Markovnikov's Rule

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Towards the 150th Anniversary of the Markovnikov Rule

Irina P. Beletskaya and Valentine G. Nenajdenko**

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Abstract: *The Markovnikov rule, known to every student of organic chemistry, was formulated 150 years ago, in 1869. During its long history (almost as long as the history of organic chemistry itself), attitudes towards this famous statement of chemical reactivity have evolved from indifference up to the 1930s, through common acceptance as a useful educational paradigm with marginal use in research up to the 1990s, to its vigorous relaunch as an important designation of regioselectivity in the last few decades. The unexpected new popularity of the classical rule is accounted for by the rapid expansion in catalytic addition reactions and their critical importance as highly effective atom-economical, regioselective methods in modern organic synthesis. A historical outline of the life and achievements of Vladimir Markovnikov is included to reveal the very wide scope of his interests as well as his prophetic predictions on structure, reactivity, selectivity, stereochemistry, and other key issues of organic chemistry.*

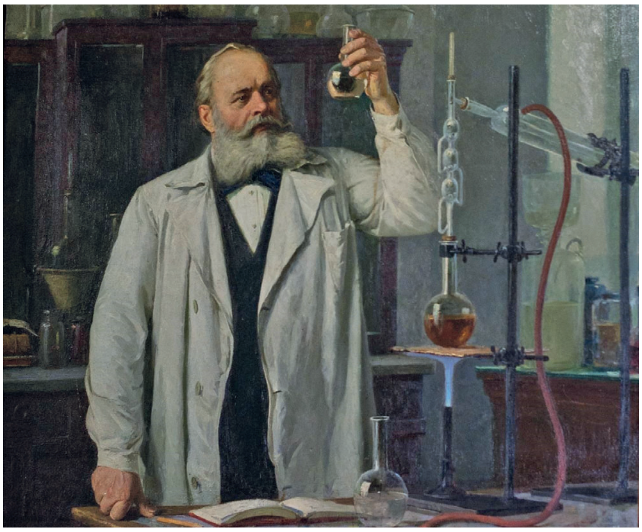


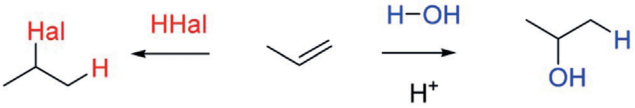
Figure 1. Portrait of Markovnikov (anonymous, property of Moscow State University).

Introduction

In his doctoral thesis, in 1869, Vladimir Markovnikov (Figure 1) formulated the famous rule that appears in almost every textbook on organic chemistry—be it a starter course or an advanced treatise—and is known to us as the Markovnikov rule. "*Experience shows that the haloid adds to the least hydrogenated carbon, that is, to the one most susceptible to the influence of other carbon units*", wrote Markovnikov in his thesis (in Russian).[1] Only a year later, part of this work was published in German, where the formulation of the rule was worded so precisely that it needs almost no update to be fit for a modern organic textbook: "*When an unsymmetrically composed unsaturated hydrocarbon reacts with hydrogen halide acid the halide atom adds to the least hydrogenated carbon, that is to the one which experiences more influence from the other neighbouring carbons*". Today this rule seems a trivial inference from the dominant theory of structure and reactivity, but then it was a major breakthrough, a daring generalization, given that even the basic concepts of structure and the chemical bond in chemistry were still undergoing painful delivery, being born amidst hot and unrelenting controversy involving all the founding fathers of modern chemistry. Among these, one of the leading roles was played by Alexander Butlerov, the senior colleague of young Markovnikov.[2]

Markovnikov formulated his rule using the reactions of hydrogen halides with simple olefins, the reactions which we now call electrophilic addition (Scheme 1). Such additions are commonly referred to as Markovnikov additions.

However—and this should be emphasized—neither Markovnikov nor anybody else in this era knew anything about the mechanisms of reactions, reactive intermediates, their relative stability, etc. These seem perfectly natural to us now, part of the common language of chemistry. This terminology appeared only in the 1930s in the seminal works or Ingold, Hughes, Robinson, Kharasch, Lapworth, and their co-work-



Scheme 1. Formation of Markovnikov products in simple electrophilic addition reactions.

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[*] Prof. I. P. Beletskaya, Prof. V. G. Nenajdenko
Department of Chemistry
Lomonosov Moscow State University
119991 Moscow (Russia)
E-mail: beletska@org.chem.msu.ru
nenajdenko@org.chem.msu.ru

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ers and contemporaries, and was generally adopted only in the post-war period.

We are so accustomed to this way of reasoning that Markovnikov's rule itself is often, if not almost always, reinterpreted in terms of carbocation stability and the mechanism of electrophilic addition.[3] This reasoning inevitably leads to a conclusion that Markovnikov's regioselectivity is the same as the regioselectivity of stepwise electrophilic additions involving carbocations as reactive intermediates. However, chemists of the 21st Century have a much better understanding of what is going on in addition reactions, so keeping Markovnikov's rule in the role of an actual rule—that is of a statement which can be directly applied to predict the outcome of a given reaction—cannot be justified. Is it now just a sentimental tribute to famous figures of the past?[4] Moreover, even in terms of electrophilic additions to alkenes, the options are wider than just following the stability of carbocations, and a more competent picture can only be drawn through the inclusion of quantum chemical modeling of reaction pathways.[5]

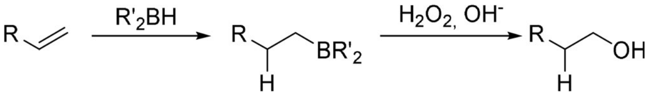
Markovnikov's Rule in the Early Literature

The history of the actual usage of this rule in chemical literature is rather intriguing. Although the rule comes from the early history of organic chemistry, its use initially was extremely rare, and mostly confined to textbooks. Only at the very end of the 19th Century did Arthur Michael undertake to review all the trends established in organic reactivity and paid careful attention to Markovnikov's major contributions. He admitted that Markovnikov emphasizes the mutual influence ("*der gegenseitig Einfluss*") of atoms in organic molecules as a key principle in all reasoning about the reactivity and selectivity of organic transformations.[6] This extremely long paper, in which the rules discovered by Markovnikov occupied only a very modest place among other, now mostly obsolete, generalizations, drew little attention at that time. It took another 30 years before Morris Kharash disclosed his seminal studies about the addition of hydrogen halides to olefins, in which he established the striking complexity of this seemingly primitive reaction and revealed the heavy dependence of both the reaction rate and regiochemistry on the reaction conditions, solvent, and other factors. These studies helped to realize how intelligent had been the choice of model reactions from which Markovnikov inferred his rule, given the extreme limitations of what had been available in those times. Moreover, Kharash unveiled the dichotomy in the regioselectivity of addition reactions and established the tradition of distinguishing between Markovnikov and anti-Markovnikov pathways.

Irina Beletskaya was born in Leningrad (St. Petersburg). She graduated, obtained her Candidate of Chemistry (PhD) degree (1958), and then her Doctor of Chemistry (1963) at the Department of Chemistry at Lomonosov Moscow State University (MSU). In 1971 she became Professor of Chemistry in the same Department, and since 1989 has led the Organoelement Chemistry laboratory there. In 1974 she was elected a corresponding member of the Academy of Science of USSR, and in 1992 became a full member of the Russian Academy of Science. She has received many awards, including in 2018 the Butlerov Prize of the Russian Academy of Science.

Valentine G. Nenajdenko was born in 1967 in Ivanovo, Russia. He graduated from Moscow State University (Lomonosov) in 1991. He completed his PhD under the supervision of Prof. E. S. Balenkova in 1994 and in 2000 received his Dr. of Chemistry degree. In 2003 he became full Professor of Organic Chemistry at the Department of Chemistry of Moscow State University. Since 2014 he has been Head of Organic Chemistry at Moscow State University. He was received numerous awards, including the Russian President Award in 1996 and 2004 and the Moscow State University Awards in 2006, 2007, and 2008.

It seems that the relaunch of interest occurred when addition reactions that gave the opposite result to what could be expected according to Markovnikov's rule—the anti-Markovnikov's addition—were discovered, first the free-radical Kharasch addition[7] and then the hydroboration reaction (Scheme 2). The relevance of the latter reaction to Markovnikov's case can not be overestimated.

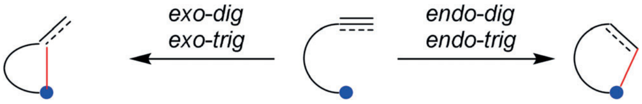


Scheme 2. Hydroboration as an example of the archetypical Markovnikov/anti-Markovnikov controversy.

Thus, the Markovnikov rule, as it is actually used, is not about the electrophilic addition and its mechanism—were it so, it should indeed have become an obsolete archaic saying fit only for a museum.[8] Rather, the rule, taken exactly as it was first formulated (with a slight correction into modern language and changing haloid for a generic residue), is actually not a rule, but rather a very useful descriptive pattern of regioselectivity and, as such, it is completely decoupled from any particular mechanism. Any addition of a reagent H-Z (Z can be any element or group of unlimited complexity) or its synthetic equivalent in a single- or multistep procedure to an unsymmetrically substituted double or triple bond can be regioselective, either following the pattern described by Markovnikov's rule (Markovnikov addition) or giving the opposite product (anti-Markovnikov addition).[9] Reactions which give mixtures of both products are nonselective and, therefore, of limited usefulness. Markovnikov was simply the first scholar who drew attention to the fact that a particular organic reaction can give either of two isomeric products, and that it is important to know which of these products is actually formed. Isomerism was regarded by Markovnikov as one of the most important features of organic compounds, and a cornerstone of the structural theory being developed by his senior colleague Butlerov.

In synthesis-oriented modern organic chemistry the regioselectivity of a reaction is much more important than its mechanism. We can even safely predict that even when the current theory of organic reactivity based on a quantitative discussion of reactive intermediates is (and will be) replaced in future by something else, for example, by direct theoretical modeling of reaction pathways on a smartphone, the empirical rules of regioselectivity, such as Markovnikov's rule—the first such rule—will remain as a very convenient, intuitive means to describe the outcome of an extremely important class of reactions.

In this respect, it would be relevant to remember that there is another very popular empirical rule for predicting regioselectivity—Baldwin's rule or rules of cyclization,[10] formulated roughly a century after the Markovnikov rule. Baldwin's rules were based on the most common nucleophilic cyclizations, and the initial goal of Baldwin was to provide a key to predict the outcome of a reaction. Certainly, the same incentive pushed Markovnikov to identify his rule or, rather, rules. The actual developments in chemistry, however, in both cases, modified the original ideas of the proposers into abstract patterns of much broader utility. Such a common fate of the seemingly very distant statements (in time of publication, scope, and background) is extremely interesting. Remarkably, the cyclizations onto unsaturated bonds (*trig* and *dig* ring closures) can be regarded as Markovnikov (*exo-dig* and *exo-trig)* or anti-Markovnikov (*endo-dig* and *endo-trig*) pathways, only they are intramolecular (Scheme 3).



Scheme 3. Baldwin's rule viewed as an intramolecular version of Markovnikov's rule (the blue circle denotes a reactive center).

The Relaunch

An even more interesting picture is revealed when we get a glimpse of the usage of Markovnikov's rule in the research literature. Markovnikov's rule was barely mentioned in the literature before the 1990s. Everybody knew about this rule from their own student years and standard textbooks, but there was no real incentive to mention it in research papers, because it was clearly too trivial a thing to talk about. However, since 1991 the name has suddenly caught the attention of research chemists, and since then we have seen a very rapid growth in its popularity (Figure 2). Thus, according to the Web of Science, "Markovnikov" as a topical lexeme has been mentioned in about 1370 papers in the last decade (2008–2018), in 570 papers in the previous decade (1997–2007), and in only 170 papers in the first 96 years (1900–1996). The use of the Markovnikov/anti-Markovnikov regioselectivity designation in titles of papers has rapidly increased (250 such papers have appeared in the last 10 years, compared with 200 for the whole previous period of over 100 years).

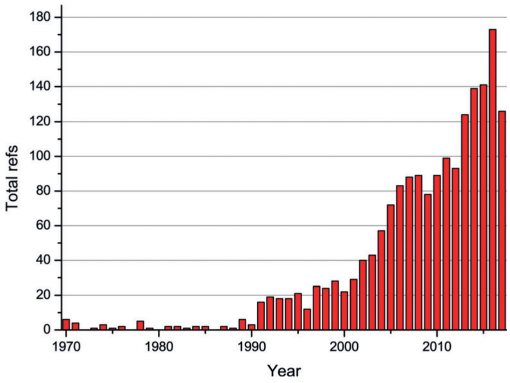
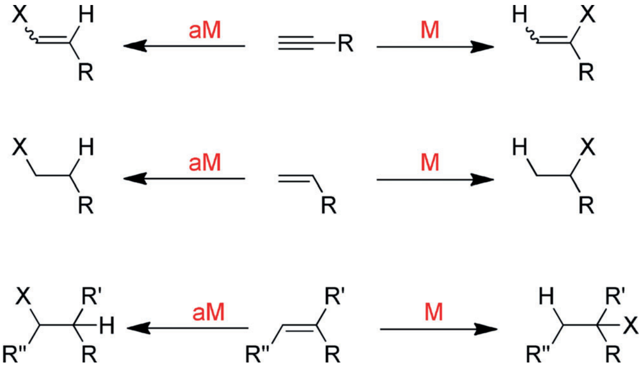


Figure 2. Occurrence of the lexeme "Markovnikov" in research articles since 1970, according to Web of Science.

The boost in the popularity of "Markovnikov" as a designation is apparently rooted in the dramatic changes in organic chemistry that have been taking place since the late 1980s: namely, the shift of thinking from mechanism-oriented to synthesis-oriented and the vigorous invasion of catalytic methods in organic synthesis. Synthetic methodology since the 1990s, and particularly after 2000, is being reshaped through the introduction of catalysis in various forms of increasing complexity: transition-metal catalysis, organocatalysis, photocatalysis, redox catalysis, and combinations of these, as well as cascades and tandem processes, etc. One of the branches of organic chemistry particularly affected by this invasion is the chemistry of addition reactions, the arsenal of which underwent an exponential inflation over the last two decades. Modern organic synthesis takes advantage of a huge arsenal of methods involving an almost infinite number of mechanisms, many of which are just hypothetical analogies, while many others belong to concerted mechanistic continuums with uncertain intrinsic molecular machinery. The variety is overwhelming, and that leads to quite a new situation in organic chemistry: the mechanisms no longer provide a solid basis for understanding and rationalizing reactions. The mechanisms of catalytic reactions are complex and variable, and are usually composed of concerted steps that often involve extreme sensitivity to reagents, catalysts, ligands, conditions, etc., and are quite often reinterpreted on the arrival of new data. We no longer infer reactivity and selectivity from the mechanism—although this indeed has been the leading paradigm of thinking in the organic chemistry taught in universities—but instead often try to guess a plausible mechanism from the reactivity and selectivity of reactions. Certainly, the development of new methods and their mechanistic interpretation is a reciprocal process, and in the future we will undoubtedly see a major update of physical organic chemistry. Nowadays, however, the accumulation of new data is so fast that, in a certain respect, the chemists of today seem to arrive at a situation roughly similar to where Markovnikov and his contemporaries were: they rapidly discovered new reactions knowing nothing about mechanisms and being unable to use them for reasoning, while today we know so much more that again we have to use something else, something paradoxically similar to the descriptive early period of chemistry. The use of the mechanism as a tool for analysis, once so cozy and instrumental, has become much less useful because of the abundance and complex interplay of factors involved in mechanistic reasoning. This makes the conclusions gained through considering mechanistic pathways ambiguous and opportunistic. In the 19th Century, chemistry and organic chemistry were largely descriptive sciences, and they still are today, and all attempts to bring in more rigorous principles and foundations, based on mechanism and quantitative trends in reactivity, have met only modest success, whereas synthetic methodology keeps flourishing vastly beyond the wildest expectations of the not too distant past. New synthetic methodology is developed and elaborated largely through experimentation, with the most important difference from the 19–20th Centuries being the magnitude of the experimental efforts through implementation of high-throughput high-performance methods of analysis and data treatment on a scale that was impossible in the past.

Not surprisingly, practical synthetic chemists prefer to designate the reaction outcome through clear and universally understood labels: Markovnikov proposed the first such label of selectivity, and his priority is indisputable.

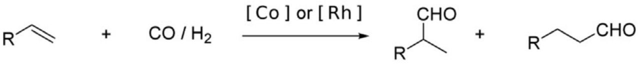
However, we may wonder why a particular reaction—addition to a carbon–carbon double or triple bond of a reagent, one part of which is almost invariably hydrogen—could become so important. Initially such reactions indeed occupied quite a modest place in the arsenal of synthetic methods because of their poor selectivity and limited scope. Again, catalysis changed their importance dramatically by enabling an almost unlimited variety of methods of a common template when one carbon atom accepts a hydrogen atom and the other carbon atom receives a residue bonded through a non-metal or a metal. These reactions include hydrohalogenation, -amination, -alkoxylation, -thiolation, -amination, -amidation, -phosphination, -alkylation, -arylation, -silylation, -boration, -alumination, -carbonylation, and -carboxylation.[9] Another advantage of Markovnikov's rule in its original form is that neither the initial polarity of the multiple bond (e.g. propylene and acrylonitrile are treated in the same manner) nor whether the new bond formed is polarized towards the carbon or the other atom makes any difference. The validity of the common pattern in all cases makes the rule very convenient, as everybody in this world understands what is Markovnikov and what is anti-Markovnikov without special explanations (Scheme 4).



Scheme 4. Markovnikov and anti-Markovnikov additions to unsymmetrical olefins and acetylenes.

The selective production of Markovnikov and anti-Markovnikov products is the most important issue for all addition reactions, including both large-scale industrial organic synthesis and state-of-the-art transformations performed in academic laboratories. Addition reactions are considered the most cost-effective, atom-efficient, and ecologically benign chemical processes from the point of view of sustainable chemistry. These reactions are carried out with 100 % atom efficiency relative to the starting reagents (all the atoms of which end in the adduct).[11] However, they are important if, and only if, the addition is regioselective and gives either the Markovnikov or anti-Markovnikov product, either of which can be welcome. It is, therefore, the designation of addition reactions with the Markovnikov/anti-Markovnikov label that makes catchy titles because it is exactly the feature demanded in organic synthesis—namely, selectivity! New reactions nowadays are described as "Markovnikov-selective" (the first example of such a definition appeared in 2001,[12] and since then the term has become popular).[13]

Especially illustrative is the example of the oxo process (the hydroformylation reaction). The hydroformylation of various olefins is used in several large-scale industrial processes of prime importance. Unlike the original reactions used by Markovnikov, it is a multistep transformation with various mechanisms involving transition-metal complexes and not one but two reagents (CO and H_2), with the regioselectivity governed by a very subtle interplay of different factors, including steric effects and transient interactions of the metal. However, formally its outcome fits nicely into Markovnikov's original template. In general, the reaction, catalyzed by cobalt or rhodium complexes, is often applied to terminal olefins to afford two aldehydes, one with a formyl group attached to an internal carbon atom (Markovnikov product) as well as its linear isomer (anti-Markovnikov product; Scheme 5). In the vast majority of such processes, it is the anti-Markovnikov product which has industrial market value (e.g. it is used in the huge plasticizer industry). In some other processes, for example, in pharmaceutical synthesis, the Markovnikov hydroformylation product is desired. Many research groups in both R&D and academic institutions are engaged in the development of catalytic systems capable of regioselectively hydroformylating alkenes.



Scheme 5. Markovnikov and anti-Markovnikov products of hydroformylation.

Markovnikov: Life and Achievements

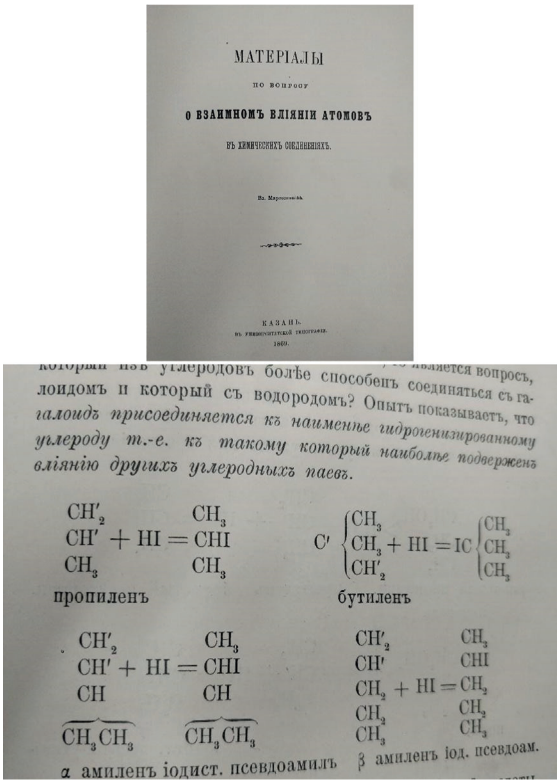
In the Russian Empire, the heart of chemistry was not Moscow or St. Petersburg, but Kazan,[14] a beautiful ancient town sitting on the vast river Volga, and a seat of one of the oldest Russian universities. There, the foundations of organic chemistry studies were laid by Nikolay Zinin (1812–1880), known for the synthesis of aniline through the reduction of nitrobenzene with iron (the Zinin reaction), and also the discovery of naphthylamines and benzidine. Karl Klaus was working on the isolation of platinum group metals from local ores and discovered the new noble metal ruthenium. For obvious reasons, none of the first chemists was a chemist by education. For example, Zinin was a brilliant mathematician and a physicist who graduated from the Department of Mathematics of the Philosophical Faculty of Kazan University.

Of particular interest is Alexander Butlerov (1828–1886), one of key proponents in the development of the structural theory of organic compounds.[2]

Butlerov's most brilliant student Vladimir Markovnikov was born on December 10, 1838 in the village of Chernorechye (near the important merchant center Nizhny Novgorod upon Volga). His father belonged to local gentry and served as a cavalry officer. After his father's resignation, the family settled in the small village of Ivanovskoe in the Knyagininsky district of the Nizhny Novgorod province. There, surrounded by an incredibly beautiful landscape, he spent his childhood. From a tender age, Vladimir had a thirst for reading books and learning. After graduating from a gymnasium (the Nizhny Novgorod Noble Institute) in 1856, he entered Kazan University in the Chambre Department of the Law Faculty, where trade and commerce were mainly taught. At that time, the natural sciences and technology were added to the curriculum, because the government already understood the dire need for the practical education and training of professionals for the emerging industries. Surprisingly, chemistry was also among the subjects to be learned, and the young Vladimir was happy enough to meet professor Butlerov, who taught chemistry and introduced him to the profession. He then began to study chemistry.[15]

It was the charisma of Butlerov that particularly affected the young scientist. "*I had had the luck to be personally acquainted with him from the first year of my admission to the laboratory, that is, from the third year of my student years.*"[16] Butlerov also highly valued Markovnikov's outstanding abilities and his fascination with chemistry. In a few years, the relationship between the teacher and the student grew into a true friendship.

The first study by Markovnikov (1860) was dedicated to aldehydes. "The author's ideas prove his ability of independent thinking and good knowledge of the subject. What he says about the meaning of chemical formulas and existing theories shows the clarity of his views and an absence of narrow-mindedness."—such was Butlerov's evaluation of Markovnikov's research.[17] Having defended his thesis (Figure 3), Markovnikov was hired as a laboratory assistant at Kazan University. At the time Markovnikov was particularly interested in isomerism. Three compounds—propionic aldehyde, acetone, and allyl alcohol—have the same composition, C_3H_6O, but markedly different properties. The reduction of propionic aldehyde and allyl alcohol resulted in the same alcohol, but different compounds were formed after their oxidation. Having realized that the study of organic compounds is impossible without mastering analysis, Markovnikov did his best to acquire analytical skills, up-to-date with the latest achievements of the time.



МАТЕРІАЛЫ

ПО ВОПРОСУ

О ВЗАИМНОМЪ ВЛІЯНІИ АТОМОВЪ

ВЪ ХИМИЧЕСКИХЪ СОЕДИНЕНІЯХЪ.

Вл. Марковникова.

КАЗАНЬ.

ВЪ УНИВЕРСИТЕТСКОЙ ТИПОГРАФІИ.

1869.

является вопросъ, который изъ углеродовъ болѣе способенъ соединяться съ галоидомъ и который съ водородомъ? Опытъ показываетъ, что *галоидъ присоединяется къ наименѣе гидрогенизированному углероду т.-е. къ такому который наиболѣе подверженъ вліянію другихъ углеродныхъ паевъ.*

$$\begin{array}{l}CH'_2\\CH'\\CH_3\end{array} + HI = \begin{array}{l}CH_3\\CHI\\CH_3\end{array} \qquad C'\left\{\begin{array}{l}CH_3\\CH_3\\CH'_2\end{array}\right. + HI = IC\left\{\begin{array}{l}CH_3\\CH_3\\CH_3\end{array}\right.$$

пропиленъ

бутиленъ

$$\begin{array}{c}CH'_2\\CH'\\CH\\\overbrace{CH_3CH_3}\end{array} + HI = \begin{array}{c}CH_3\\CHI\\CH\\\overbrace{CH_3CH_3}\end{array} \qquad \begin{array}{l}CH'_2\\CH'\\CH_2\\CH_2\\CH_3\end{array} + HI = \begin{array}{l}CH_3\\CHI\\CH_2\\CH_2\\CH_3\end{array}$$

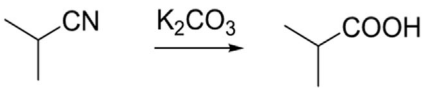
α амиленъ іодист. псевдоамилъ

β амиленъ іод. псевдоам.

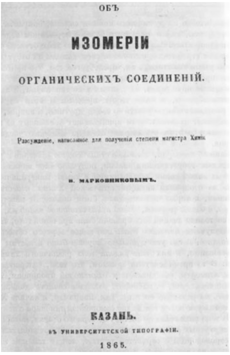
Figure 3. Title page of the Doctoral thesis by Markovnikov (1869) and the first formulation of the famous Markovnikov rule.

Butlerov and Markovnikov were among the first scholars of the time to realize that a graphic image of a molecule is insufficient to describe the full complexity of structure, as the flatness of paper limits our ability to imagine the true molecule in space. They did come very close to unveiling the spatial structure of a molecule, to what is now called its stereochemistry. Markovnikov's seminal studies of isomerism of organic compounds employed such cleverly chosen models as butyric and isobutyric acids (Scheme 6).[18] Further investigation of the properties of the obtained isomers led him to realize how important the interaction of atoms in a given molecule is.

In 1862 Markovnikov taught a course on inorganic chemistry in Kazan in place of Butlerov who was traveling abroad, and then, in 1863, a course on analytical chemistry.



Scheme 6. Synthesis of isobutyric acid by Markovnikov.



ОБЪ
ИЗОМЕРІИ
ОРГАНИЧЕСКИХЪ СОЕДИНЕНІЙ.

Разсужденіе, написанное для полученія степени магистра Химіи

В. МАРКОВНИКОВЫМЪ.

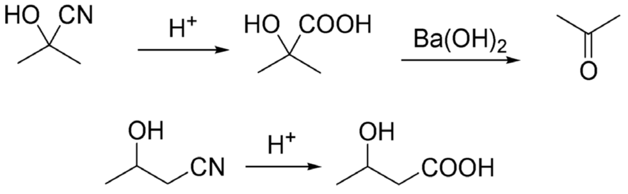
КАЗАНЬ.
ВЪ УНИВЕРСИТЕТСКОЙ ТИПОГРАФІИ.
1865.

Figure 4. Title page of Markovnikov's Master thesis, 1865.

Later he passed his master's exam and in 1865 at the age of 28 defended his master's thesis "*On the isomerism of Organic Compounds*", in which he described how to predict how many isomers could be expected for various classes of compounds (Figure 4).

We know little about Markovnikov's family life. The position of laboratory assistant with a small salary forced him to seek additional earnings. He started to give lessons at home. One of his students was Lyubov Rychkova, a granddaughter of the famous Russian geographer and naturalist of the 18th Century, Pyotr Rychkov. Gradually the friendship between the student and teacher evolved into love, and in 1864 the couple got married. She knew three foreign languages, helped him with translations, copying works, and accompanied him on his trips abroad. In 1865, after defending his master's thesis, Markovnikov was sent to Germany for two years for further studies in leading laboratories. The Imperial Ministry of Public Education allotted support for the trip, but with the agreement that on return Markovnikov would serve for four years in the institutions of the Ministry.

While abroad, Markovnikov listened to the lectures of well-known scientists, and devoted much time to work in the laboratories of E. Erlenmeyer, H. Kopp (Heidelberg), H. Kolbe (Leipzig), G. Kirchhoff, and A. Bayer (Berlin). At the same time, he used the opportunity to order and buy chemicals and labware (flasks, including the new conical flask invented by Erlenmeyer, thermometers, rubber hoses, sintering furnaces, analytical scales, etc.) for Kazan University. Despite his young age and lack of experience, Markovnikov apparently did not shun hot arguments with famous senior colleagues, such as Kekulé and Kolbe, on the matters of new theories concerning organic reactions and structure. In fact, Kolbe—at first bitterly disgusted by the stubbornness of the younger fellow, later came to agree with his arguments and began to distinguish him from other guest students—used to respectfully call him "Herr Doctor". On his return to Kazan in 1867, Markovnikov invested the experience gained during his trip to new studies, and soon prepared an article on acetonic acid, having obtained it from acetone cyanohydrin. Having synthesized isomeric 2-hydroxybutyric acid he also proved its relationship to hydroxyisobutyric acid (Scheme 7).[19]



Scheme 7. Synthesis of isomeric hydroxybutyric acids.

In 1868, upon Butlerov's departure to St. Petersburg, Markovnikov was appointed extraordinary professor (a lower grade of professorship in Russian universities), was soon promoted to full professorship, became a head of the laboratory, and started to teach a course on organic chemistry. The laboratory in Kazan was too small to accommodate everyone who wanted to work with Markovnikov and the University had to reject many students. Nevertheless, the studies performed both at home and abroad very soon, in 1869, led him to writing his doctoral thesis "*The Materials on the Mutual Influence of Atoms in Chemical Compounds*". In his thesis, he collected and analyzed available data on reactions of similar compounds, and arrived at a number of generalizations on what we now would refer to as trends in relative reactivity and regioselectivity depending on substituent effects, including the statement to become the Markovnikov rule known to us. The work contained no less than 10 generalizations, among which the one we are discussing was not the most elaborate or emphasized. Partly because of such an abundance, there was confusion on what exactly should be accepted as Markovnikov's rule. Curiously and very symptomatic of his manner of thinking in everything he did in his long carrier as a scientist—be it organic reactions, sorts of Caucasian oils, methods of disinfection, names of organic compounds, and even noble wines of Crimean winemakers—Markovnikov loved to systematically treat things and devise detailed and hierarchical classifications and generalizations. Almost all of his papers describing experimental research contained a section, often typeset in italics, containing an attempt to generalize the observed trends in the reactivity or selectivity, as we would now interpret it. Papers on similar subjects often appeared as long series under common titles. Such practice become widespread in the 20th Century, but such persistence in pursuing research goals then was quite rare.

Markovnikov devoted his thesis to Butlerov, the man who brought him to chemistry and deeply influenced his thought: "*I feel it my duty to devote my modest work to you, my esteemed mentor, because the thoughts in my thesis are the further development of what you have stated... If there is something new in my work, the development of it would be impossible without your initial provisions*".

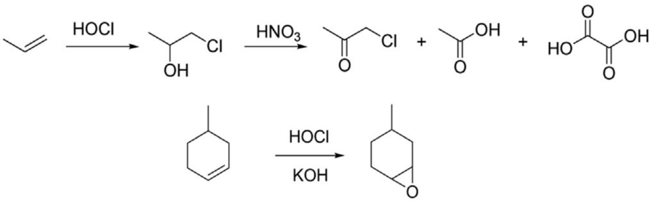
It should be stressed that Markovnikov's appraisal of his teacher's influence was not formal politeness of a student towards his senior. Indeed, Markovnikov's ideas could hardly have been formulated so early were it not for the solid and consistent foundation of organic structure promoted by Butlerov in the same years. Markovnikov examined the interaction of atoms in a number of reactions, including reactions that were later defined as free-radical substitution, addition, and elimination. He noted the attenuation of this influence with increased chain length (at a time when the very idea of a carbon chain was far from obvious and adopted by everybody) and showed that the C−H bond of a secondary carbon atom is more reactive than the same bond with a primary carbon atom.

Butlerov supported the thesis and suggested translating it into German. Markovnikov replied: "*If the ideas I convey are of interest, all who wish can take advantage of my Russian paper.*" Although this decision has quite often been put down to a sort of patriotic obstinacy that interfered with the prompt recognition of the seminal contribution, the attitude of the young scientist was rather expected and not unprecedented: at the time, the choice of the main language for scientific exchange had not yet been settled and papers often appeared in the native languages of scholars. Furthermore, at the time, Markovnikov himself most probably failed to understand the impact of his contribution. In his later career, Markovnikov eagerly published his results in the leading German and French journals.

In fact, only a year later, Markovnikov did publish a very small extract including only a more exact statement of the rule and a few supporting examples in German; however, not as a separate article, but as a rather strange addendum to a very large experimental paper. This short text drew little attention at the time of its publication.

Interestingly, in 1875 Markovnikov published a paper in French[20] that was explicitly devoted to “the laws governing direct addition reactions”. In this paper, he gives the most generalized and elaborate version of the rule involving not hydrogen halide, but a generic reagent XY, and states that the more negative[21] part of a reagent adds to more substituted atom. This statement of his rule is, therefore, so exact and detailed that only electrophilic addition is described by it. This is not surprising because other types of addition were unknown in the 19th Century, at least before the discovery by Michael of addition to electron-deficient olefins. Moreover, in the same rule he explicitly specifies that the direction of addition can change depending on the reaction temperature, thus envisaging kinetic and thermodynamic control. Last but not least, this paper was almost certainly the first attempt to speak about organic reactivity in terms of (electro)negativity. This brilliant rule never caught on. It is strange since this paper and this version of the rule can be regarded both as an extremely profound insight into organic reactivity and also another big step forward. It failed because of its extremely elaborate and, therefore, very restrictive formulation, apparently superfluous for the needs of reaction classification both at the time of appearance and far ahead. Had the Markovnikov rule been fixed in this version, its impact on later chemistry would not have been so long-lasting. The history rightly dictated that the provisional, but simpler and convenient (German) version would become associated with the Markovnikov rule and not the ultimate and elaborate (French) version.

Moving on to Markovnikov’s other contributions, one of the reactions to which he paid special attention in his thesis was the preparation of chlorohydrins through the addition of hypochlorous acid to alkenes.[22] Markovnikov was able to both correctly interpret the available experimental data and determine the regiochemistry of the addition of HOCl to propylene (Scheme 8). 30 years later the data were confirmed by Michael.[23] Interestingly, the regioselectivity established by Markovnikov fully agrees with modern views on this reaction as a sequential addition of an electrophile and a nucleophile to the double bond. Furthermore, he was the first to develop the synthesis of epoxides from alkenes via chlorohydrins.



Scheme 8. Examples of HOCl addition to a double bond from Markovnikov’s papers.

No less remarkable was Markovnikov’s views on issues related to stereochemistry. Again, we’d like to stress that at the time almost no scientist dared to imagine how a molecule might be built of individual atoms. At that time it was called the mechanical structure, in reference to mechanics—the branch of physics dealing with spatial positions and movements of bodies. Mechanical structure was different from the chemical structure, which referred only to what could be inferred from the mutual transformation of molecules through reactions. Chemical structures were thus expressed by chemical formulas showing only the constituent atoms in the correct ratios and groupings, but not their physical arrangement in space. Markovnikov wrote to defend his teacher’s ideas about “mechanical structure of molecules”: “*Butlerov does not think of the chemical bond* via *only elementary atoms, but at the moment he leaves in question all assumptions about their location in space.*” However, Markovnikov himself already thought about ways to express the relative positions of atoms in a molecule through formulas. He wrote: “It is difficult to imagine that there is no direct, quite definite relationship between a chemical reaction and physical position of atoms in a particle (molecule).”[24] If this is not an early insight into what would become stereochemistry a good while later, then what is it?

In 1869, after defending his doctoral thesis, Markovnikov was promoted to ordinary professor of the chemistry department of Kazan University: his academic carrier was on the rise. However, his work in Kazan did not last long. In 1871, six professors of Kazan University, including Markovnikov, resigned in protest against the dismissal of their colleague, a professor of anatomy, Pyotr F. Lesgaft. Lesgaft was a very popular figure among the students at a time when, after the beginning of radical political and economic reforms in Russia, the free-minded people began to breed political ideas, and universities were often faced with students discontent and even revolts. They were often supported by some of the professors, but certainly not by the conservative university authorities. Markovnikov wrote about his decision to Butlerov, who was then at St. Petersburg’s University. However, Butlerov did not approve of this decision because he believed the university would be affected. Markovnikov respectfully but firmly objected: “*Your reproach that we've deliberately chosen to harm our native University is hardly fair. We did not benefit from resigning. but sacrificing our careers, we hoped to benefit the University.*”[25]

After a short stay at the new Novorossiisky University in Odessa, Markovnikov was invited to Moscow University, where chemical education was still at a very poor level. The existing chemical laboratory belonged to the Faculty of Mathematics and Physics, it occupied a few rooms and a damp basement, and could accept no more than 20 students. Markovnikov agreed to accept this invitation only on the condition that the university administration would allot funds for setting up a well-equipped chemical laboratory.

Markovnikov walked into a very poor situation: without a responsible head of laboratory for almost two years, all the equipment, initially very poor and outdated, was badly worn out or altogether lacking. It is difficult to believe, but the chemical laboratory at Moscow University was then vastly inferior not only to the Kazan and St. Petersburg Universities, but also to that in the recently established university in Odessa.

The situation was so grave that Markovnikov wrote to his teacher: "*Things still go wrong for me in Moscow. Setting up a new laboratory seems unrealistic and brings me close to despair.*" However, he took over the nearly impossible task with zeal and passion, sparing no efforts in achieving the goal. Only 14 years later (September 1887), could the university at last boast a new and really excellent laboratory, full with students. This date can be considered the start of chemical education and research, particularly in organic chemistry, in Moscow University.

The number of students studying natural science at Moscow University increased from 17 in 1873 to 705 in 1898. The laboratory allowed for both research and teaching in inorganic, analytical, and organic chemistry, and many talented students took their first steps there to becoming scientists. Markovnikov's school produced many famous scholars, including Ivan A. Kablukov, Nikolay M. Kizhner, Mikhail I. Konovalov, Nikolay Ya. Demyanov, Alexey E. Chichibabin, and many more. The first female researcher in Russian chemistry, Yulia V. Lermontova, after obtaining her doctoral degree at Goettingen University, worked for several years together with Markovnikov and published important research. Thus, Markovnikov resulted in Moscow becoming one of the most important centers of chemical education and research in the Russian Empire, and since then has regularly attracted, and still attracts, the ambitious talented youth from all parts of the nation and abroad.

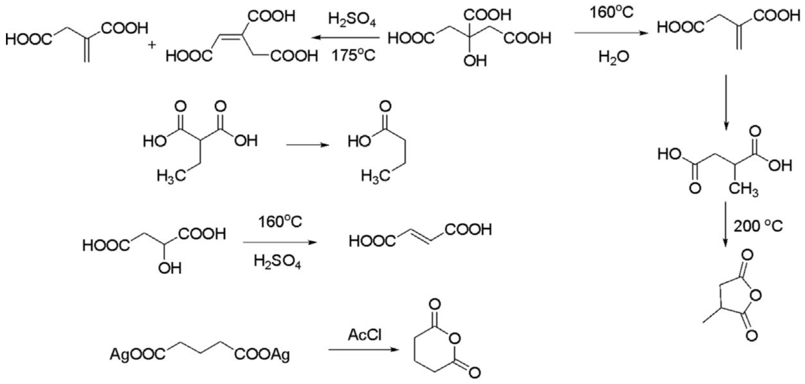
The first ideas about multiple bonds in unsaturated hydrocarbons (the structural formulas of ethylene and acetylene) were suggested by Erlenmeyer. Markovnikov disliked the notion of "multiple bonds", and thought it rather misleading as it implied increased strength, although he did write that "only the primary bond is strong, while others burst readily",[26] and gave experimental proof of his viewpoint. In this situation Markovnikov behaved as a consistent and rigorous follower of the structural theory of his teacher Butlerov: he yearned for strict language allowing for the adequate description of static molecular structures. However, most chemists of the time paid little attention to such subtle differences and agreed to use spontaneous names and notions appearing during the course of studying not the structure, but reactions and transformations. In this regard, the efforts of Markovnikov to develop a more consistent and less misleading chemical language were not appreciated by his contemporaries.

Similar was Markovnikov's dissatisfaction with the way of drawing the benzene ring in the manner proposed by Kekulé and generally adopted to be true. The structure showed three identical double bonds but, as he wrote: "The calorimeter shows that transition from benzene to dihydrobenzene is much more difficult than the subsequent transitions to C_6H_{12}". This statement provides some of the first evidence for aromatic stabilization, but developing a detailed theory of aromatic stabilization was not possible without the realization of the quantum nature of chemical bonding, and thus it had to wait more than half a century.

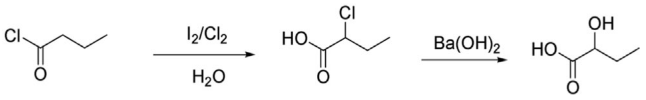
He continued to develop his ideas about isomerism using the transformations of dibasic acids, such as methylsuccinic and ethylmalonic acid. He studied the pyrolysis of citric and malic acids, and synthesized a number of dibasic and tribasic acids (Scheme 9).[27] He revealed the ready decarboxylation of malonic acid derivatives[28] and the formation of five- and six-membered cyclic anhydrides.[29]

On studying the transformation of carboxylic acids and their derivatives, Markovnikov disclosed the halogenation of carboxylic acids at the α-position as well as the ready hydrolysis of α-chlorosubstituted acids. He used this reaction as yet another important example of the influence of neighboring atoms on the reactivity, thus anticipating one of the most important and fruitful heuristics in theoretical organic chemistry—the substituent effect. In fact, the observation of the increased reactivity of halides in substitution reactions depending on the neighboring atoms was stated as another Markovnikov rule. This rule was more widely known by his contemporaries than the classical one, both because the substitution reactions were much better studied and used, and also because it appeared in a full paper written in German. As a practical result, the synthesis of α-hydroxy acids was elaborated (Scheme 10).[19]

In 1881, Markovnikov began systematic studies on the composition of Caucasian oils, and faced the rather unexpected disapproval of many of his colleagues, who insisted that a true scholar should pursue only pure science, and not stray from this path under any circumstances. Curiously, as we



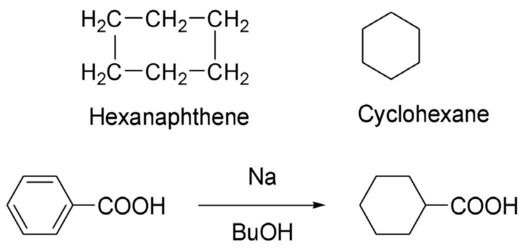
Scheme 9. Markovnikov's study of bi- and tribasic acids.



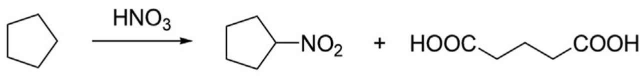
Scheme 10. The synthesis of α-hydroxy acids according to Markovnikov.

remember, young Markovnikov had made exactly this choice, changing his vocation from applied economics and technology to the newly emerging field of pure fundamental chemistry. Having reached maturity and fame as an academic scientist, however, Markovnikov no longer avoided the applied aspects of his science, as such aspects had in the meantime begun to emerge. We should remember that the regular chemical technology was born as a branch of industry only towards the end of the 19th Century. He could not help sarcastically wondering: *"…why indeed our* ***natural*** *scientists do not want to choose for their most learned studies the matters connected with the* ***nature*** *of their land, of Russia…"* It should be noted that at that time petroleum was used only on a rather small scale as a source of kerosene (a cheap domestic fuel for cooking and illumination) and some simple lubricants. Quite soon, however, the demand for this chemistry would grow exponentially. The important results from Markovnikov's studies were the determination of aromatic hydrocarbons in oils, followed by the study of their composition and possible useful transformations. No less important was the discovery of non-aromatic cyclic hydrocarbons in oil, for which the generic name "naphthenes" was proposed, still in common use in Russia. His interest in cycloalkanes was also apparently associated with seeking further support for Butlerov's structural ideas, as this class of compounds offered an unprecedented wealth of data on various kinds of isomerism. For example, Markovnikov was the first to obtain cyclohexanecarboxylic acid through reduction of benzoic acid, thus confirming the interrelation of benzene and cyclohexane derivatives (Scheme 11).[30]

Together with his student Ogloblin, Markovnikov published the results of his studies in the 1881 paper entitled "Study of Caucasian Oils", which was awarded the prize of the Russian Physico-Chemical Society. One of the methods used to separate and identify the hydrocarbon fractions was treatment of the oil with sulfuric or nitric acids. By using the alkane nitration reaction discovered by one of his students, Mikhail Konovalov (the Konovalov reaction), he synthesized a number of nitro derivatives of cycloalkanes, and discovered oxidative ring cleavage, a reaction of industrial importance for the future technology of polymers (Scheme 12).[31]

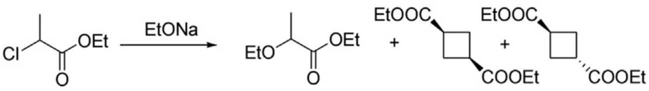


Scheme 11. The transformation of benzene into cyclohexane derivatives.



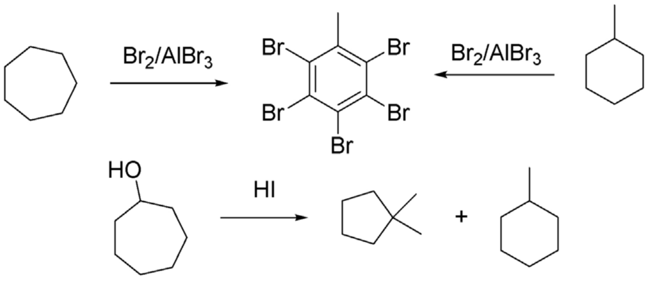
Scheme 12. Nitration of cycloalkanes ("naphthenes").

Markovnikov was the first to synthesize a cyclobutane derivative, and did so as early as 1881.[32] Although this synthesis was somewhat fortuitous and could not be developed into a regular method of synthesis, his priority for the first preparation of a small cycle derivative is indisputable (Scheme 13). Only a year later, Freund published the synthesis of cyclopropane, the smallest carbocycle.[33]



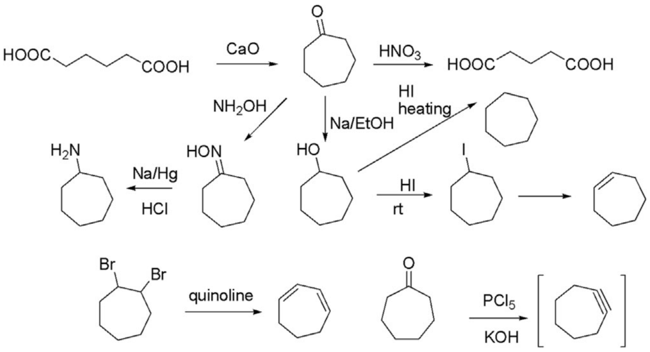
Scheme 13. The first cyclobutane derivatives obtained by Markovnikov.

Markovnikov was one of the first to discover skeletal rearrangements taking place in the presence of acidic reagents, in what we now call carbocationic rearrangements. These became in the 20th Century one of the key processes in large-scale petrochemistry and catalytic reforming.[34] For example, he demonstrated the conversion of cycloheptane into pentabromotoluene by bromination in the presence of anhydrous aluminum bromide (Scheme 14).[35] He also observed the transformation of seven-membered rings to five- and six-membered derivatives.



Scheme 14. Ring contractions.

Markovnikov synthesized many cyclic hydrocarbons in his laboratory and developed new methods for the synthesis of cyclic ketones, naphthenic acids, and other important derivatives. Besides cyclohexane, Markovnikov predicted and then proved the presence of cyclopentane derivatives (such as "methylpentamethylene") in oils. Through pyrolysis of the calcium salt of suberic acid he succeeded in obtaining cycloheptanone (suberone),[36] the reduction of which gave cycloheptanol, and later on many other cycloheptane derivatives (alcohol, amine, oxime, cycloheptene, and cycloheptadiene) were prepared (Scheme 15). The attempted synthesis of cycloheptyne was unsuccessful, thus providing the first hints for the future development of ideas, known to us as ring strain.[37]



Scheme 15. Reactions of seven-membered rings described by Markovnikov.

Figure 5. The founders of the Russian Physical and Chemical Society.

The First International Petroleum Congress held in 1900 in Paris awarded Markovnikov a gold medal in 1900 for outstanding achievements in petroleum chemistry. Stanislao Cannizzaro, a famous Italian chemist and statesman, appraised Markovnikov's achievements in this area saying: "*They (the works) enriched the science with a new type of important carbon compounds to be forever associated with his name.*"

In addition to his studies in the field of organic and petroleum chemistry, Markovnikov participated in finding practicable sources of Glauber's salt in salt lakes of the Volga basin and the Caucasus region, and tried to understand the origin of such lakes. Thus, Markovnikov contributed to the development of the famous mineral water resorts in the North Caucasus.

"*The scientist you may not become, but you should be a citizen*", he used to say to his students, paraphrasing the famous patriotic verse by Nikolay Nekrasov. Many times he proved this in his lifelong service to Russia. During the Russian–Turkish war of 1877–1878, Markovnikov went to battlefields in Romania. Here, he helped to arrange for assistance in combating the plague and cholera epidemic, and worked out practical rules on sanitation and disinfection in hospitals, in ambulance trains, and on the battlefield. Moreover, he declined to accept the monthly stipend of four hundred roubles in gold per month, the amount paid to all professors sent to the theatre of military action. During a cholera epidemic, Markovnikov analyzed a selection of local Russian tars in an attempt to replace the use of carbolic acid as a disinfectant, as phenol was then imported from abroad and had been in scarce supply. In 1878 during the outbreak of the "Vetlian plague", Markovnikov, together with Otradinsky, published a booklet "The plague in Russia", which became widely popular at the time, and also compiled "The Practical Guidelines for Disinfection". In the same year, during an inspection visit to the Kursk hospital, Markovnikov caught a deadly disease typhus but, luckily, he recovered.

After 1884, Markovnikov was, for 18 years, elected to leading positions in the Chemistry Division of the Society of Naturalists, including the position of chairman, which he held for many years. Later the department became the Moscow branch of the Russian Physical and Chemical Society and played a significant role in the development of science in Russia (Figure 5). Markovnikov contributed as many as 90 reports to the meetings of the Society. His former students also made outstanding contributions to the Society proceedings: Konovalov reported the nitration of paraffins, Kizhner spoke on the isomerization of cycloalkanes, and Zelinsky elaborated the synthesis of carbocycles (naphthenes). The Society published a collection of works on the history of chemistry in Russia, and in 1897 celebrated the 150th anniversary of the establishment of the first chemical laboratory (1747).[38]

Despite such achievements and devoted service, Markovnikov was forced in 1893 to leave the position of the Head of Laboratory at Moscow, and even to leave the apartments allocated to him in the university premises. Officially this was announced as necessary according to some bureaucratic regulations imposed by the Ministry of Public Education. The instruction was to dismiss professors after 25 years teaching experience, foolish because he was only 55 years old and full of ideas and vigor. Furthermore, it was done in such an insulting way that Markovnikov took it as, in his own words, a catastrophe. Nevertheless, even after such an afront Markovnikov decided to stay at Moscow State University and continue his research.

In 1901, on the day of celebration of the 40th anniversary of his pedagogical and scientific career, Markovnikov on accepting a diploma of an Honorary Member of Kazan University gave a speech and said: "*I will indulge myself to conclude my speech by addressing the young people and scientists with a humble advice. If you don't want once in the future to find yourself in a state of bitter annoyance and moral anguish, never put off until tomorrow what can be done today. I would be happy if my words and my experience would encourage at least somebody of those present here to adhere to the essence of this old saying.*"

Markovnikov's death was sudden. He became sick on a trip from St. Petersburg to Moscow, suffered a stroke, and expired on January 29, 1904. Condolences from everywhere arrived to the Society where he served for so many years. Letters from St. Petersburg, Kazan, Kiev, Warsaw, Odessa, Yuryev (now Tartu), London, Paris, Kharkov, Baku, and Ivanovo-Voznesensk (now Ivanovo) signed by ordinary researchers and scholars of world renown were received in dozens. Vladimir Ipatief, one of the founders of the modern petroleum chemistry, wrote from St. Petersburg: "*I feel devastated after the death of the most respected Vladimir Markovnikov, who worked so efficiently for the benefit of the Russian science.*" The next year a very detailed account of the life and scientific achievements of Markovnikov, including a list of more that 60 papers published in the most influential German and French journals of the epoch (Annalen, Berichte, Compte Rendue etc.), was written for *Chemische Berichte* by Herman Decker;[39] Decker was a German chemist born in Russia, and known for the Forster–Decker method to selectively synthesize secondary aliphatic amines.

Thus, we see that the academic career of Markovnikov had been long and full of formidable achievements. His name, however, is engraved in the history of science owing to one of his earliest observations made during his studentship in the times when organic chemistry was just appearing as a regular branch of science, and when all the organic substances known along with all their reactions performed throughout all the laboratories in the world could have been be written in a thin notebook.

Markovnikov's Legacy

A few years ago, Moscow State University began memorial proceedings devoted to the works of one of the founders of the national school of organic chemical research. Each year, in January, a special memorial conference in the name of Markovnikov (Markovnikov Readings) is held. In 2019 the 5th Markovnikov Readings was held. In 2016 the memorial medal (Figure 6) was established to be awarded for outstanding achievement in the field of organic chemistry.

Figure 6. The Markovnikov Medal.

Winners of the Markovnikov medal:
2017: I. P. Beletskaya (Lomonosov Moscow state University)
2017: O. N. Chupakhin (Postovsky Institute of Organic Chemistry, Ural Branch of the Russian Academy of Sciences, Ekaterinburg)
2017: B. A. Trofimov (Favorsky Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk)
2018: O. G. Sinyashin (Arbuzov Institute of Organic and Physical Chemistry, Kazan)
2018: V. N. Gevorgyan (University of Illinois at Chicago)
2019: V. V. Zhdankin (University of Minnesota Duluth)
2019: V. N. Charushin (Ural State University, Ekaterinburg)
2019: D. E. Lewis (University of Wisconsin-Eau Claire)

The 150th anniversary of the Markovnikov rule is approaching and in June 2019 a major international conference—the Markovnikov Congress—will be held in Kazan, organized jointly by Kazan and Moscow Universities.

Вл. Марковниковъ

Conflict of interest

The authors declare no conflict of interest.

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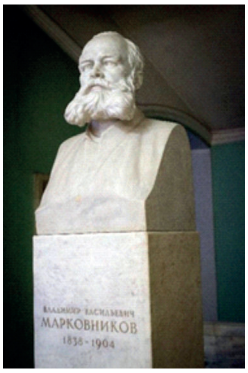
Essays

Markovnikov's Rule

I. P. Beletskaya,*
V. G. Nenajdenko* ________ ▮▮▮–▮▮▮

Towards the 150th Anniversary of the Markovnikov Rule



As a general rule: During its 150 year long history the Markovnikov rule, formulated by Vladimir Markovnikov, has undergone a rather incredible evolution. After starting as an empirical rule describing a particular organic reaction, it has become an important designation of regioselectivity that is applicable to a huge range of important organic transformations.