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Discovery of the Michael Reaction

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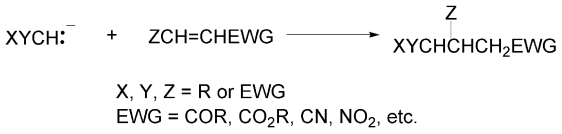
This essay deals with the details of the discovery of the Michael addition reaction, focusing on Arthur Michael, an American chemist, after whom it is named. Michael envisaged the possibility of an addition reaction of sodiomalonate ester or sodioacetoacetate ester to α,β-unsaturated acid esters and confirmed this by experimentation. Some instances of the Michael addition were observed prior to Michael's crucial finding, and the validity of his credit as the discoverer is discussed. At the same time, a general consideration is made on chemical creativity with reference to the individuality in the career and the personality of A. Michael.

Introduction

The Michael reaction,[1–3] addition of stabilized anions (e.g., enolate) to α,β-unsaturated carbonyl and related compounds, is a prototype for the conjugate addition reactions of various nucleophiles[4,5] that now find wide utility in organic syntheses (Scheme 1).



$$\mathrm{XYCH}{:}^{-} + \mathrm{ZCH{=}CHEWG} \longrightarrow \mathrm{XYCH\overset{Z}{C}HCH_2EWG}$$

X, Y, Z = R or EWG
EWG = COR, CO_2R, CN, NO_2, etc.

Scheme 1.

The reaction is named after the American chemist Arthur Michael (1853–1942), who was peculiar in both his career and research activity. Details about his career, achievements, and personality may be gleaned from his memoirs,[6] biographical articles,[7] and essays on his works.[8–10] None of these, however, provides sufficient background on the chemistry, both specific to Michael's work and state of the art at the time, his motives, and the course of events leading to his crucial findings. Moreover, his role in the discovery and the generalization of the Michael reaction is not always described correctly. It is the aim of this essay, therefore, to bridge these lacunae and to establish Michael's crucial role.

Stumble in Youth and Studying Abroad

Arthur Michael (Figure 1) was born in Buffalo, New York, on August 7, 1853 to a well-off real-estate investor.[10] At classical school, Michael received private instruction in chemistry, and in his leisure time, he enjoyed performing chemical experiments in a home laboratory that his father had set up for him. Toward the end of his teens, he experienced a great trial: his plan to enter Harvard College was foiled by a serious illness. After wavering about his future career following his recovery, Michael decided to study chemistry in Germany. During a family sojourn in Germany in the summer of 1871 (the year of the establishment of the German Empire), Michael had the fortune to be admitted to the Chemical Laboratory of Professor August W. Hofmann at the University of Berlin, notwithstanding his insufficient chemistry background. A year later, Michael moved to the laboratory of Robert W. Bunsen at Heidelberg University, where he received basic training in experimentation, and after studying for two years, Michael returned to Berlin to work in the laboratory of Hofmann (1875–1878). A first-hand account by an American professor outlines the impetuous behavior of Michael in the Bunsen laboratory, and it vividly depicts some aspects of Michael's temperament and the nature of his experiments. C. L. Jackson, who studied with Bunsen and Hofmann at the same time as Michael and who later contributed greatly to education and research in organic chemistry at Harvard University in its early stage, stated the following in his autobiographical speech:[11]

"My next analysis was copper pyrites, then rhyolite (a rock), chrome ion and triphiline (a mineral phosphate). This last was suggested to me by Arthur Michael, who proposed we should do it together, so we started at the same time. He spoilt his work so often that he had to begin again seven times, but worked so fast that he got a good result at the same time that I plodded to the end of my single analysis."

To conclude his studies in Europe, Michael spent an additional year working with Adolphe Wurtz in Paris and Demitrij I. Mendeleev in St. Petersburg, and then, in 1880, he

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Figure 1. Arthur Michael around 1886. Photo courtesy of the Digital Collections and Archives, Tufts University.

returned to America. He became an assistant in the chemical laboratory at Tufts College and then, after a short period, was promoted to a professor of chemistry. He devoted himself to teaching and training his students as well as to his own research, successfully overcoming the disadvantages of working at a small institution. Michael made great use of his ample knowledge and experience he obtained in Europe, and even used his own money to cover research expenditures. In 1887, Michael first reported on the reaction that bears his name.

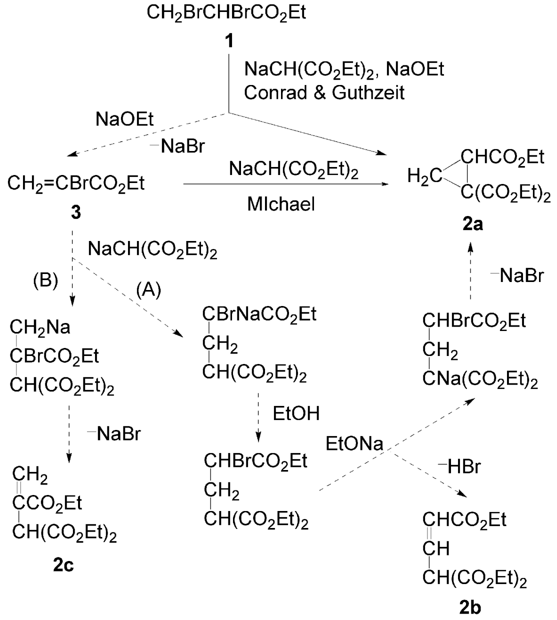
Evolving Research Activity

Michael's early work, which began after his return to Hofmann's laboratory, seemed to be focused on various separate problems in preparative and structural organic chemistry. Among his noteworthy achievements was the first synthesis of natural phenol glucosides (helicine, salicin, methylarbutin, etc.),[12] work that began during his stay in Paris. Chloroacetoglucose, the first of its kind, had been prepared by a French chemist,[13] and Michael treated it with potassium phenolate. The improvement of this method led to the Koenigs–Knorr synthesis (use of more reactive acetobromo sugars), known as an important standard method for glycosidation.[14] Another series of work at that time was on the constitution of coniine, a simple piperidine alkaloid, which was discontinued on the elucidation of its structure by the Hofmann group in 1885.

Around the mid-1880s, Michael's interest in his research gradually shifted to general and theoretical problems in organic chemistry. One of these foci was the problem associated with geometrical isomerism.[10] The concept of the tetrahedral carbon atom was introduced by Jacobus H. van't Hoff and Joseph Le Bel in 1874 to explain optical isomerism, and the former had extended this idea to account for the isomerism associated with the C–C double bond, that is, geometrical isomerism. However, a number of leading organic chemists at the time were skeptical about the highly imaginative and visual way in which young van't Hoff made his explanation, and these chemists tried to solve the problem of C–C double bond isomers without a new concept. Therefore, in the early 1880s, when Michael started his research work in the U.S.A., the structural relationship between maleic and fumaric acids, for example, was still in hot dispute.[15] In 1886, Michael proposed his own concept of alloisomerism,[10,16] which reduced the individuality of the isomeric compounds to merely differences in energy content and withholding the structural implication – the prefix "allo-" was assigned to the more-stable isomer, and thus fumaric acid was allomaleic acid. In this way, one could be, Michael contended, free from the spell of the uncertain and unreliable concept, and the method might be adaptable to the putative presence of more than two double-bond isomers and to contingent isomerism in the case of methylene compounds like itaconic acid. In fact, he allegedly reported cases in which more than two isomers were found especially in cinnamic acid derivatives,[17] though these were proved later to embrace polymorphic compounds.[18] In any case, Michael strived persistently to maintain his stand on stereoisomerism, even after other chemists came to accept the new theory.

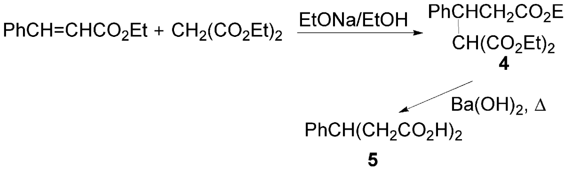
Towards the Crucial Experiments

In the mid-1880s, Michael noticed a paper by M. Conrad and M. Guthzeit[19] that reported the formation of a cyclopropane derivative by the reaction of diethyl 2,3-dibrompropionate with diethyl sodiomalonate. The formulation was based on an analogy with the case of W. H. Perkin Jr.,[20] who assigned the diethyl cyclopropan-1,1-dicarboxylate structure to the product obtained by the reaction of 1,2-dibromethane with sodiomalonyl ester. At that time, the cyclopropane structure was not yet generally accepted, as R. Fittig had coincidently conducted the same reaction as Perkin with a different aim and had assigned a vinyl malonate formula for the product.[21] Michael considered that the debate might be ended by his concept of alloisomerism.[16a] Thus, he treated 2-bromacrylic acid ester with sodiomalonic acid ester and indeed found that the product was identical to that reported by Conrad and Guthzeit.[22] Although Michael thought the product was the allo isomer of **2c**, he would not be convinced of its formation via the direct substitution of the vinylic bromine atom in **3** with a malonate residue. Considering carefully the reason why both reactions starting from 2,3-dibrompropionate and 2-bromacrylate afforded the same product, he came to the realization that it might concern an addition reaction, provided that in the Conrad–Guthzeit case the latter compound formed from the former, initially by elimination. Then, the two-way addition A and B was, Michael reasoned, possible (Scheme 2), and A would be preferred, as the negative organic residue should add to the β-position of the double bond by analogy of the addition reaction with the hydrogen halides.[23]



Scheme 2.

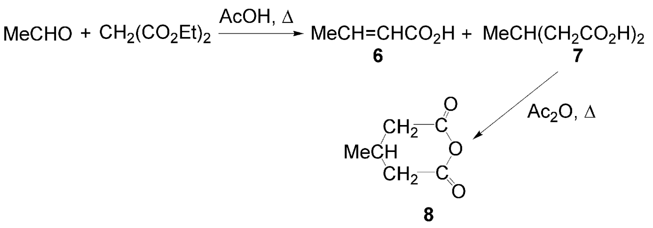
Michael was expeditious to test his idea in experiment, namely, the capability of the reaction between unsaturated acid esters with the sodium salt of active methylene compounds (i.e., enolate anions). Typically he heated a mixture of sodium ethoxide in ethanol, diethyl malonate, and ethyl cinnamate in a sealed tube in a water bath for 6 h. After usual work-up and distillation of the product at reduced pressure, Michael obtained a heavy oil boiling at 213–215 °C/15 mm Hg with very little unchanged malonic and cinnamic ester. Elemental analyses showed that product **4** had a molecular composition of $C_{18}H_{24}O_6$, indicating the direct union of the cinnamate with the malonate.[25] Eureka! Subsequent experiments revealed that the reaction proceeded smoothly even at ambient temperature, and after the reaction mixture stood for several days, product **4** was obtained in nearly theoretical yield. Upon hydrolysis of **4** with barium hydroxide, followed by decarboxylation with heating 3-phenylglutaric acid, **5** was obtained as crystals (Scheme 3). The reactions of ethyl cinnamate and diethyl citraconate with ethyl sodioacetoacetate were also examined. Although elemental analyses of the product in the reaction of the latter indicated it to be the normal addition compound, those in the former case suggested that it lost a molecule of ethanol by a secondary reaction.[26] Sparing the time to elucidate the constitution of these products, Michael put the results and his thoughts together promptly in a paper, which was published in German in early 1887 in the *Journal für Praktische Chemie*.[25a] He subsequently published the English version in the *American Chemical Journal*[25b] (founded in 1878 by I. Remsen, and later incorporated into *J. Am. Chem. Soc.*). Editor's note: In 1998 the journals *Liebigs Annalen* and *Chemische Berichte* were merged with other European chemistry journals to form *EurJOC* and its sister journal *EurJIC*. Similarly, *Journal für Praktische Chemie* was relaunched as *Advanced Synthesis & Catalysis* in 2001.



Scheme 3.

Claim of Priority from Claisen

Soon after the publication of the above papers a response by Rainer Ludwig Claisen appeared in *J. Prakt. Chem.*, claiming priority as related to the discovery of the novel addition reaction (in April).[27] In the course of the studies in his laboratory on the condensation reactions of aldehydes with malonic acid and its diester,[28] byproducts like **7** were found to form in addition to alkylidene products (e.g., **6**; Scheme 4). Claisen maintained that the former was ascertained to be produced by the addition reactions of malonic acid or its diester to the double bond of the condensation products and that the possible generality of this reactivity was also described in the paper. He conclusively stated that the reactions reported by Michael represented mere additional examples of those observed many times before by him and others. Actually, after the Claisen–Komenos report, condensation–addition products like theirs were shown also to form in the reaction of formaldehyde with diethyl malonate by Perkin Jr.[29] and in the reaction of benzaldehyde with ethyl acetoacetate by A. Hantzsch.[30–33] Immediately, Michael sent his reply (received on May 14), insisting the originality of his discovery.[35] He executed, he wrote, the crucial reactions based on his own thought without knowing of the precedents of Claisen–Komenos.[28] No reaction was observed by Michael for the reaction of cinnamate ester and acetoacetate or malonate esters under the conditions outlined by Claisen–Komenos. Michael even pointed out that the reactions of Claisen might represent a special case in which the double bond was appended by two carboxyl or carboxylate groups. It would be of great consequence that the simple unsaturated acid esters were found to react generally with sodiomalonate or sodioacetoacetate. In the end of Michael's paper, Ernst von Meyer, the son-in-law of Hermann Kolbe, who was in charge of the Editor at this time, added his comment as a footnote, which would be valid arbitration even in the modern sense. The footnote reads: "*the way how this combination (of malonate ester with unsaturated acid ester) resulted was clearly known by Mr. Claisen and correctly described. Mr. Michael contributed to make the reaction remarkably practical by the use of sodium compounds of malonate and acetoacetate esters and to have substantially generalized.*"



Scheme 4.

Apart from the claim of Claisen, the discovery of Michael garnered little response from organic chemists for some years, a situation that proved fortunate for him. Towards the end of that fruitful year, a gifted woman scientist, Miss Helen Abbot of Philadelphia, joined Michael's group as a graduate student. Michael and Abbot married the next June, and they boldly took an 18-month honeymoon trip around the world. Mrs. Michael already had a good career as a scientist before her marriage and had published several papers, especially on plant chemistry, which are credited with the first expression of chemotaxonomical ideas.[36]

Securing of the Priority

When Michael left Boston in early summer of 1888, he actually left several matters unsettled in his research. With respect to the new addition reaction, his goals for the moment would be the clarification of the abnormal result observed in the reaction of ethyl cinnamate with ethyl sodioacetoacetete and the elucidation of the scope of the reaction in reference to the type of double-bond compounds (the Michael acceptor) and active hydrogen compounds (the Michael donor). Similarly, the problems of the alloisomerism were of great concern for Michael, especially because he had challenged Wislicenus to dispute geometrical isomerism in a paper[37] just before his marriage. He also set about to work on tautomerism, particularly on the structure of acetoacetate ester.[38] The response of Wislicenus was published in August 1888,[39] just after the Michael couple left for their trip. As a matter of fact, Michael could not be completely free from the research in his mind during the trip. He would sometimes give directions to his collaborators and would manage to engage in the preparation of manuscripts only when he found time. In this way, his response to Wislicenus' refutation[40] was sent to the editor from Cairo in May of 1889.

After returning late in 1889, Michael was called to the newly established Clark University as Director of the Chemical Laboratory, an appointment that was not realized due to a fallacy in the contract.[10] It was at the private laboratory in the Isle of Wight, a leisure spot in England, that he could set to work on the tasks described above in relation to the newly found reaction, as well as to other emergent problems. Early in 1891, Michael responded to a preliminary paper of K. von Auwers,[41] which reported the synthesis of polybasic fatty acids by the application of the Michael reaction. First of all, Michael promptly submitted a paper[42] detailing the results so far obtained on the structure of the abnormal product obtained from the reaction of sodioacetoacetate with cinnamate[26] without any conclusive assignment.[43] This was published as Part II of the consecutive title "On the Addition of Sodioacetoacetic and Sodiomalonic Ester to Unsaturated Acid Esters," and Michael did not forget to add the reservation for his studies on this theme. The Part III paper[46] dealt with the addition reactions of diethyl maleate, diethyl fumarate,[41] diethyl citacoate, diethyl mesaconate, and diethyl itaconate, the reactions being carried out mostly with powdered sodium in absolute ether in place of sodium ethoxide in ethanol. Higher boiling points and elemental analyses of the products indicated that the addition reactions occurred, but further decisive characterization was lacking for the latter three reactions.[47] In addition, Michael conducted an experiment to test the reactivity of the unsaturated carbon bond in the β–γ position to carbethoxyl group. Namely, diethyl allylmalonate was heated with diethyl sodiomalonate, but no sign of the addition reaction was detected. In Part IV,[49] Michael described the addition reactions of diethyl acetylenedicarboxylate and ethyl phenylpropiolate with sodiomalonate, and the reaction of benzalacetone with sodioacetoacetate. At the end of the paper, he concluded as follows:

"Ungesättigte Körper von der Constitution R–HC˙–HC˙–X oder R–C̈–C̈–X, worin R irgend ein positiv oder negativ organisches Radical, und X ein stark negatives Radical (–$COOC_NH_{2N+1}$, CN, CHO, COC_NH_{2N+1} sind Beispiele) bedeutet, vermögen sich in der Art mit Natriummalon- und acetessigäther, sowie Derivaten derselben und verwandter Körper, zu vereinigen, dass Natrium an den, nach dem positiv-negativen Gesetz, negativen ungesättigten Kohlenstoff, und der Rest der Verbindung, unter Kohlenstoffbindung, an den relativ positiven, ungesättigten Kohlenstoff sich anlagern."

["Unsaturated substances of the constitution R–HC˙–HC˙–X or R–C̈–C̈–X,[50] wherein R means some positive or negative organic radical[51] and X a strongly negative radical ($COOC_NH_{2N+1}$,CN, CHO, COC_NH_{2N+1} are examples) can combine with sodiomalonate and sodioacetoacetate in such way that the sodium atom adds, in keeping with the positive–negative rule, to the unsaturated negative carbon and the rest of the compound (the counterpart) to the relatively positive unsaturated carbon."]

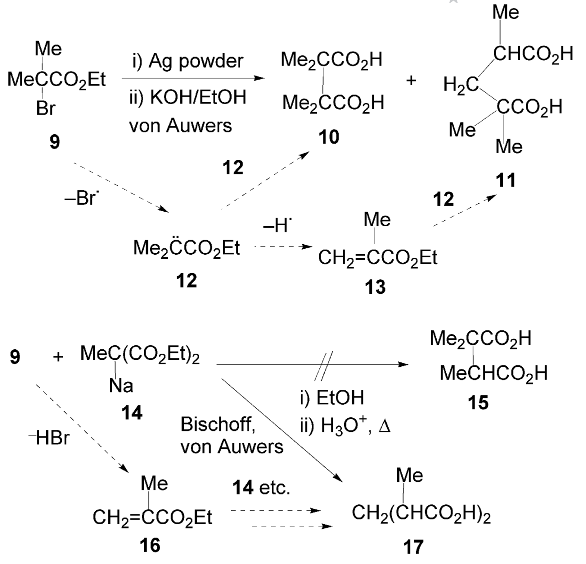
Thus, Michael had managed to summarize, hurriedly and broadly, the important traits and the scope of the new reaction.

Clarification of Hidden Michael Addition Reactions

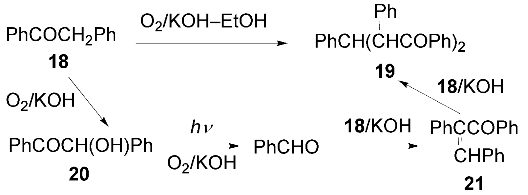
In addition to the cases of Claisen–Komenos, Perkin, and Hantzsch described in the previous section, several organic chemists came across reactions in which the Michael addition was involved, though not perceived as such, around the time of its discovery by Michael. These "hidden" Michael reactions were clarified first after Michael's achievement. These events served to bring about the general recognition of the reaction.

The works of von Auwers on the Michael reaction, which hurried Michael as described above, is traced back to engagement in studies on the stereoisomerism of benzil oximes in the laboratory of Victor Meyer.[52] Since they sought to ascribe the cause of the restricted rotation between the two adjacent oxime carbon atoms, they noticed the report of C. Hell, which described the formation of two isomeric dicarboxylic acids by treatment of ethyl 2-bromo-2-methylpropionate (**9**) with metallic silver.[53] von Auwers clarified that these two compounds were structurally different rather than a representation of a new type of stereoisomer (Scheme 5): one compound was expected tetramethylsuccinic acid (**10**) and the other was 2,2,4-trimethylglutaric acid (**11**).[54] With this result, von Auwers suspected the report of C. A. Bischoff on the putative synthesis of 2,2,3-trimethylsuccinic acid (**15**) through the reaction of **9** with diethyl sodiomethylmalonate (**14**) followed by hydrolysis and decarboxylation.[55] Through the investigations of von Auwers[56] and Bischoff[57] this product was actually proven to be 2,4-dimethylglutaric acid (**17**). Moreover, in the 1890 paper reporting the result, the former mentioned the possible production of glutaric acid derivative by assuming an addition reaction of methacrylate **16** formed through elimination. Probably around that time von Auwers came to notice the crucial report of Michael and realized the utility of the Michael reaction for the syntheses of polybasic fatty acid esters. He performed successively the reactions of diethyl sodiomalonate with ethyl crotonate, ethyl methacrylate, ethyl 3,3-dimethylacrylate, diethyl fumarate, and triethyl aconitate. A number of 2-alkyl-substituted carballylic acids were also shown to be efficiently synthesized by the reactions between sodioalkylmalonates and diethyl fumarate. von Auwers summed up these results in a preliminary paper[41,58] in 1891, citing firstly the paper by Michael that was published four years earlier.

In the Hantzsch dihydropyridine synthesis,[32] which was discovered in 1882, two mol of ethyl acetoacetate and one mol of acetoaldehyde and ammonia were originally condensed. In an attempt to obtain the nitrogen-free intermediate in a crystalline form, Hantzsch conducted the reaction by using benzaldehyde and primary amines instead of acetaldehyde and ammonia, respectively, and obtained the Claisen–Komenos-type product as described in the previous section, though no comment was given for the mechanism of formation of such a compound. A more complicated and hidden Michael reaction is also known. In 1871, N. Zenin reported the production of highly crystalline compound **19** (benzamarone, $C_{35}H_{28}O_2$) by treatment of desoxybenzoin (**18**) in alcoholic potassium solution under air bubbling.[59] It was eventually clarified through the work of several chemists, especially E. Knoevenagel,[60] that benzaldehyde, formed by autooxidation of deoxybenzoin to benzoin (**20**) followed by photolysis, condensed first with **18** to produce benzylidenedeoxybenzoin (**21**; the Claisen–Schmidt reaction), and the Michael addition to this product of the deoxybenzoin anion results in the formation of benzamarone (Scheme 6).



Scheme 5.



Scheme 6.

Chemical Instinct

All the details in the findings and the development of Michael's novel addition reaction have been so far traced, and here the cause leading him to success is considered in connection with chemical creativity.[61] Although his chemical knowledge was mostly self-taught, Michael soaked up the latest chemistry at that time during his training stay in Europe. He absorbed eagerly not only the knowledge of organic chemistry but also that of other fields (e.g., thermodynamics at Heidelberg and Berlin and periodic law at St. Petersburg). Thus, his attainments in chemistry were built in his own individual way, and he grew accustomed to considering chemical problems basically and theoretically. As a man of artist-like sensitiveness and self-will, he would not be ready to accept the veracity of claims lacking enough evidence and challenged others to debates on various aspects. The first prominent instance of such a kind was exemplified by his polemic attitude toward Wislicenus for his work on geometrical isomerism, as previously mentioned. Michael refuted the discussion in Wislicenus' papers on the basis of the premise that the addition to double bonds always proceeded in a *cis* manner. He pointed out the possibility of the *trans* addition and put forward some evidence for it, though that evidence was never conclusive.[62] Even so, this fact would indicate Michael's keen and unconstrained thinking.

Michael's finding of the novel reaction was realized by the following three steps: (1) He noticed the formulation of cyclopropane by Conrad and Guthzeit as the product from the reaction of 2,3-dibromopropionate with diethyl sodiomalonate from the viewpoint of alloisomerism. (2) He carried out the reaction of ethyl 2-bromoacrylate and diethyl sodiomalonate and found that the compound obtained was the same as that of Conrad and Guthzeit. (3) He envisaged the possibility of the addition of malonate to the double bond of acrylate and executed promptly the experiment for verification.

As for step 1, Michael's interest in the Conrad–Guthzeit product would indicate, in addition to his concern about alloisomerism, his prodigious knowledge of and his deep insight into organic reactions. Since Michael had much experience with reactions of halogenated crotonic and cinnamic acids,[63] and he might have known that base treatment of 2,3-dihalogenated fatty acids would result in elimination rather than substitution to give 2-halogeno-2-alkenoic acids, he would have good reason to be suspicious of the Conrad–Guthzeit formulation. In any case, his chemical instinct would perceive that something dubious was there. By the way, it was said[7] that his students, probably of later years, were very impressed by Professor Michael's almost uncanny ability to predict the course of an organic chemical reactions, which was referred to as "chemical instinct and a sixth sense." Thus, his excellent intuition as well as his casual concern gave him the incentive to carry out the experiment in step 2. The result obtained was exactly just what he had expected, but Michael's chemical instinct did not allow him to accept that as it was. It is not clear whether he suspected that the reaction of 2-bromoacrylate ester, a vinyl bromide, with malonate diester would give smoothly the substitution product, as he would have designed the experiment, in the very least, on the basis of his expectation for such a possibility to some degree. In any case, Michael sought to consider thoroughly the reaction course through which the reactions of both Conrad–Guthzeit and himself would proceed to give the same product and logically deduced the intervention of the elimination–substitution mechanism. Thus, as step 3, the reaction of ethyl cinnamate with sodiomalonate was conducted and found to afford smoothly the addition product. Here, Michael had fully shown his outstanding ability as both a theorist and an experimentalist. At that time, when the role of the electron in chemical bonding was quite unknown, it was remarkable that Michael came to think of the possibility of an addition reaction of an organic residue to the double bond of an unsaturated ester. This would be possible again only with Michael's unconstrained way of thinking, which we noticed also in his argument of the *trans* addition. Young Michael was shrewd to test what he conceived in experiment, which led to a big discovery.

As described in the previous section, the evidence, which suggested the addition reaction of sodiomalonate or sodioacetoacetate to α,β-unsaturated esters, was accumulating in the 1880s and 1890s, and even if the reaction were not discovered by Michael, it would happen that others, such as von Auwers, Bischoff, or Knoevenagel, might sooner or later discover the addition reaction. However, Michael discovered this novel reaction in an earlier instance as the product of his refutative spirit and his great abilities in logical analysis.

Is Arthur Michael Duly Called the Discoverer of the Reaction that Bears His Name?

In this section, a discussion is to be attempted on whether Michael deserves credit for discovering the reaction that bears his name. As a matter of course, it relates closely with the definition of the Michael addition reaction, which seems fortunately to be now rather fixed in the way as described in the outset of this essay − the addition reactions of stabilized anions (or nucleophiles) to α,β-unsaturated carbonyl or related compounds (or electron-deficient alkenes and alkynes).[3] The related conjugate addition reactions are often called Michael-type reactions though the scope of this term is not always clear.

Michael, in one of his first papers reporting the new reactions, cited the works of A. Claus as examples of the formation of higher carbon analogs by addition reactions to C–C double bonds, in which the reaction of allyl iodide with potassium cyanide upon heating in a sealed tube gave 1,2-propanedicarbonitrile (1873)[64b] and a related reaction of 2,3-dichloropropene to 1,2,3-propanetricarbonitrile (1881),[64a] and both reactions involved hydrocyanation reactions and the conjugate addition of a carbon nucleophile. Moreover, the addition reaction of alkoxide anions (the oxa-Michael addition)[65] was reported as early as 1878 by F. Loydl[66a] and later by T. Purdie[66b–66d] and A. v. Baeyer.[66e,67] However, both reactions are commonly regarded as Michael-type additions.

The addition of malonic acid and malonate ester to alkylidene derivatives was found by Claisen–Komenos before Michael's crucial experiments, though these were carried out without reference to the former reactions. In the former case, the Michael addition products were obtained under the conditions of aldehyde condensation by reagents like acetic acid, a mixture of acetic acid and acetic anhydride, or hydrochloric acid. Perkin Jr.[29] conducted his reaction under similar acidic conditions (1886), whereas Hantzsch used secondary amines (1885).[30] It is notable that Claisen–Komenos firstly noticed the addition of malonic acid or malonate ester to alkylidene compounds, an example of the Michael addition, but these reactions are not typical in the structural features of unsaturated substrates or in the reaction conditions, namely, the double bonds are doubly activated by two carboxyl groups and reactive enough to give the addition products under acidic conditions.

Contrastingly, Michael conceived the possibility of the addition of sodioacetoacetate or sodiomalonate esters to simple α,β-unsaturated ester from the analogy of hydrogen halides to the latter and found that this type of addition did occur. With this finding, the Michael addition firstly held the basis for the generalization and practical utility as stated in E. von Meyer's comment. Moreover, it is significant that the features of the reaction with regard to the reactants and the orientation of the addition were first defined by Michael. Thus, in conclusion, it can be safely said that A. Michael discovered the Michael reaction, at least, substantially, although examples of this reaction were observed prior to Michaels's crucial finding.

Epilogue

After four years freelance work on the Isle of Wight, Michael resumed his duties as a professor at Tufts in 1894 and remained in this position until 1907, when he held an emeritus status. During this period, Michael was not very active in the promotion of his reaction; rather his major concern was directed toward basic principles in organic chemistry. He strived for debates on various theoretical aspects, such addition–elimination reactions, rearrangements, tautomerism, steric hindrance, and ring strain, standing on his original theory[8,68,69] and own experiments. A. B. Lamb, who was a student of Michael and later a prominent Harvard professor,[70] described vividly the influential status of Michael, then in his early forties, in the college.[71] Meanwhile, he suffered misfortune to lose his life partner and then a medical doctor due to the influenza virus in 1904. After retirement, his research was continued in a private laboratory built close to his marvelous house at Newton Center, Greater Boston. From 1912 on, Harvard University provided a professorship for graduate education to Michael[72] and he supervised graduate works by staying at his own laboratory all the time. After 1936, when he became emeritus and was over the age of 80, his interest in research still persisted.

Other than chemistry, Michael had a wide range of hobbies, in all of which he was exhaustive and extravagant. Noteworthy was his collection of Oriental art,[6] which was obtained through his friendship with Ernest Fenollosa, an enthusiastic Orientalist. When young, Michael was fond of mountain climbing and spent his vacations in the Alps, the Canadian Rockies, or the Selkirks. In 1897, he was a member of the U.S.–England party that achieved consecutively the first ascents of Mt. Lefroy and Mt. Victoria, which constitute the grand vista of Lake Louise. The leader of the English members was J. Norman Collie, an organic chemist, known as the first person to propose polyketide condensation in the biosynthesis of phenols.[73] In later years, Michael became absorbed with gardening, and his gorgeous flower garden was compared with the Public Gardens. He was also a most enthusiastic golfer. Michael died in February 1942 during a wintering stay in Orlando, Florida.

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[1] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic, Amsterdam, **2005**, pp. 286–287, p. 628.

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[3] M. E. Jung in *Comprehensive Organic Synthesis* (Ed.: B. Trost), Pergamon, Oxford, **1991**, vol. 4, ch. 1, pp. 1–67.

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[6] a) E. W. Forbes, L. F. Fieser, A. B. Lamb, *Harvard University Gazetta* **1943**, *38*, 246–248; b) L. F. Fieser, *Biog. Mem. Nat. Acad. Scis.* **1975**, *46*, 331–366.

[7] W. T. Reed, *Ind. Eng. Chem.* **1930**, *22*, 1137–1138.

[8] A. B. Costa, *J. Chem. Educ.* **1971**, *48*, 243–246.

[9] a) D. S. Tarbell, A. T. Tarbell, *Essays on the History of Organic Chemistry in the United States, 1875–1955*, Folio Publishers, Nashville, **1986**; b) D. S. Tarbell, *Chem. & Eng. News*, April 6, **1976**, 111–112.

[10] P. J. Ramberg, *Hist. Stud. Phys. Biol. Scis.* **1995**, *26*, 89–138. In this essay, Michael's commitment to stereochemical problems during 1887–1899 is delineated comprehensively.

[11] G. S. Forbes, *Biog. Em. At. Cad. Cis.* **1964**, 95–128. In this memoir for Professor Jackson, an interesting comparative critic between the ways of Bunsen and Hoffmann on the management of laboratories from an educational standpoint is given: the former left his workers alone, whereas the latter was more directive.

[12] A. Michael, *Compt. Rend.* **1879**, 355–358 and subsequent papers.

[13] A. Colley, *Ann. Chim. Phys.* **1870**, *21*, 363.

[14] See ref.[1] pp. 246–247, 615–616.

[15] A. Ihde, *J. Chem. Educ.* **1959**, *36*, 330–336.

[16] a) A. Michael, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1381–1386; b) A. Michael, *Am. Chem. J.* **1887**, *9*, 274–289 and the voluminous subsequent papers on this theme by him.

[17] a) A. Michael, G. M. Browne, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1378–1381; b) A. Michael, G. M. Brown, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 550–556; c) A. Michael, H. Pendleton, *J. Prakt. Chem.* **1889**, *40*, 63–68; d) A. Michael, W. W. Garner, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 900–908; e) A. Michael, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2497–2498.

[18] H. Stobbe, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2739–2754.

[19] M. Conrad, M. Guthzeit, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1185–1188.

[20] a) W. H. Perkin, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 54–59; b) W. H. Perkin, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 323–373; c) W. H. Perkin, *J. Chem. Soc.* **1885**, *47*, 801–855.

[21] a) R. Fittig, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 372–373; b) R. Fittig, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2592–2593; R. Fittig, *Justus Liebigs Ann. Chem.* **1884**, *227*, 25–31.

[22] A. Michael, *J. Prakt. Chem.* **1887**, *35*, 132–136.

[23] Michael reasoned that the α-carbon atom of unsaturated esters is more negative by the influence of the neighboring ester group than the β-carbon atom, and hence, a more positive metal atom should add to the former and a more negative malonate radical (anion) should add to the latter. This idea was referred to as the negative–positive principle of Michael for some time[24] until accounts based on the conjugation concept appeared. In addition, Michael found that reaction course A explained reasonably the formation of cyclopropane compound **2a** as well as that of **2b**. Thus, he reserved his conclusion on the structure of the product in his crucial paper.[25]

[24] a) A. Michael, *J. Prakt. Chem.* **1888**, *37*, 173–530; b) A. Michael, *J. Prakt. Chem.* **1899**, *60*, 325–327.

[25] a) A. Michael, *J. Prakt. Chem.* **1887**, *35*, 349–356; b) A. Michael, *Am. Chem. J.* **1887**, *9*, 112–124.

[26] The reaction product from ethyl cinnamate and ethyl acetoacetate was obtained as crystals, and Michael assigned tentatively the cyclobutanone structure formed by a Dieckmann-type cyclization.[25b] For later studies of this product by him and the

product from diethyl citraconate and acetoacetate by others, see later description.

[27] L. Claisen, *J. Prakt. Chem.* **1887**, *35*, 413–415.

[28] T. Komenos, *Justus Liebigs Ann. Chem.* **1883**, *218*, 145–169. This represents one of three continuous papers led by the introductory paper of Claisen on the condensation reactions of aldehydes with malonic acid, malonic ester, and acetoacetic ester: L. Claisen, *Justus Liebigs Ann. Chem.* **1883**, *218*, 121–129. Michael apologized[35] that he overlooked the findings of Claisen, which were described subordinately in a group of lengthy papers.

[29] a) W. H. Perkin, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1053–1057; b) E. Haworth, W. H. Perkin, *J. Chem. Soc.* **1898**, *73*, 330–345.

[30] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2579–2586.

[31] Hantzsch conducted this reaction in connection with his studies on dihydropyridine synthesis, which was discovered in 1882 and is now known with his name.[32]

[32] a) See ref.[1] pp. 194–195, 595–596; b) A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1–82.

[33] Though not cited by Claisen, Wislicenus reported in 1887 that a similar type of reaction was observed in the treatment of phthalyl chloride with diethyl sodiomalonate.[34]

[34] J. Bredt, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 603–605.

[35] A. Michael, *J. Prakt. Chem.* **1887**, *36*, 113–114.

[36] A. T. Tarbell, D. S. Tarbell, *J. Chem. Educ.* **1982**, *59*, 548–549.

[37] A. Michael, *J. Prakt. Chem.* **1888**, *38*, 6–39.

[38] A. Michael, *J. Prakt. Chem.* **1888**, *37*, 473–530.

[39] J. Wislicenus, *Justus Liebigs Ann. Chem.* **1888**, *246*, 342–355.

[40] A. Michael, *J. Prakt. Chem.* **1889**, *40*, 29–44.

[41] K. Auwers, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 307–314.

[42] A. Michael, P. G. Freer, *J. Prakt. Chem.* **1891**, *43*, 390–395.

[43] Although Michael's thought on this problem swung from cyclobutanone[25b] to lactone structures,[44] he finally reached a correct conclusion that the product in question was a 1,3-cyclohexanone derivative when he found a few years later that the reaction of benzalacetone with sodiomalonate resulted in the same type of secondary reaction.[45]

[44] A. Michael, *J. Prakt. Chem.* **1891**, *44*, 113–129.

[45] A. Michael, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2126–2130.

[46] A. Michael, O. Schulthess, *J. Prakt. Chem.* **1892**, *45*, 55–63.

[47] The compound obtained by Michael from diethyl citraconate and ethyl acetoacetate was found 40 years later to be triethyl 4-acetobutane-1,2,4-tricarboxylate, which formed after the initial isomerization of citraconate to itaconate.[48] It has also been disclosed that the normal addition product was obtained when the reaction was conducted in the presence of Na or NaOEt/Et_2O in place of NaOEt/EtOH.

[48] P. C. Mitter, A. C. Rov, *J. Indian Chem. Soc.* **1928**, *5*, 33–48.

[49] A. Michael, *J. Prakt. Chem.* **1894**, *49*, 20–25.

[50] Of course dots or double dots on carbon did not denote radicals in the present sense. Since around 1886, Michael was reluctant to use Kekulé–van't Hoff double or triple bond notation and used instead the dot signals as in these cases or the same one bar as in a single bond.

[51] At the time, the term "radical" was used to mean "residue" or "group".

[52] V. Meyer, K. von Auwers, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 3510–3529.

[53] C. Liebermann, *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 2229.

[54] K. von Auwers, V. Meyer, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 293–311.

[55] a) C. A. Bischoff, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 2089–2097; b) C. A. Bischoff, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 631–646.

[56] K. Auwers, L. L. Jackson, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1599–1617.

[57] C. A. Bischoff, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1464–1468.

[58] For the subsequent full papers, see: a) K. Auwers, E. Köbner, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1923–1937; b) K. Auwers, E. Köbner, F. v. Meyenburg, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2887–2901; c) K. Auwers, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 364–378; d) K. Auwers, *Ber. Dtsch. Chem. Ges.* **1895**, *28*,1130–1133.

[59] N. Zinin, *Zentralbl.* **1871**, 210–211.

[60] a) E. Knoevenagel, R. Weissgerber, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 436–441; b) E. Knoevenagel, R. Weissgerber, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 441–446; c) E. Knoevenagel, *Justus Liebigs Ann. Chem.* **1894**, *281*,25–126.

[61] a) J. A. Berson, *Chemical Creativity*, Wiley-VCH, Weinheim, **1999**; b) J. A. Berson, *Chemical Discovery and the Logicians' Program*, Wiley-VCH, Weinheim, **2003**.

[62] For a discussion on this problem, see: ref.[9a] pp. 50–53 and ref.[9b]

[63] a) A. Michael, L. N. Norton, *Am. Chem. J.* **1880**, *2*, 11–19; b) A. Michael, L. N. Norton, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1202–1222; c) A. Michael, G. M. Browne, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1378–1381.

[64] a) A. Claus, *Justus Liebigs Ann. Chem.* **1873**, *170*, 125–136; b) A. Claus, *Justus Liebigs Ann. Chem.* **1878**, *191*,33–93; c) A. Claus, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1089–1093.

[65] D. Enders, A. Haertwig, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **1998**, 1771–1792 and references cited therein.

[66] a) F. Loydl, *Justus Liebigs Ann. Chem.* **1878**, *192*, 81–89; b) T. Purdie, *J. Chem. Soc.* **1881**, *39*, 344–356; c) T. Purdie, *J. Chem. Soc.* **1885**, *47*, 855–878; d) A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 3454–3460.

[67] von Auwers mentioned the possibility of the ethoxylated product as the intermediate in the conversion of methaacrylate **16** into the corresponding addition product, which gave **17** (see Scheme 5).[56]

[68] F. Henrich, *Theories of Organic Chemistry* (translated by T. B. Johnson, D. A. Hahn), Wiley, New York, **1922**, pp. 569–584.

[69] W. H. Brock, *The Fontana History of Chemistry*, Fontana Press, London, **1992**, pp. 517–521.

[70] A. B. Lamb taught physical chemistry and contributed greatly to the American Chemical Society as a journal Editor and President.

[71] a) A. D. Bliss, *J. Am. Chem. Soc.* **1955**, *77*, 5773–5780; b) F. G. Keys, *Biog. Mem. Nat. Acad. Scis.* **1956**, 199–234.

[72] A. B. Lamb played a major role in this appointment.

[73] E. C. C. Baly, *Obituary Notices of the Royal Society* **1943**, *4*, 329–356.

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