporated into the current German chemical literature. Although he was fluent in the German language, it was his custom to send his manuscripts to his friend Johannes Thiele for conversion to the German idiom.

These first papers of Nef were concerned with derivatives of *p*-benzoquinone and were largely critical of some published work of

A. Hantzsch. In this Nef again established a pattern: he was ever the iconoclast. In these researches, as in many that followed, he prepared a large number of compounds which were described with extraordinary care and precision. His training with Baeyer was reflected in the great stress he laid on careful manipulation and experimentation; he was most particular regarding cleanliness and the orderly assembling of apparatus, and worked as quantitatively as possible. He believed in simple apparatus and in not carrying on too many experiments simultaneously. He kept a file of research samples. These traits he imparted later to his students. Wherever they were, all of the Nef students kept their desks and their laboratories scrupulously neat. The story is told of the wrath visited upon a luckless graduate student when Dr. Nef (then at Chicago) entered the laboratory and found a burnt match on the floor, and of the time when the doctor, watching a reaction which at last got out of hand, backed away from the apparatus and fell over a laboratory stool which should not have been at that spot.

The summer of 1889 was spent in Switzerland, where Nef became very much interested in mountain climbing. This set a pattern that was repeated in later years; he spent many summers (every one from 1891 to 1897) in the Alps, making numerous difficult ascents. He loved the mountains.

Before leaving for Switzerland in 1889, Nef was offered and accepted a three-year contract at Clark University, Worcester, Massachusetts, as Assistant Professor of Chemistry at a salary of $2000 a year. A new laboratory was to be built and equipped. Following the resignation of Professor Arthur Michael, Nef was named, in April, 1892, the Director of the Chemical Laboratory. This university was brand new and was to be operated as a graduate school. Its President was G. Stanley Hall and its benefactor was Jonas Gilman Clark. It opened September 1, 1889.

From 1889 to 1891 Dr. Nef lived in Worcester with his mother, whose mind had begun to fail badly. In the summer of 1891, the son Ulrich, as his mother addressed him, took her to Switzerland where

she first stayed with relatives at Herisau and finally at a Protestant sanatorium, Kurhaus Heinrichsbad, near Herisau, where she died December 12, 1910. Her son visited her there frequently in the academic summer vacations.

While at Clark, Nef worked on the structure of the salts of β-keto esters and of nitroparaffins and he initiated his researches on bivalent carbon compounds, especially the isocyanides and the fulminates. All, however, was not well with the new university. Promised funds were not forthcoming. In 1891 Dr. Arthur A. Michelson represented the aggrieved faculty in discussions with President Hall and in 1892 eight important faculty members resigned. These included J. U. Nef, Associate Professor of Chemistry, A. A. Michelson, Professor of Physics, and Franz Boas, Docent in Anthropology. Nef, at least, was not stepping off a precipice. Another new university was starting. And this one had assured financial backing.

The University of Chicago opened on October 1, 1892, with funds donated by John D. Rockefeller, who contributed to it $37,708,000 during the period 1890 to 1910. Its President was William Rainey Harper. Born in a log cabin at Muskingum, Ohio, Harper was a great university president, a species of humanity always rare on the American scene and now essentially extinct. With the Rockefeller gratuities, Harper gathered together a great faculty which even included nine previous presidents of colleges and universities. John Ulric Nef received the professorship in Chemistry, beginning October 1, 1892, under a contract designating a salary of $3000, payable monthly, and including a private research assistant. He had insisted upon the latter. Here he remained for the rest of his life.

Nef had always hoped to transfer to this country the German concept of a University Research Institute with one Professor in charge of all the graduate work. He never attained this objective, and indeed it would have been contrary to American democratic tradition. He did succeed in establishing what were probably some of the first postdoctoral research appointments in the United States, in an embodiment of the German university concept of the Assistant to the

Professor of Chemistry. The first appointment of this nature was made at Clark University and was awarded to Dr. V. Paepcke, a student of Victor Meyer. He was succeeded by Dr. M. Ikuta, who followed Nef to Chicago. Dr. Ikuta was in turn replaced by Doctors John C. Hessler, A. F. McLeod, Ernest Anderson, F. W. Upson, J. W. E. Glattfeld and Oscar F. Hedenburg, in that order. Doctors Glattfeld and Hedenburg served together and were in part financed by a special grant to Nef from an anonymous donor. At that time, 1914–1916, Dr. Nef was doing little laboratory work, but he told Hedenburg and Glattfeld exactly what to do and he kept all the notes himself. Nef employed another German university usage when he hired Julius Stieglitz, his eventual successor as department chairman, in 1892 as a Docent. This German type of position, carrying little honor and no pay, was understandably never popular in the United States.

Nef was not named to the head professorship in the Department of Chemistry at Chicago until 1896, although he acted as such. Nef was temperamental and impulsive and in 1894 President Harper felt constrained to write him as follows:

"Your letter of April 6th has been received. I am not willing that you should carry out the plan which you indicate in it, and I hope that you will not do anything rash."

Later on, Nef turned over most of the administrative detail of the department to Dr. Julius Stieglitz, while retaining a firm rein on all matters of policy. The task of instructing large classes of undergraduates in a science in which most of them showed little interest was always irksome to Nef. In Alexander Smith, however, he did select one of the great freshman chemistry teachers of all time. The chemistry department was first housed temporarily and unsatisfactorily in a city flat, but in 1896 the fine Kent Chemical Laboratory was ready for occupancy and the department moved therein.

Although John Ulric had stated that "a scientist should be married to his science," he was married, when he was thirty-six years of age, on May 17, 1898, at Rochester, N.Y., to Louise Bates Comstock,

one of his students. Louise Nef was a highly cultivated young woman who had spent five or six years in Europe, traveling and studying. She was an accomplished piano player and, having been a graduate student in chemistry, she understood and appreciated her husband's profession. The young couple spent the summer of 1898 traveling in Europe. They were ideally suited to each other and the marriage was a happy one. It was not to endure, however, and Mrs. Nef died on March 20, 1909, of pneumonia. The loss of his wife was a great sorrow to Professor Nef. He never remarried. One son, John Ulric Nef, Jr., was born of this union on July 13, 1899. The son, of the third generation bearing this name, is a distinguished historian and is likewise a Professor at the University of Chicago, where he was the principal founder of the Committee on Social Thought, of which he is the chairman.

In 1903 Dr. Nef suffered a severe nervous breakdown caused by intense overwork, and this was followed by a second in 1911. He had planned to spend the summer of 1915 in the Canadian Rockies with his devoted son, then a lad of sixteen years. Nef's mountaineering was not restricted to the Swiss Alps. In the summer of 1908 he had astonished the Colorado natives at Estes Park by hiking from Elkhorn Lodge to the summit of Long's Peak and back in a single day. His Swiss friends had commented, "Er könnte nicht laufen, er müsste immer springen" (he could not walk, he must always spring). On his 1915 walking trip in the northwest, begun in June, he soon found himself in poor health, and at the end of July he proceeded to San Francisco, where a medical examination showed him to be suffering from acute dilation of the heart. He died on August 13, 1915, at the early age of fifty-three, while on a visit to his student, Dr. Herman A. Spoehr, at the Coastal Laboratory of the Carnegie Institution located at beautiful Carmel-by-the-Sea in California.

One of Nef's students, the late Professor William Lloyd Evans, has described Nef as follows:

"Nef was rather small of stature with a massive brow and bright,

penetrating eyes. He had an all-consuming and contagious love for his science. One became fascinated with the rapidity of his thought, which so outdistanced even the marvelous speed of his words that his students could only take sketchy notes which they would later piece out and amplify in order to get the full value of his lecture. His eager restless enthusiasm for the problems in which he was engrossed developed in him an appearance of brusqueness which amounted almost to impatience when the research did not progress smoothly. Back of this intellectual eagerness, however, dwelt kindly human qualities. He was by temperament intense and found his relaxation in long walks which he pursued at an unaccompaniable speed. He loved music and was a weekly attendant during the season of the Chicago Symphony Orchestra."

Nef was a member or fellow of the American Chemical Society, Deutsche chemische Gesellschaft (1885), American Association for the Advancement of Science (Secretary, Section C, 1893), Chicago Academy of Sciences (1893), National Institute of Social Sciences, New York (1914), American Academy of Arts and Sciences (1891), Royal Society of Sciences in Upsala (1903), and the National Academy of Sciences (1904). He was awarded an honorary LL.D. by the University of Pittsburgh in 1915.

Save for three early articles (1884–1887) and his last (1917) posthumous one, Nef never published with a co-worker. Even his Ph.D. dissertation was published with his name as sole author. The aid of his personal research assistant was acknowledged in his articles and the work of his doctoral students was referred to and occasionally briefly described. The dissertations directed by him were all published, mainly in the American chemical literature, under the sole authorship of the student with an acknowledgment to Professor Nef and with the statement that the work was initiated at his suggestion. Actually, the work was directed by Nef in detail and he saw every one of his research students daily. Because of this rather unusual situation, a bibliography of these articles by his students is appended herewith. Some of the Nef articles in *Liebigs Annalen* run to several

hundred pages. Altogether, he published alone 34 articles constituting over 1500 printed pages.

John Ulric Nef and his school were interested in the chemical reactivity of carbon compounds. Their work foreshadowed the modern radical theory and the modern transition state theory. Since the electronic nature of the covalent bond was not then known, Nef placed his emphasis upon the numerical nature of valence and upon bond dissociation preliminary to reaction. He began by attacking the Kekulé concept that the valence of carbon was always four and studied thoroughly those compounds, such as carbon monoxide, the isocyanides, and the fulminates, wherein carbon appeared to be in a lower valence state. His work with these poisonous and dangerous compounds was done largely with his own hands and represents organic experimentation of the most precise and difficult type. He established the fact that in these substances the valence of carbon changed from two to four by addition to one carbon alone. He then extended these established facts by exploiting the apparent tendency of carbon to react in the valences of two and four as a general phenomenon in the reactivity of carbon compounds. He considered that a carbon compound, as an alkyl halide, first dissociated into a reactive bivalent carbon radical which then could react further in several ways. His study of the Wurtz reaction was explained as follows, the yields of products noted being those actually isolated by him.

$$2CH_3-CH_2I \rightarrow 2CH_3-CH< + 2HI$$

$$2HI + 2Na \rightarrow 2NaI + 2H$$

$$2H \rightarrow H_2$$

$$CH_3-CH< \rightarrow \underset{|}{CH_2}-\underset{|}{CH_2} \rightarrow CH_2=CH_2 \ (21.7\%)$$

$$CH_3-CH< + H_2 \rightarrow CH_3-CH_3 \ (25.8\%)$$

$$2CH_3-CH< + H_2 \rightarrow 2CH_3-CH_2-$$

$$2CH_3-CH_2- \rightarrow CH_3-CH_2-CH_2-CH_3 \ (50.0\%)$$

By this theory of initial dissociation into unstable and nonisolable bivalent carbon fragments and their subsequent recombination, he

arrived at what appeared to be a general theoretical concept which he hoped would carry the banner for carbon (organic) chemistry as did, so successfully, the Arrhenius ionic dissociation theory for inorganic chemistry. This theory of methylene dissociation was indeed a logical one for the time. It contained the germs of truth and served to stimulate further work. An excellent summary of these speculations is to be found in Nef's 1904 article in the *Journal of the American Chemical Society;*[2] this article is a published address presented before the International Congress of Arts and Science, at St. Louis, Missouri, on September 20, 1904.

Our modern theory of the transition state is foreshadowed in the words of Nef:[3] "Excluding all reactions called ionic, a chemical reaction between two substances always takes place by their union to form an addition product. The one molecule being unsaturated and partially in an *active molecular condition,* absorbs the second molecule. The resulting addition product often dissociates spontaneously giving two molecules." (Italicization added.)

It is now known that the main step in the formation of free radicals is the homolytic scission of a covalent bond with the resultant formation of free radicals that may recombine in a bewildering number of ways.

$$C{:}C \rightarrow C^{\circ} + {}^{\circ}C$$

These radicals are not predominantly bivalent, although in the case of diazomethane dissociation modern chemists have found evidence for the transient existence of the true methylene radical ("carbene"), which Nef had long sought unsuccessfully to isolate.

$$\begin{array}{l} CH_2{=}N{=}\overline{N}| \leftrightarrow CH_2{-}N{\equiv}N| \\ \quad\oplus\quad\ominus\quad\downarrow\ominus\qquad\oplus \\ \qquad\qquad CH_2{:} + |N{\equiv}N| \\ nCH_2{:} \rightarrow (CH_2)_n \end{array}$$

[2] J. U. Nef, *J. Am. Chem. Soc.,* 26:1549–77 (1904).
[3] *Ibid.,* p. 1577.

It is of interest to note that electron magnetic resonance instrumentation now demonstrates that a free radical may have an indefinitely long life when trapped in a hole or imperfection in a crystal lattice.

The Nef explanation of the Gautier (1869) carbylamine reaction, involving the intermediate dichloromethylene radical,[4] is currently accepted. Substituting electron pairs for satisfied valence bonds, we have the following:

$$CHCl_3 + K^{\oplus}OH^{\ominus} \rightarrow [Cl_2C^{\circ}_{\circ}] + K^{\oplus} + Cl^{\ominus} + H_2O$$

$$[Cl_2C^{\circ}_{\circ}] + R^{\times}_{\circ}\overset{\times\times}{N}{}^{\times}_{\bullet}H \rightarrow [R^{\circ}_{\times}\overset{H^{\oplus}}{N}{}^{\times}_{\bullet}\overset{\circ\circ}{C}{}^{\times}_{\times}Cl_2]^{\ominus} \xrightarrow{2KOH}$$

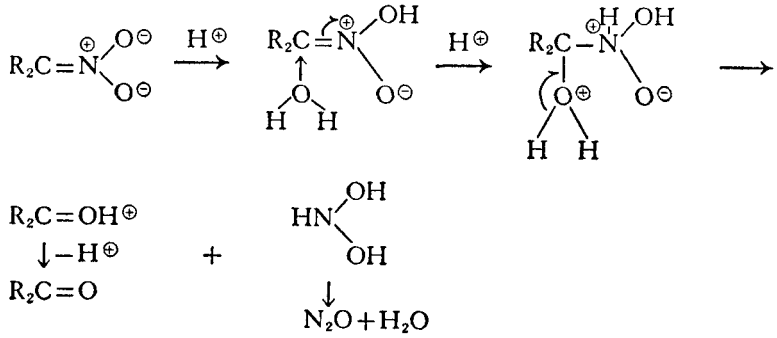
$$R^{\circ}_{\times}\overset{\times}{N}\overset{\times}{\underset{\times}{\circ}}C^{\circ}_{\circ} + 2K^{\oplus} + 2Cl^{\ominus} + 2H_2O$$

When Nef initiated his early work on the tetrahalogeno derivatives of *p*-benzoquinone, there were three formulas in vogue for *p*-benzoquinone. Of the three, the currently accepted one, originally proposed but not established by Fittig, was put on a sound experimental basis by Nef. He next turned his attention to the sodium salts of β-ketonic esters, for which he favored the formula in which the metal was attached to oxygen rather than to carbon. He thus served to draw attention to this possibility, now explained by a resonating anion.

$$R-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-OR' \overset{\text{Base}}{\rightleftharpoons} R-\underset{\underset{O}{\|}}{C}-CH=\underset{\ominus\underset{O}{\|}}{C}-OR'$$

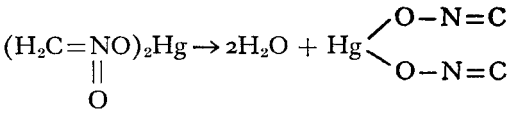
From the sodium salts of β-ketonic esters he proceeded logically to a study of the sodium salts of primary and secondary nitroalkanes. Nef insisted upon an enolic structure for the salt and showed that acids did not regenerate the nitroalkane but gave a carbonyl compound. In modern terms,[5]

[4] J. Hine, *J. Am. Chem. Soc.*, 72:2438 (1950).
[5] E. E. van Tamelen and R. J. Tiede, *J. Am. Chem. Soc.*, 74:2615 (1952).

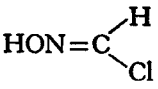


The above synthesis of a carbonyl compound, from the salt of a nitroalkane, is known as the Nef reaction[6]—one, however, of several "Nef reactions"!

In order to study the various salts of nitromethane, it became desirable to prepare mercuric nitromethane. This substance had been previously reported as a dangerous, explosive yellow salt. In preparing the compound, Nef noted that the warm liquid filtered from it gradually deposited a crystalline substance which he recognized as the fulminate of mercury. The genius of Dr. Nef enabled him to see at once the far-reaching importance of this chance observation. It served to establish the true formulas of the fulminates, long known and considered by Liebig and Gay-Lussac to be salts of a dibasic acid. Nef formulated the reaction as follows:



He recognized that the carbon atom in fulminic acid, isolable only as its salts, was apparently bivalent. In conclusive proof of this, he isolated the carbon hydrohalide addition compound.



This compound crystallized from ether at 0° in long, transparent

[6] W. E. Noland, *Chem. Revs.*, 55:137–55 (1955).

needles. At room temperature it soon became green and exploded with violence. It was extremely poisonous.

Nef also studied prussic acid, its salts, and the alkyl isocyanides. He was greatly interested in the peculiar compounds $2(RNC)\cdot 3HCl$ and in the products obtained by the action of alkyl hypochlorites upon metallic cyanides. He favored the bond formula $H-N=C$ for prussic acid and, in common with many organic chemists of his day, he did not like tautomeric or shifting structures, stating that "to explain the behavior of an organic compound one formula is sufficient." It was during and following these studies on the truly bivalent carbon compounds that he initiated his speculations upon the role of bivalent carbon in all other organic reactions. These speculations, with much experimental data purported to support them, were published in four long articles in *Liebigs Annalen.* The fourth appeared in 172 pages of Volume 298 in 1897. One of the Nef students, Herman A. Spoehr, states: "I believe it is safe to say that the 172 pages of this volume of the *Annalen* which constituted this paper were for many years the most thoroughly thumbed of any of the journals in the chemistry library here. By Nef's students this paper was frequently regarded as a *pons assinorum* to a degree." One of the important points to be derived from these articles is the emphasis placed by Nef upon *all* the products of an organic reaction and not just the one desired end-product. To Nef by-products were as important as the main product in that the former gave clues to the chemical nature of the substance or reaction he was studying. In this respect he did not overlook polymerization reactions. He writes:[7] "Experience has shown that many unsaturated compounds can not be isolated; but polymerize spontaneously. It is clear that when the per cent. of active particles present in an unsaturated compound becomes relatively great the possibility of their uniting with each other to form condensed molecules increases." Here, indeed, is the true concept of our modern theory of polymerization, which had to be laboriously rediscovered by others many years later.

[7] J. U. Nef, *J. Am. Chem. Soc.,* 26:1563 (1904).

It is not surprising that Nef was intrigued with that most unsaturated of carbon compounds, acetylene. He prepared and studied the mono- and di-halogen substituted alkynes, all poisonous and spontaneously combustible compounds. Diiodoacetylene possesses an odor deceptively like the isocyanides and dissociates explosively at 100° into its elements. Nef formulated this substance as $I_2C{=}C$, but later physical data indicate the linear formula $I{-}C{\equiv}C{-}I$, although a small proportion of the other may be a tautomer. In connection with his studies on acetylene chemistry, Nef established the ethynylation of a ketone, a reaction which has been exploited in recent times and which constitutes a key step in the commercial synthesis of Vitamin A.

$$R_2C{=}O + NaC{\equiv}CR \xrightarrow{HOH} R_2C\begin{matrix} C{\equiv}CR \\ OH \end{matrix} + NaOH$$

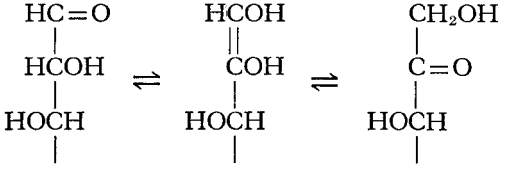
The above is the "Nef reaction" of the acetylene specialists and is not to be confused with the previously cited "Nef reaction" of the nitroparaffin chemists. In respect to Nef's 1899 paper on phenylacetylene, the *Annalen's* editor Volhard wrote to him, "Ihr schönen Arbeiten erachte ich für eine Zierde der *Annalen*" (I consider your fine manuscript an adornment for the *Annalen*).

During the last period of his life and for the eleven years 1904 to 1915, Nef and his students devoted their entire attention to a comprehensive study of the dissociation of the sugars in the presence of alkaline solutions of varying strengths, and in the presence of various oxidizing agents in neutral, acid, and alkaline media. The results of these investigations were presented in three long articles in the *Annalen* appearing at intervals of three years and entitled "Dissoziationsvorgänge in der Zuckergruppe" (Dissociation Processes in the Sugar Group); at the Ohio State University these articles have been so thoroughly thumbed that all three volumes have had to be rebound. The experiments were designed in the hope that they might throw some light on the fermentation of sugars.

During this period he trained most of his major students, who

thereafter continued in carbohydrate research, with other students, in universities and research institutes located mainly in the Midwest. I cite, in this respect, the names of Ernest Anderson (Arizona), William Lloyd Evans (Ohio State), J. W. E. Glattfeld (Chicago), Oscar Hedenburg (Mellon Institute), W. Lee Lewis (Northwestern), Herman A. Spoehr (Carnegie Institution), and Fred W. Upson (Nebraska). Among earlier students at Chicago were S. F. Acree (National Bureau of Standards), Lauder W. Jones (Princeton), and William McPherson (Ohio State). Considering that Nef only had 25 Ph.D. students at Chicago, this is a very high percentage (40 percent) of students who made later marks in fundamental research activities. All of these men were imbued with the intense research spirit of Nef and all of them respected and revered their great teacher.

In his extensive and difficult experimentation in the alkaline sugar reactions, Nef separated the saccharinic acids (alkali rearrangement products of the reducing sugars) and established the structures of their various types. With Oscar Hedenburg, he discovered the second crystalline form of gluconono (and mannono) lactone, now known to be the unstable 1,5-lactone. From the aldonolactones he prepared their acyclic alkyl esters. He showed that oxidation of an alkaline solution of an aldonic acid with a stream of air resulted in the next lower aldose. This is the useful "Nef reaction" of the sugar chemist and represents the third "name" reaction ascribed to him. He utilized the concept of enediol formation in explaining the complex changes produced by alkali on the sugars.



It can be noted from the above formulas that the carbonyl group has moved down and up the chain through two carbon atoms.

This process can continue, and recent tracer experiments [8] indicate that it can go all the way to the end of the chain, resulting in the formation of a host of ketose and aldose structures by inversion of asymmetry in the intervening optically active centers. The other significant reaction occurring in these alkaline solutions is chain degradation with the production, especially, of DL-lactic acid. Nef and his students studied this change and the intermediates concerned in it.

Nef's untimely death in 1915 brought his own researches to an abrupt end, but they were continued by his students. His contributions to theoretical and synthetic chemistry were profound and his influence on the development of organic chemical research in the United States has been immeasurable.

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[8] J. C. Sowden and R. R. Thompson, *J. Am. Chem. Soc.*, 80:1435 (1958).
[9] L. W. Jones, "John Ulric Nef," *Proc. Am. Chem. Soc.*, 44–72 (1917).

KEY TO ABBREVIATIONS

Am. Chem. J.=American Chemical Journal
Ann.=Liebigs Annalen der Chemie
Ber.=Berichte der deutschen chemischen Gesellschaft
J. Am. Chem. Soc.=Journal of the American Chemical Society
J. Chem. Soc.=Journal of the Chemical Society (London)
J. prakt. Chem.=Journal für praktische Chemie
Proc. Am. Acad. Arts Sci.=Proceedings of the American Academy of Arts and Sciences

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