

THE BEGINNINGS OF SYNTHETIC ORGANIC CHEMISTRY: ZINC ALKYLs AND THE KAZAN' SCHOOL

David E. Lewis, University of Wisconsin-Eau Claire

It is scant exaggeration to say that modern organic synthesis would be almost inconceivable without the important carbon-carbon bond-forming reactions involving the addition of organometallic reagents to aldehydes, ketones and acid derivatives. Today, the addition reactions of organometallic reagents of most elements of the periodic table have been explored in great detail, permitting the synthetic organic chemist to exploit the unique reactivity of the alkyl derivatives of many elements of the periodic table to obtain that degree of control that gives modern organic synthesis much of its power.

The rise of organometallic compounds as tools in organic synthesis is probably best traced to the development of the Grignard addition reaction in 1900 (1), but the real origins of organometallic synthesis date from some 30 years earlier in the city of Kazan', at European Russia's eastern frontier. The position of Kazan' at the crossroads between east and west had long been exploited in the name of trade. Its transformation to an educational center only began with the establishment of Kazan' University in 1804 at the urging of the intellectuals in St. Petersburg (with little enthusiastic support from the Kazan' community). Despite its isolation and its location at the fringe of society, Kazan' University had, by the end of the nineteenth century, established a school of chemistry that was pre-eminent in Russia, supplying many department chairs and professors of chemistry to Russian and foreign universities.

The two decades following Wöhler's 1828 discovery of the synthetic production of urea (2) were watershed years in the development of organic chemistry.

During the 1830s and 1840s the concept of the radical as an entity, which passed through chemical transformations unaltered, was established, thanks to the work of Liebig, Wöhler, Bunsen, and Dumas. Then, in 1852, Sir Edward Frankland published the paper in which he proposed that elements have a set saturation capacity—the first proposal of the concept of valence (3). In the course of this work, Frankland had synthesized the first organometallic compounds, the dialkylzincs (3), an achievement of crucial importance to the work that comprises the subject of this paper.

Thus, by the mid-1850s, the stage was set for the next great advance in the discipline of organic chemistry, and the last three years of the 1850's may, indeed, be characterized as a nexus in the development of organic chemistry. It was during these years that Friedrich August Kekulé and Archibald Scott Couper developed what has become known as the structural theory of organic chemistry. On the basis of the earlier work of Frankland and Kolbe, in which the concept of valence had been placed on a firm footing, Kekulé (4) and Couper (5) independently developed the concept of a compound as a material in which all valences of all participating atoms could be satisfied.

It is almost certain that this theory, as first proposed, was largely designed to accommodate the known facts; whether either Kekulé or Couper was completely aware, when he first proposed it, of the real potential of this new theory may be argued (6). This author contends that the full realization of what this new theory could do belonged first to the great Russian organic chemist, Aleksandr Mikhailovich Butlerov (1828-1886). It was

certainly Butlerov, who was a professor at Kazan' University at the time, and his students who first followed up experimentally on the predictive power of the new theory.

By this time, the Chemistry Department at Kazan' had already begun its rise under Nikolai Nikolaevich Zinin (1812-1880) and Karl Karlovich Klaus



A. M. Butlerov (1828-1886)

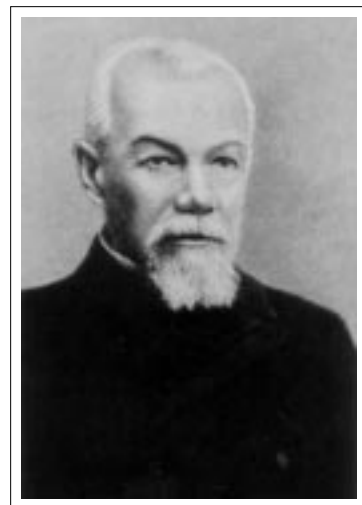
(1796-1864), whose contributions to chemistry have often been overshadowed by those of his more famous colleague. Butlerov had studied under both Zinin and Klaus, but his commitment to a career in chemistry at the time may have been marginal, at best (7). In fact, he had written his kandidat dissertation on the diurnal butterflies of the Volga region (8). However, with the departure of Zinin for St. Petersburg and Klaus for Dorpat, Kazan' University needed an instructor in chemistry, and Butlerov was appointed to the position, ultimately succeeding Klaus as Chair at Kazan'. The move was a fortunate one for Russian organic chemistry, for Butlerov became one of Russia's greatest organic chemists. Butlerov spent the years following his return in 1858 from a *komandirovka* (salaried study abroad) in Western Europe in developing and testing his own version of structural theory. It was Butlerov who first coined the term "chemical structure" and used that concept to systematize chemists' thinking about compounds. By 1860 he was expounding his structural theory of organic chemistry in his classes, and his textbook (9) was the first based solely on structural theory.

Butlerov saw that the wider acceptance of structural theory would depend in part on its ability to predict new isomers of organic compounds and on the experimental confirmation of the existence of these new isomers by synthesis, as he stated explicitly in his presentation to the Speyer Congress on September 19, 1861 (10). He immediately began using the theory first to predict the number of isomers of simple organic compounds and then to attempt the synthesis of these compounds. It is perhaps fitting, therefore, that Butlerov should have been among the first to confirm predictions

of the existence of new compounds by synthesis. It is uncertain how the possibility of the double displacement reaction between a dialkylzinc and an acid chloride occurred to him; but in his Speyer presentation on structural theory he explicitly mentioned the reaction between ethylsodium and carbon dioxide to form propionic acid, which had been reported by Wanklyn in 1858 (11). For whatever reason, in 1863 he took the step of treating phosgene with diethylzinc (12). The result was both historic, this being the first synthesis of a tertiary alcohol, and ironic. The existence of tertiary alcohols had been predicted by Kolbe (13), the most adamant opponent of the new structural theory, and this first synthesis was accomplished by Butlerov, its most ardent champion. This reaction, which he subsequently expanded into a general method for the synthesis of tertiary alcohols by the reaction between a dialkylzinc and an acid chloride, became known as the Butlerov reaction. Butlerov continued his research into tertiary alcohols and their dehydration products after his move to St. Petersburg in 1869, taking with him a tradition of organic synthesis begun at Kazan'.

Butlerov was succeeded at Kazan' by two of his students, Aleksandr Mikhailovich Zaitsev (1841-1910) and Vladimir Vasil'evich Markovnikov (1838-1904). Both had come to Kazan' University as students in economic science at a time when all students in that subject (*kameralisty*, many of whom were training for bureaucratic jobs in government) were required to complete two years of chemistry. This requirement thus brought them into contact with Butlerov, who was a dynamic and inspiring lecturer; both young men fell under the master's spell.

Butlerov may well have seen that the strengths of the two young men were complementary. Markovnikov was a daring and brilliant theoretician whose master's dissertation on structural theory (14) broached ideas that became widely accepted only decades later. Zaitsev, on the other hand, was a superb experimen-



A. M. Zaitsev (1849-1910)

talist, as his record plainly shows. As a student under Kolbe at Marburg, he had completed the first synthesis and characterization of a sulfoxide (15). He also accomplished the first synthesis of a sulfonium salt (16) and worked in Wurtz' laboratory on problems in carboxylic acid chemistry. Both Zaitsev and



V. V. Markovnikov (1838-1904)

and Markovnikov graduated in the *kameral* division.

At this time, graduates from the *kameral* division were not considered the equal of graduates in the physical-mathematical division when it came to assigning laboratory assistantships in chemistry. Zaitsev and Markovnikov are among the group of brilliant chemists whose graduation in the *kameral* division and desire for further study in chemistry resulted in a re-evaluation of this status; Butlerov helped to promote this agenda.

Despite what one might expect from their common admiration of Butlerov and the common path of their early careers (both worked under Butlerov and Kolbe, and both began their independent careers as extraordinary professors at Kazan'), Zaitsev and Markovnikov feuded bitterly for much of their lives. Indeed, Zaitsev's appointment to the second chair of chemistry as Markovnikov's junior colleague in 1870 may have been one of the minor precipitating factors in Markovnikov's rancorous departure from Kazan' shortly thereafter. (It should be noted that Markovnikov had been one of the official examiners of Zaitsev's master's dissertation and had written a report which, while overtly positive, carried a strongly negative subliminal message.)

One may speculate on the origins of this feud, but it is my opinion that one major contributing factor may be traced to the time both spent in Kolbe's laboratory. In the *kandidat* dissertation that Zaitsev submitted to Kazan' University in 1863, he had shown himself willing to compromise with Kolbe (17), who vigorously opposed structural theory. In contrast, Markovnikov remained inflexibly in the structural theory camp. Zaitsev's pliability may have seemed a betrayal of the "Russian" position to the intensely Russian nationalist, Markovnikov—an unpardonable sin.

At Kazan', Zaitsev continued the line of research into the reactions of dialkylzincs begun by Butlerov, and the credit for developing and extending the scope of this synthetic method really belongs to Zaitsev and his students. In 1865 Frankland and Duppa reported the reaction between diethylzinc and diethyl oxalate to give the ethyl ester of α -ethyl- α -hydroxybutyric acid (18). Much of Zaitsev's earliest work as an independent researcher involved extending the Butlerov reaction to include the interaction of organozinc compounds with other carbonyl compounds. Of greater importance, perhaps, was his insight that the notoriously sensitive dialkylzinc reagents could be replaced by a mixture of the alkyl iodide and zinc metal. This *in situ* formation of the alkylzinc iodide allowed much greater flexibility and ultimately led to the development of the Grignard reaction.

This new, general synthesis of tertiary alcohols was later extended by Zaitsev and his students to reactions between organozinc reagents and a variety of compounds. The co-author on many of these early works was another of the brilliant organic chemists to come from the Kazan' school: Egor Egorevich Vagner (1849-1903), who later became Professor of Chemistry at the University of Warsaw. Better known in the west as Georg Wagner, the terpene chemist, Vagner had entered Kazan' as a student in law, where he came under the influence of Zaitsev as his mentor had come under the influence of Butlerov when he himself had entered as a student in economic science. By the time Vagner was a student, the two-year chemistry requirement of graduates in the *kameral* division was no longer in force. However, like his own mentor, Zaitsev had an excellent reputation among his students, and it is not unreasonable to speculate that *kameral* students at Kazan' may well have passed along to incoming students their opinion that Zaitsev's lectures were worth attending. (Even today, it



E. E. Vagner (1849-1903)

is not uncommon for the student “underground” to recommend certain professors to students fulfilling science requirements in a nonscience major).

Zaitsev’s development of organozinc synthesis proceeded apace during the 1870s and 1880s. Under his direction, Vagner developed a general synthesis of symmetrical secondary alcohols from the interaction of ethyl formate with dialkylzincs (19). With his student I. I. Kanonnikov, Zaitsev extended the synthesis to the reaction between zinc and formate esters in the presence of a mixture of alkyl halides to give unsymmetrical secondary alcohols (20). He continued his work on the synthesis of unsymmetrical tertiary alcohols by exploring the reaction between alkylzinc halides and ketones (21). It was during this work that Zaitsev discovered, with his student D. Ustinov, that the reaction between the propylzinc reagent and 4-heptanone gave not the expected tertiary alcohol, but the reduction product, 4-heptanol (22). During this same period, Zaitsev’s brother and student, Mikhail Mikhailovich, studied the reaction between alkylzinc halides and anhydrides, which leads to the formation of ketones (23).

In 1875 Vagner was sent on a *komandirovka* at St. Petersburg to study directly under Butlerov, a move encouraged by Zaitsev despite the impact on his own research group of losing such a talented student. Continuing his study of alkylzinc halides, Vagner extended the Zaitsev synthesis to the addition of alkylzinc halides to aldehydes, thus developing a general synthesis of unsymmetrical secondary alcohols (24). This general synthesis of alcohols from alkylzinc halides and carbonyl compounds is generally referred to as the Zaitsev-Vagner synthesis. One of the more noteworthy features of the Zaitsev-Vagner synthesis is the success with which it yields alcohols from allylic halides. The formation of Grignard reagents from allylic halides is often problematic because of the facile coupling of the alkyl groups by S_N2 displacement of the halide from a second molecule of the allyl halide by the already-formed allylmagnesium halide. This cross-coupling reaction is much less a problem in the reactions of the less nucleophilic alkylzinc reagents.



S. N. Reformatskii (1860-1934)

Kazan’ and Zaitsev were fortunate that Vagner’s departure was followed fairly rapidly by the emergence of the next synthetic organic chemist from the “nursery” at Kazan’: Sergei Nikolaevich Reformatskii (1860-1934), who later became Professor of Chemistry at Kiev University. The son of a pastor, Reformatskii had been expected to enter the priesthood; but on graduation from the Kostroma Spiritual Seminary he entered Kazan’ University and instead encountered Zaitsev. Following his graduation with the gold medal in 1882, Reformatskii remained at Kazan’ and eventually began working on the reaction that bears his name, publishing the first paper in 1887 after he had become Privatdozent at Kazan’. It may well be that the successes obtained by using unsaturated, allylic alkyl halides suggested an extension of the Zaitsev-Vagner synthesis to α -haloesters in place of the allylic halides. The substitution was successful, and Reformatskii published what became the most enduring of the synthetic methods based on zinc alkyls (25). For the better part of a century the Reformatskii reaction was the method of choice for the synthesis of β -hydroxy carbonyl compounds until the design of elegantly controlled aldol additions in the 1980s.

The development of the Grignard synthesis just over a decade after Reformatskii’s first publication spelled the end of most organozinc syntheses of alcohols. The final paper to emerge from Kazan’ on the synthesis of alcohols from alkylzinc reagents (26) was a one by another Zaitsev student, Aleksandr Erminingel’ovich Arbuzov (1877-1968), who succeeded Zaitsev at Kazan’ and was to achieve international stature for his pioneering work with organophosphorus chemistry. The greater ease of formation and use of the Grignard reagent made it generally superior to the corresponding zinc reagent, especially in the hands of less experienced chemists. The very dominance of the Grignard reagent after 1900, however, pays silent testimony to the experimental ability of the Kazan’ chemists, who were able to use organozinc reagents to prepare alcohols with such success. Even so, the final chapter of the organozinc story may not yet have been written, for in the early 1980s, Noyori ob-



A. E. Arbuzov (1877-1968)

served that—in contrast to the Grignard reagents—dialkylzincs are amenable to asymmetric addition to aldehydes in the presence of a chiral dialkylaminoalcohol catalyst to give secondary alcohols with high levels of asymmetric induction (27).

In conclusion, it is no exaggeration to assert that modern organic synthesis would be inconceivable without the formation of carbon-carbon bonds by the reaction between an organometallic reagent and a carbonyl compound. Thus, modern organic synthesis owes a great debt, seldom acknowledged, to the chemists at Kazan' University and their pioneering chemistry with zinc alkyls.

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ABOUT THE AUTHOR

David E. Lewis is Professor of Chemistry, University of Wisconsin-Eau Claire, Eau Claire, WI, 54702-4004; lewisd@uwec.edu. His research interests are in synthetic organic chemistry and the contributions of 19th- and early 20th-century Russian organic chemists to the development of modern organic chemistry.

Save to Library. by oswaldo Nuñez. Synthetic Organic Chemistry. Sex Pheromone of the Pine False Webworm *Acantholyda erythrocephala*. Save to Library. In the case of 1-Naph-NMBCB the analysis of the antitumour activity has been preceded by toxicological experiments on CD-1 mice, in order to determine the lethal (LD) and the maximal tolerated (MTD) doses together with the spectrum of histological alterations caused by its iv administration. The login is the email address provided to the American Chemical Society and the password is your ACS member number. If you have any problems, please email mainz@illinois.edu. If you are not a member and want to order an individual article, please check the membership/back-issue order form. The beginnings of synthetic organic chemistry: zinc alkyls and the Kazan' school. David L. Lewis University of Wisconsin-Eau Claire. 37. Organozinc compounds in organic chemistry contain carbon to zinc chemical bonds. Organozinc chemistry is the science of organozinc compounds describing their physical properties, synthesis and reactions. Organozinc compounds were among the first organometallic compounds made. They are less reactive than many other analogous organometallic reagents, such as Grignard and organolithium reagents. In 1848 Edward Frankland prepared the first organozinc compound, diethylzinc, by heating ethyl iodide in the presence of zinc. While the oxygenation reaction of zinc alkyls occurs by radical pathways, the reported results stand in clear contradiction to the widely accepted free-radical chain mechanism. View. Show abstract. The synthesis, structure and reactivity of several diimine ligands are presented. The syntheses of five representative β^2 -diimine (BDI) zinc alkyl complexes and one β^2 -oxo- β^1 -diimine (BODDI) zinc alkyl are described. BDI ligands with varying backbone and N-aryl substituents display different solid state structures. $[(BDI)ZnR]$ are synthesized by the reaction of $(BDI)H$ with ZnR_2 in quantitative yield.