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Bianka Tchoubar: A Revolutionary in French Organic Chemistry

Abstract
Virtually unknown in her homeland, Bianka Tchoubar, born in 1910 in Kharkiv, brought about a true paradigm shift in French organic chemistry of the 20th century. Originality of research ideas, scientific rigor and legendary perseverance earned her respect and recognition in the world scientific community. This eccentric Parisian of Ukrainian origin became the first woman to enter the French National Center for Scientific Research (*Centre National de la Recherche Scientifique*, CNRS) upon its creation in 1939. Bianka Tchoubar's contribution to the study of reaction mechanisms and salt effects in organic chemistry were of paramount importance, and so were her efforts to present these novel scientific concepts to the audience of French organic chemists through the clear and concise expression of her books. The name of this great Ukrainian researcher may be found in the pages of French organic chemistry textbooks, where the Demjanov ring expansion reaction is called the Demjanov–Tiffeneau–Tchoubar rearrangement. This article aims at presenting the outstanding scientific legacy and turbulent life path of this researcher to the world scientific community.
Keywords: mechanisms of organic reactions; charged intermediates; salt effects; molecular rearrangements; alicyclic compounds; history of chemistry

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Б'янка Чубар – революціонерка французької органічної хімії

Анотація
Маловідома на Батьківщині уродженка Харкова Б'янка Чубар зуміла створити справжню зміну парадигми у французькій органічній хімії XX століття. Оригінальністю наукових ідей, експериментальною майстерністю та непохитністю власних переконань ця науковиця здобула неабияке визнання у Франції та цілому світі. Ексцентрична парижанка українського походження стала першою жінкою, що увійшла до дослідницького штату Національного центру наукових досліджень Франції (*Centre National de la Recherche Scientifique,* CNRS) під час його створення 1939 року. Внесок науковиці у механістичні дослідження органічних реакцій, а також їх педагогічне опрацювання є неоціненними. Прізвище великої українки гордо майорить у французьких підручниках органічної хімії, які вшановують її експериментальні дослідження, називаючи реакцію розширення аліциклів, відому як перегрупування Дем'янова, перегрупуванням Дем'янова–Тіффано–Чубар. Пропонована стаття має на меті репрезентувати науковій спільноті України та світу видатні здобутки й непростий життєвий шлях цієї дослідниці.
Ключові слова: механізми органічних реакцій; заряджені інтермедіати; сольові ефекти; молекулярні перегрупування; аліциклічні сполуки; історія хімії

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Figure 1. Bianka Tchoubar with a cigarette. The portrait is reproduced from reference [1]

Biography

1. Early Life and Education

Bianka Tchoubar was born on the 22nd of October, 1910, in the Ukrainian city of Kharkiv, which was then part of the Russian Empire. The Tchoubar family belonged to the Jewish sect of the Karaites [2].

Bianka's father, Ilya Tchoubar, was a Kharkiv lawyer with Menshevik views. He was a member of the Liberal Party of Constitutional Democrats (Cadets) and a person close to its leaders, Pavel Milyukov and Vladimir Nabokov. To avoid political repression after the advent of Bolshevik power in Russia and the occupation of the Ukrainian People's Republic, the Tchoubar family (a couple with two children, Bianka and her brother Serhiy) were forced to leave Ukraine in 1920. The family settled in Constantinople, then the capital of the still-existing Ottoman Empire. Due to political instability caused by World War I, the collapse of the Ottoman Empire and the Turkish War of Independence, the Tchoubar family only lived in Constatinopole for a short time and moved to Budapest in 1922, where the brother of Ilya Tchoubar lived. The parents then moved to Paris, and the girl and her brother stayed with their uncle, where they were able to study French. The family reunited in Paris in 1924 [3].

After settling in Paris, Bianka Tchoubar converted to Orthodox Christianity in 1925, but soon became disappointed in religion and began to adhere to an agnostic worldview [2].

Bianka's father died of a heart attack in the early 1930s, leaving his wife and two children with little livelihood. To survive, Bianka's mother worked at minimal-wage and non-permanent jobs, selling perfumes during the day and being a cloakroom attendant at a theater in Paris in the evenings. The family lived in extreme poverty [3].

Bianka Tchoubar and her brother began their studies at a Russian school in the 16th arrondissement of Paris, set up by the French government for the children of political migrants from the Russian Empire. It was at this school that Bianka Tchoubar first became interested in the natural sciences, including chemistry, under the tutelage of Mademoiselle Chamier, a Russian chemist who had collaborated extensively with Marie and Pierre Curie in the past. Bianka Tchoubar later reminisced about this teacher as her mother in chemistry [3]. The figure of Marie Curie was extremely important to Bianka Tchoubar; she has repeatedly stated that she had never missed any of Curie's public lectures in Paris [1].

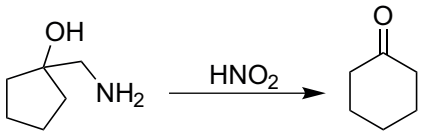
Bianka Tchoubar continued her studies in chemistry, getting admitted to the Sorbonne University in 1929. In 1931, she received the Bachelor of Science Degree and began her research work under the guidance of the then-famous Parisian chemist Professor Paul Freundler, a close friend and colleague of Joseph Achille Le Bel. The choice of the laboratory for her graduate research activities was due to Bianka Tchoubar's interest in asymmetric nitrogen reactions.

In Professor Freundler's group, the young scientist first met with the rejection of her ideas about organic ions by her French colleagues. The conflict of scientific worldviews stemmed from the considerable conservatism of the French scientific community to any new concepts, especially if they came from the so-called "Anglo-Saxon world" [1]. Despite the disagreement of her supervisor, Bianka Tchoubar devoted her Master thesis to the study of charged organic species in tertiary amine reactions with ethyl iodoacetate, which contributed to her Higher Education Degree in Chemistry, awarded in 1932 (*Diplôme d'Études Supérieures de Sciences Chimiques*) [3].

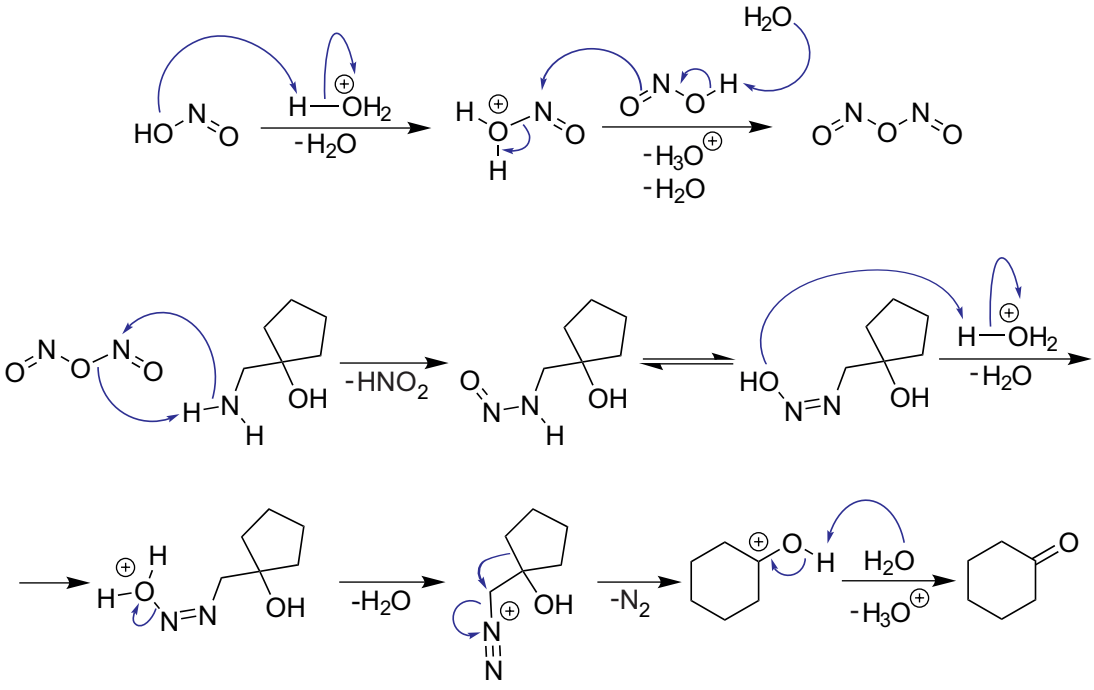
2. Scientific Work with Marc Tiffeneau

In 1933, Bianka Tchoubar began working in the laboratories of the Faculty of Medicine of the University of Paris, under Marc Tiffeneau's supervision. Despite world recognition of his achievements, Marc Tiffeneau had limited recourse to resources in France and was forced to work in the field of pharmaceutical chemistry. He became Bianka Tchoubar's most important mentor. Bianka's first research article on the interaction of Grignard reagents with chlorocyclohexanones was published in 1934 in *Proceedings of the French Academy of Sciences* (*Comptes rendus de l'Académie des Sciences*) [4]. In the laboratory of Marc Tiffeneau, Bianka Tchoubar first met Jeanne Lévy, an organic chemist, who later became one of her research collaborators [3].

In 1937, Bianka Tchoubar established the Laboratory of Organic Chemistry, which studied a variety of atomic transfer reactions. She was appointed also as a trainee researcher at the newly established French National Center for Scientific Research (*Centre national de la recherche scientifique* – CNRS), becoming the first female researcher to enter this institution for science (Figure 1) [2]. She then became interested in molecular rearrangement reactions and proposed a mechanism for nitrite deamination of alicyclic primary amines with ring expansion (Scheme 1) using quantum mechanical theories of chemical bonding. These were considered to be the so-called "English ideas" in France at the time, and viewed as unwelcome. Despite numerous disagreements and criticism of peers, the joint research of Bianka Tchoubar and Marc Tiffeneau made it possible to definitively establish the mechanism of the Tiffeneau–Demjanov rearrangement (or, as it is known in France, the Demjanov–Tiffeneau–Tchoubar rearrangement) (Scheme 2) [5, 6].



Scheme 1. Demjanov–Tiffeneau–Tchoubar rearrangement



Scheme 2. Demjanov–Tiffeneau–Tchoubar rearrangement mechanism

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Bianka Tchoubar's research slowed down significantly in 1939–1945 due to the outbreak of World War II, when she took an active part in the French national resistance to the fascist occupation [2].

The sudden death of Marc Tiffeneau in 1945 further complicated Bianka Tchoubar's scientific career. However, after the war in 1945, Bianka's longtime friend Jeanne Lévy, an Associate Professor of Medicine at the University of Paris at that time, was appointed to establish a new Institute of Medicine in Paris, known today as the Fournier Institute (*Institut Fournier*) [2, 3]. Bianka Tchoubar joined the research department of the newly established Institute, and in 1946 published her thesis "Contribution to the study of alicyclic expansion mechanisms: nitrite deamination of 1-aminomethylcyclohexanols" [2]. Bianka Tchoubar managed to present these radically new ideas in physical organic chemistry while obtaining her doctorate.

The significant delay in defending her doctoral thesis was caused by the political instability in France of 1930s, as well as by the outbreak of World War II. The completion of her PhD was also delayed by the unwillingness of the French scientific community to accept the innovative but "English" concepts Bianka Tchoubar promoted. The young researcher explicitly stated her interest in charged intermediates of organic reactions. Her ambition was to rule the notions of "affinity capacity" and "migratory aptitude" out of organic chemistry as they did not provide satisfactory explanations for the observed patterns in alicyclic expansion reactions. Such ideas of Bianka Tchoubar were severely criticized in Parisian scientific circles of that time [2]. During the defense of the Bianka Tchoubar's thesis, the opponent, French spectroscopist Pauline Ramar-Luca, called the presented explanations of the reaction mechanisms "ephemeral theories". The only supporter of the young scientist's novelties was the chairman of the doctoral jury, Edmond Bauer. The theoretical chemist was impressed by the Bianka's work and accepted her ideas with enthusiasm and encouragement.

The Bianka Tchoubar's doctoral thesis was the first French research work to explain organic reaction mechanisms in terms of mesomerism and the formation of charged intermediates. Bianka Tchoubar was responsible for bringing the widely accepted ideas of Hans Meerwein, who postulated the existence of carbocationic intermediates in the pinacol–pinacolone rearrangement between 1922 and 1927, to French organic chemistry [2].

3. "Anglo-American" Theories and Center No.12 of the French National Center for Scientific Research

French colleagues never refrained from criticism for Bianka Tchoubar's pertinent and witty interpretations of the mechanistic features of chemical reactions "with English accent". Rejection and occasional ridicule of her ideas did not cease even after she was awarded her doctorate degree. It should be noted that French organic chemistry in the twentieth century had a rather strong "chauvinistic inclination" [7]. Achievements of quantum mechanics introduced into chemistry by the American and British chemists led by Linus Pauling and Christopher Ingold were rejected. That the 1912 Nobel Prize in Chemistry that was jointly awarded to two French researchers, Victor Grignard and Paul Sabatier seemed to have an impact to this field of science in France. This gesture of recognition of the French chemical science led to its isolation and Franco-centricity for the decades to come. There was an excessive and sometimes biased emphasis on selected research only because of their performance in France, a politicized approach to research funding and staffing, and deliberate prevention of scientific progress through the introduction of external scientific ideas from the so-called "unfriendly" countries. Moreover, the extremely influential Parisian chemists Charles Prévost and Albert Kirrmann monopolized French organic chemistry in the post-war period. They had been promoting Prévost's theory of organic reactions from their position of power, despite its ridicule at the international level. Prévost's accounts of organic reactions formulated in terms of "syniony" and "metiony", despite their outright inconsistency, had thus become the only acceptable theory in French laboratories and classrooms after World War II. In addition to the anti-British and anti-American sentiments that prevailed in the French society after World War II, as a result of the Vichy regime's propaganda, the French government had also established control over the circulation of English literature, manifested in its artificially limited availability [7].

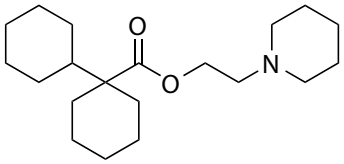
The French reluctance to accept the revolutionary ideas of their British and American counterparts was the main reason of the Bianka Tchoubar's scientific career slowdown at the French National Center for Scientific Research. Due to the inconsistency of political views, her appointment to a full-time research position was delayed until 1955. In 1957–1958, Bianka Tchoubar organized countless seminars, at which

she presented the electronic theories of organic reactions [1–3, 7]. As a summary of seminar reports, in 1960, she wrote a book "*Mechanisms of Organic Reactions*", which was the first French textbook to present the quantum theories of chemical bonding. The famous quotation of Claude Bernard was chosen as the epigraph for this book: "If a theory was considered perfect and was no longer tested, it would have become a dogma" [8, 9]. The book was positively accepted by the world scientific community and translated into six languages [1–3, 7]. The presentation of the already widely accepted quantum-mechanical theories of chemical bonding to the French audience has led to a paradigm shift in the 20th century French organic chemistry [7].

As early as in 1961, Bianka Tchoubar was appointed Director of Research at the French National Center for Scientific Research and headed her first research group at the Institute for Chemistry of Natural Substances in Gif-sur-Yvette, Île-de-France. Bianka Tchoubar's ideas were recognized even more widely in 1968, when she was appointed Director of Research at Center no.12 of the French National Center for Scientific Research in Thiais, Île-de-France. This research group included more than 70 chemists who conducted extensive research in various fields of organic chemistry. It was the largest center for organic chemistry research in France at that time [2].

Scientific research at Center no.12 has focused on the fundamental study of organic reaction mechanisms. Considerable attention was also paid to the synthesis of biologically active substances and drug development. Under the supervision of Bianka Tchoubar at the CNRS Center no.12, the antispasmodic drug *Spasmodex* was developed. The active compound of this drug is dihexyverine (2-(piperidin-1-yl)-ethyl-[1,1'-bi(cyclohexane)]-1-carboxylate) (Figure 2) [3].

Colleagues and students reminisce about Bianka Tchoubar being a gifted research supervisor, whose priority was a friendly atmosphere in the group. Bianka Tchoubar took each and every aspect of the research papers published under the CNRS Center no.12 affiliation as her personal responsibility. For these reasons, no research work in these laboratories was published without prior review by Bianka, even as she did not claim co-authorship in these works, thereby paving the path for young scientists. That is why, in 10 years of managing the laboratories of Center no.12, she agreed to put her name in 5 publications only, instead giving the real distinction to her colleagues [2, 3].



Dihexyverine (Spasmodex)

Figure 2. Dihexyverine structure

Monday seminars of young researchers were another tradition at Center no.12, led by Bianka Tchoubar. Former graduate students of Bianka recall that she appeared to be always shrouded in a thick cloud of cigarette smoke at the seminars. Her presence in the front rows of the auditorium was ubiquitous, where she actively and passionately discussed research results. Not self-serving, this scientist never used her established authority to dominate scientific discussions, which earned her the respect of colleagues [1–3].

Bianka Tchoubar tirelessly incorporated the ideas of quantum chemistry into the interpretation of the results obtained in her own laboratories. Despite the experimental nature of her own research, she was also interested in the achievements of theoretical branches of chemistry, which were developing extremely rapidly in that period [2].

4. Scientific Research in the USSR and Last Years of Life

Bianka Tchoubar first met with Yevhen Shilov at the IUPAC International Congress of Applied Chemistry in Paris in 1957. Dr. Shilov was the Head of the Laboratory of Organic Reaction Mechanisms of the Institute of Organic Chemistry of the Ukrainian Soviet Socialist Republic Academy of Sciences (Figure 3). Having common interests and like-minded scientific views, a deep friendship grew between Bianka Tchoubar and Yevhen Shilov. Likewise, these same commonalities led to the subsequent friendship with his son, Oleksandr Shilov, who later became an academician of the USSR and of the Soviet Academy of Sciences [10]. The friendship with the Shilovs was the impetus for Bianka Tchoubar's research in the field of coordination chemistry.

In 1974, Bianka Tchoubar began studying the reduction of molecular nitrogen in coordination compounds of iron. She conducted such research in collaboration with colleagues and friends from the former Soviet Union, including Yevhen Shilov from the Academy of Sciences of Ukraine, with whom she met several times at the Institute

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Figure 3. Bianka Tchoubar with the Head of the Laboratory of Organic Reaction Mechanisms of the Institute of Organic Chemistry of the Ukrainian Soviet Socialist Republic Academy of Sciences Dr. Yevhen Shilov in Paris (1957).
The picture is reproduced from reference [10]

of Organic Chemistry of the National Academy of Sciences of Ukraine in Kyiv. Much of the research in this period of her life was conducted with the leading Soviet organic chemists Alla and Oleksandr Shilov (Figure 4), as well as with the 1956 Nobel Laureate in Chemistry Nikolai Semenov [1–3]. The results of iron complexes investigation led to amassing of a significant array of data on the salt effect influence on organic reaction kinetics [2, 11].

During her last years at the French National Center for Scientific Research, Bianka Tchoubar actively collaborated with the French spectroscopists Didier Astruc and Georges Bram. Their joint research was dedicated to the study of microwave activation effects on organic reactions, as well as to the organic reactions occurring in the absence of the solvent [3].

Bianka Tchoubar officially retired from the French National Center for Scientific Research in 1978, but never left her love of science behind, continuing to be active in new for her fields of organic chemistry.

In 1981, Bianka Tchoubar was awarded the Louis Jecker Prize (*Prix Jecker*) of the French Academy of Sciences. Interestingly, Bianka's mentor, Marc Tiffeneau, received this award three times: in 1911, 1922 and 1923 [3].

Together with André Loupy in 1988, she wrote a book "*Salt Effects in Organic and Organometallic Chemistry*", which was translated into several foreign languages [2, 11].

The last experiments Bianka Tchoubar conducted were designed to study solvent effects on the competition of S_N2 and $E2$ reactions [2]. Her last paper was a literature review "*Salt Effects as a Result of Ion Vapor Exchange*" published in the *Chemical Review*, co-authored with André Loupy and Didier Astruc [12]. In total, Bianka Tchoubar authored some 140 scientific papers [3].

Bianka Tchoubar passed away on April 24, 1990, and was buried at the Sainte-Geneviève-des-Bois cemetery in the Essonne department, Île-de-France.

■ Books

Mechanisms of organic reactions (1960)

This textbook easily fitting in a lab coat pocket was a huge success and quickly earned the nickname of "The Little Tchoubar".

Figure 4. Bianka Tchoubar with the Shilovs. Left to right: Alla Shilova, Bianka Tchoubar, and Oleksandr Shilov. The figure is reproduced from reference [2]

The first four chapters of the book are dedicated to molecular orbital hybridization, bond polarity and polarizability, inductive and mesomeric electronic effects, and modern theories of acids and bases. These sections reflected the influence of Christopher Ingold's research in the field of organic chemistry [9].

The remaining nine chapters cover some issues of chemical kinetics and transition states, as well as individual aliphatic substitution reactions, elimination and addition reactions, as well as prototropic processes, carbonyl group reactions, and aromatic substitutions [9].

There were several mechanistic interpretations that turned out to be proven wrong with time. In particular, the textbook proposes a carbanion mechanism of deuteroexchange with halogenated substrates, instead of *E*2. However, the overall content of the textbook has withstood the test of time, with such inaccuracies being rare occurrences [13].

Salt effects in organic and organometallic chemistry (1988)

This book was co-authored with André Loupy.

The first chapters of the book discuss the basics of the theory of Lewis acids and bases, ion pairs, salt effects in chemical bond cleavage, electrophilic and nucleophilic induction of heterolytic bond cleavage in halogenated substrates, specific salt effects in S_N2 reactions, salt effects during multiple bonding reactions in ketones, esters, and nitriles, drying effects, bifunctional catalysis and electrophilic addition to carbon-carbon double bonds.

Subsequent sections examine salt control over regioselectivity, stereoselectivity of substitution, addition, and elimination reactions, as well as the means of controlling the chemical equilibrium by salt and solvent effects.

The final section of the book analyzes the role of the aforementioned phenomena in organometallic chemistry [11, 14].

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