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Inga Fischer-Hjalmars (1918−2008): Swedish Pharmacist, Humanist, and Pioneer Quantum Chemist

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Supporting Information

ABSTRACT: A wide variety of questions can be asked about the molecules that compose the physical reality around us and constitute biological life. Some of these questions are answered by the science called biology, others find their answer in chemistry, whereas the answers to the most fundamental questions are only to be found in the theories of physics. Inga Fischer-Hjalmars (born Fischer) belonged to the rare group of scientists who asked questions of all these kinds. Her life and career is a fascinating story of devotion, strive, and an unyielding curiosity about nature. As a young pharmacist, she had a central role in the development of the local anesthetic Xylocaine (also known as lidocaine), but the major part of her career was dedicated to explain the biological, chemical, and physical properties of molecules using the most fundamental principles available: quantum mechanics. Inga Fischer-Hjalmars was a pioneer in applying quantum mechanics to chemical problems, and she became the first female professor in theoretical physics in Sweden. Beside her scientific work, Inga Fischer-Hjalmars was a human rights activist dedicated to the freedom of oppositional and Jewish scientists in the Soviet Union. For this engagement, she was awarded with the New York Academy of Science's Human Rights of Scientists Award in 1990.

KEYWORDS: *First-Year Undergraduate/General, Upper-Division Undergraduate, History/Philosophy, Organic Chemistry, Physical Chemistry, Drugs/Pharmaceuticals, Women in Chemistry, MO Theory, Valence Bond Theory, Quantum Chemistry*

The year is 1943. In a basement in central Stockholm (Kungstensgatan 45), a group of nine young scientists are working intensively to develop a new local anesthetic, which will become one of the greatest innovations ever made in Sweden. Their laboratory is located 13 feet below the street level in a dark and poorly ventilated cellar, built to serve as a air-raid shelter. Their laboratory bench is a rough and heavy stone table, and most of their equipment is either homemade or bought on the secondhand market.[1a−c]

Clearly the material conditions are flawed, but the work is lead by a young and very dedicated chemist, Nils Löfgren. Löfgren's inexhaustible enthusiasm for his work rubs off on his colleagues, and the devotion of the young scientists is perhaps best illustrated by the fact that they all act as laboratory rabbits by testing the candidate compounds on their own finger tips. In fact, one person (Bengt Lundquist) would later on make a spinal injection on himself. One of the fellows is Inga Fischer, only 24 years old and a newly graduated pharmacist (B.Sc.).[1a−c]

EARLY LIFE

Inga Fischer was born in Stockholm on the 16th of January 1918. She grew up in a family with an intellectual tradition and, for their time, highly educated women. Her mother was a schoolteacher in mathematics and geography, but gave up her work when she married Inga's father who was a civil engineer. Her mother's sister was a chemical engineer in Denmark.[2a−c]

Inga's father, Otto Fischer, began his career as a railway engineer in Canada. Later on he started his own parquetry factory in Sweden. Although being a skilled engineer, he was a mediocre businessman, and as a result, family finances were very limited most of the time. Inga's intellectual abilities and interest for the natural sciences were recognized at an early age. However, in the 1930s, there was no government system for the financing of higher education in Sweden, meaning that only children of affluent families had the chance to go to high school. As male education was a natural priority in those days, Inga's studies had to stand back for her brother's education. Fortunately, she could get financial support from her mother's relatives in Denmark that made it possible for her to continue to high school. When her father's firm went bankrupt, the family's financial problems became more severe and Inga had to give private lessons to contribute to the family finances. After high school, her only opportunity to keep in contact with the natural sciences was to become a pharmacist. It was a relatively short and inexpensive education that she could afford by giving private evening lessons to high school students. Although unable to finance her studies, Inga's father had an important role in stimulating her scientific interests. Beside his daily work as a struggling businessman and engineer, Otto Fischer had a great interest in physics, as described by Inga:[2a−c]

> *Each morning he spent one to two hours at his desk, before going to the office, and these early hours were mainly devoted to mathematical physics. He followed the development of relativity and quantum theory with great interest... When I was about sixteen he started to tell me about his work. On long Sunday walks in the woods, he told me about his attempts to bring the whole of physics within a single frame of reference. In those days I was not able to understand the details of his research, but I became fascinated by the general scientific perspective.*[2a]

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With a bachelor's degree in pharmacy, Inga got a job in a drugstore and started to earn her own living. Nevertheless, her insatiable interest in science led her to take classes in mathematics and natural sciences at Stockholms Högskola (which today is Stockholm University). Her intention was to become a schoolteacher, but she would never achieve that goal. As a student, Inga Fischer became involved in Nils Löfgren's research on local anesthesia, and so she found herself in the gloomy basement laboratory (Figure 1).[2a−c]

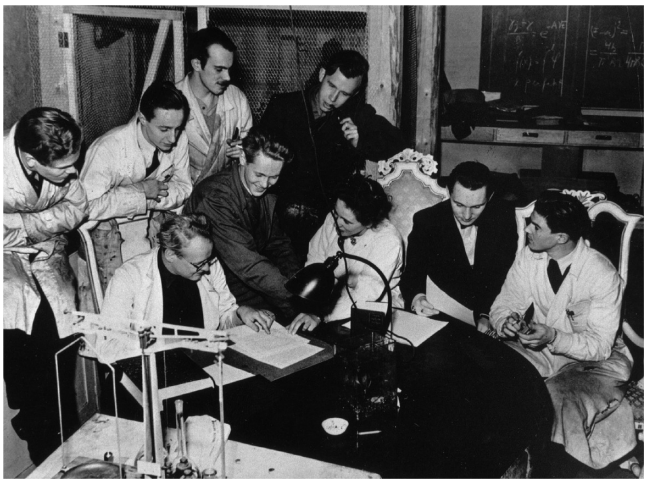


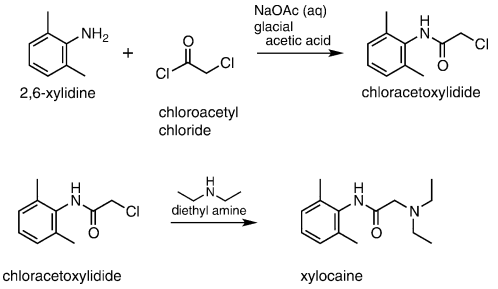
Figure 1. Discussion in the Xylocaine laboratory. From the left: Lars-Erik Tammelin, Göte Östlund, Nils Löfgren, Lars Ehrenberg, Gunnar Widmark, Bengt Lundquist, Inga Fischer, Gunnar Molander, and Elis Sundström. (Photo credit: Astra-Zeneca)

XYLOCAINE

Löfgren's team synthesized several series of structurally similar compounds, guided by the structure of the best local anesthetic known in those days, procaine (also sold as Novocain). One of the substances, with the IUPAC name 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, turned out to be a much more potent local anesthetic than any of the contemporary drugs on the market. Initially, the substance was given the working name LL30, because it was the 30th synthesis in a series suggested by the group leaders Nils Löfgren and Bengt Lundquist; later it would be named Xylocaine.[1a,b,3a,b]

Although Inga Fischer was not on the patent of Xylocaine,[3b] it has been said that she synthesized this particular compound for the very first time. This issue was recently clarified through Gunnar Widmark, a former co-worker of the Xylocaine research team.[3c] When Inga Fischer joined the group, Xylocaine or LL30 had already been synthesized in very small amounts by its inventors Nils Löfgren and Bengt Lundquist. The synthesis is an acylation of 2,6-xylidine with chloroacetyl chloride in glacial acetic acid, followed by alkylation of the product chloroacetoxylidide with diethyl amine (Scheme 1).[3a,b,d] Löfgren and Lundquist had also made the initial tests that revealed the promising anesthetic effect of Xylocaine. However, to proceed with the development, it was necessary to make further tests, but there was a problem with this. The starting material (2,6-xylidine) could be synthesized, but the methods available gave a mixture of similar compounds, which were very difficult to separate. After some time, Löfgren managed to secure 50 g of 2,6-xylidine, which was enough to make a single batch of Xylocaine for further tests. Failure was not an option, so

Scheme 1. Synthesis of Xylocaine



Löfgren wanted the synthesis to be performed by someone he trusted. Since Inga had a reputation of being very skillful and precautious in the laboratory, it fell on her fate to make the first synthesis of Xylocaine on a larger scale.[3c] Xylocaine is one of the most successful commercialized scientific advances ever made in Sweden, and to participate in such project as a young scientist gave Inga a good start in her career. In 1944, Inga Fischer graduated with a master of science in chemistry.[2a,b]

Nils Löfgren worked hard to get Xylocaine out on the market. After being rejected by the pharmaceutical company Pharmacia, Löfgren turned to Astra, in those days a small company close to bankruptcy. Astra's board of directors saw the potential of Xylocaine, which became the first cash cow of the company. The success can be understood in two ways. First of all, Xylocaine is a much better local anesthetic than its predecessor procaine. Not only does it have a stronger painkilling effect, also the duration of the effect is many times longer. An equally important reason for the success of Xylocaine is of practical matters. Procaine is a relatively unstable chemical compound (it is an ester), which had to be stored as a solid powder. Before using it, the powder was dissolved in water and sometimes mixed with epinephrine (adrenaline), which makes the local anesthetic effect last longer. Obviously, this was impractical in many situations, for example, in a field hospital. By comparison, Xylocaine is a relatively stable compound, which can be stored in a water/epinephrine solution for a long time. The practical usefulness of Xylocaine made local anesthesia an attractive alternative to narcosis in many cases of light surgery and it also became very popular among dentists. For these two reasons, the world market for local anesthetics increased dramatically after the release of Xylocaine in 1948.[1a,b]

With a master's degree and the Xylocaine experience, it was not difficult for Inga Fischer to get the job as assistant to the Nobel laureate Hans von Euler-Chelpin. He had left the field that earned him the Nobel Prize in 1929, enzymatic fermentation of sugars, and turned to the problem of identifying and characterizing nucleic acids from different tissues and organisms. In particular, he was interested in the possible differences between DNA from tumors and normal tissue. This research required a spectrophotometer, but due to the ongoing World War II, it was impossible to buy an instrument from abroad, and at that time there was no manufacturer of such equipment in Sweden. Thus, the only alternative left was to construct a spectrophotometer.[2a,b] This project and the investigations that followed[4a−c] made Inga aware of her limitations as a general chemist. Once again she decided to continue her studies and to immerse herself in physical chemistry, the interdisciplinary field between chemistry

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and physics. Again she found the topic of her graduate studies in the laboratory of Nils Löfgren.[2a]

In addition to synthesizing and testing new compounds, Löfgren's group made efforts to understand the local anesthetic effect in terms of chemical structure. In the quest for this knowledge, Inga Fischer became a leading force.[1a,3c] During a visit in Oslo, she learned from the Norwegian chemist Odd Hassel how to construct an apparatus for measuring the electric dipole moment of molecules.[2a,b] With a self-made device, she studied the substances synthesized in Löfgren's laboratory (Figure 2) to find whether there was a connection between the

Figure 2. Inga Fischer in the laboratory (mid 1940s). (Photo credit: Astra-Zeneca)

electrostatic properties of the compounds and their biological activity.[5a−c] It should be emphasized that this was an ambitious and difficult task in the 1940s, as virtually nothing was known about the molecular structure of the receptor proteins with which the drug molecules interact. This work, together with experimental studies of the physical and biochemical properties of water (for example, hydrogen bonding), led Inga Fischer to the licentiate degree (Swedish: Filosofie Licentiat) in chemistry in 1950.[2a,6]

QUANTUM CHEMISTRY

Inga's interest for the physical basis of chemistry was not satisfied by these experimental studies. While she was still working on her licentiate degree in chemistry, she began to study physics. After some time, she was offered part-time work as the assistant of Oskar Klein, who was then head of the department of theoretical physics at Stockholms Högskola. Klein collaborated with the department of zoophysiology, concerning the kinetic theory of certain biochemical reactions. Because the project was of a chemical nature, it was suitable for someone with Inga's background. In 1949, Inga Fischer defended her licentiate thesis in physics.[2a]

Just as before, Inga posed new and more profound questions about the molecules she was working with. She realized that a fundamental understanding of chemistry must be based on the physical laws governing the world of atoms, molecules, and the electrons within them. Quantum mechanics had by this time been in use for a couple of decades, but few applications addressing chemical problems had been made. Anyone familiar with Inga's previous studies and work was not surprised that this borderland between physics and chemistry became the area to which Inga Fischer devoted most of her working life. In her own words:

> *Due to my curiosity I wanted to know more about the molecules than what was being taught in chemistry...*[2b]
> *My interest in theoretical physics deepened. I wanted to apply quantum mechanics to the molecular problems I was investigating by experimental physical chemistry.*[2a]

Oskar Klein was now a valuable acquaintance for Inga. Klein was one of the world's leading theoretical physicists of his days and one of the pioneers in the development of quantum mechanics. He had a broad network of colleagues in the international physics community and actively collaborated with influential people such as Niels Bohr, Wolfgang Pauli, Paul A. M. Dirac, and Lise Meitner.

Klein sent Inga to a conference in Paris to find someone who could teach her more about molecular quantum mechanics, or quantum chemistry as it had already come to be known.[7] This was in the spring of 1948 and the first time for Inga to travel outside Scandinavia, which she later described as a very exciting event. In Paris, many of the leaders in quantum chemistry at the time gathered, including Linus Pauling, Robert S. Mulliken, Alberte and Bernard Pullman, and a young Englishman named Charles Coulson (Figure 3). During the conference, Inga Fischer was introduced to Charles Coulson, which resulted in Inga spending the winter of 1948−1949 doing research at King's College in London.[2a,b]

Figure 3. Attendees of a quantum chemistry conference in Paris 1948. Inga Fischer sits to the left in the front row, while Charles Coulson is standing to the right in the back row. Several prominent conference participants are sitting in the front row, such as Louis de Broglie (third from left), Chandrasekhara V. Raman (fourth from left), Robert Mulliken (fifth from left), and Linus Pauling (sixth from left). (From the book: *Selected Papers of Robert S. Mulliken*, University of Chicago Press, 1975.)

Charles Coulson and Inga Fischer made a rigorous investigation of the dissociation of the hydrogen molecule (H_2).[8a] To fully understand the impact of their work, it is necessary to briefly review some fundamental ideas in the history of quantum chemistry. When quantum mechanics was young, there was a debate on how the molecular wave function should be set up. Two, as it then seemed fundamentally different, approaches had been suggested; the valence bond (VB) method and the molecular orbital (MO) method.[8b]

In the VB method, the spatial part of the molecular wave function is set up as a linear combination of products of atomic

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orbitals. The notation $\varphi_a(1)$ means that electron 1 occupies an atomic (1s) orbital centered on nucleus a.

$$\Psi_{VB} = \varphi_a(1)\varphi_b(2) + \varphi_a(2)\varphi_b(1) \quad (1)$$

In the above eq 1, which is the (un-normalized) zero-order VB wave function for the hydrogen molecule, both terms are said to be *covalent*, since the electrons are located on different nuclei.

In the MO method, the spatial part of the molecular wave function is set up as a linear combination of products of molecular orbitals, which in turn are linear combinations of atomic orbitals. Here, the notation $\phi(1)$ means that electron 1 occupies the molecular orbital ϕ (conventionally denoted σ_g in the case of H_2), which is the linear combination of atomic (1s) orbitals $\varphi_a + \varphi_b$.

$$\begin{aligned}\Psi_{MO} &= \phi(1)\phi(2) + \phi(2)\phi(1)\\ &= [\varphi_a(1) + \varphi_b(1)][\varphi_a(2) + \varphi_b(2)] + [\varphi_a(2) + \varphi_b(2)]\\ &\quad [\varphi_a(1) + \varphi_b(1)]\\ &= \varphi_a(1)\varphi_a(2) + \varphi_a(1)\varphi_b(2) + \varphi_b(1)\varphi_a(2) + \varphi_b(1)\varphi_b(2)\\ &\quad + \varphi_a(2)\varphi_a(1) + \varphi_a(2)\varphi_b(1) + \varphi_b(2)\varphi_a(1) + \varphi_b(2)\varphi_b(1)\end{aligned} \quad (2)$$

This expression differs from the VB wave function (eq 1) as it contains so-called *ionic* terms, in which both electrons are located on the same nucleus (e.g., $\varphi_a(1)\varphi_a(2)$). A closer inspection of eq 2 shows that the MO wave function is 50% ionic and 50% covalent, in contrast to the VB wave function (eq 1), which is completely covalent. Neither the VB, nor the MO method, gives the exact energy. Nevertheless, both methods can easily be improved upon by adding configurations including orbitals of higher energy to the wave functions (configuration interaction).

Whereas the VB wave function is too much covalent at short internuclear distances, the most severe failure of the MO method is that the ionic character of the wave function of symmetric systems (e.g., the hydrogen molecule) remains even at large internuclear distances, when the system should dissociate homolytically into atomic hydrogen ($H_2 \rightarrow 2H^{\bullet}$). Inga Fischer and Charles Coulson solved these problems for the H_2 molecule by introducing two different spatial orbitals for the two electrons of different spin, $\varphi_a + \lambda\varphi_b$ and $\lambda\varphi_a + \varphi_b$. Insertion of these asymmetric orbitals into the MO wave function (eq 2) gives the Coulson–Fischer wave function.[8a]

$$\begin{aligned}\Psi_{CF} &= \phi(1)\phi(2) + \phi(2)\phi(1)\\ &= [\varphi_a(1) + \lambda\varphi_b(1)][\lambda\varphi_a(2) + \varphi_b(2)]\\ &\quad + [\varphi_a(2) + \lambda\varphi_b(2)][\lambda\varphi_a(1) + \varphi_b(1)]\\ &= (1 + \lambda^2)[\varphi_a(1)\varphi_b(2) + \varphi_b(1)\varphi_a(2)]\\ &\quad + 2\lambda[\varphi_a(1)\varphi_a(2) + \varphi_b(1)\varphi_b(2)]\end{aligned} \quad (3)$$

The covalent–ionic degree of this wave function can be determined by minimization of the energy with respect to the parameter λ (i.e., by using the variation theorem). The optimum value of the parameter λ depends on the internuclear distance. At the equilibrium geometry (d_{H-H} = 0.74 Å), λ becomes equal to one, meaning that the Coulson–Fischer wave function is identical to the MO wave function. At large internuclear distances, the optimum value of λ approaches zero, meaning that the two electrons are localized at different nuclei, as in the VB wave function.[8a]

This investigation showed that contemporary methods of quantum chemistry were severely limited in describing bond formation and dissociation and consequently also for determination of potential energy surfaces (PES) of chemical reactions. The paper pointed out which way the development of more accurate methods had to take, which a few years later resulted in the development of the unrestricted Hartree–Fock (UHF) formalism.[8c] Furthermore, this was one of the earliest papers showing that the VB and MO methods are two different approximations of the more general method of configuration interaction (CI). It seems fair to say that the Coulson–Fischer paper is a milestone in the development of quantum chemistry.[2c]

After her work with Coulson, Inga was well equipped to continue her research in quantum chemistry. She continued her earlier research on hydrogen bonding with a series of quantum chemical studies, and in 1952, she defended her doctoral thesis in theoretical physics with the title *Studies of the Hydrogen Bond and the Ortho-Effect*.[9a] The thesis was, and still is, unusual in that it contains experimental as well as theoretical work. At the dissertation, the third opponent was Stig Hjalmars, later to become professor in mechanics at the Royal Institute of Technology in Stockholm, who as his final question asked Inga to marry him! Inga's answer was positive and so she added Hjalmars to her name.[9b]

Inga became assistant professor (Swedish: Docent) at Stockholms Högskola and stayed there until 1959, when she was offered a professorship in mathematical physics at the Royal Institute of Technology (KTH). In 1963, she was appointed professor at Stockholm University and succeeded her mentor Oskar Klein. Thereby, Inga Fischer-Hjalmars became the first female professor in theoretical physics in Sweden. In 1978, she was elected a member of the Swedish Royal Academy of Sciences.[2a−c]

Among her more important contributions to our understanding of molecular quantum mechanics is an extensive study of the relatively complicated electronic structure of the ozone molecule (O_3).[10a−c] Inga performed calculations of configuration interaction type and for the first time the multiconfigurational nature of the ozone molecule wave function was shown.[2c] Most impressive, all integrals and MO coefficients were calculated using a desk calculator.[10c]

With time, Inga came back to what first led her into science: the molecular basis of biology. But there, quantum chemistry runs into problems: typical biomolecules are comparatively large, which makes quantum mechanical calculations complicated and computationally expensive. At best, quantum chemical methods scales with the number of electrons to the fourth power (i.e., the square of the square), meaning that each doubling of the number of electrons makes the calculation 16 times longer.

To tackle large systems with the limited computers available in the 1960s, Inga developed approximate methods based on parametrization and adaptation to empirical data.[6,11a−d] More precisely, she critically examined the foundation and justification of the zero differential overlap (ZDO) approximation and the Pariser–Parr–Pople (PPP) method.[11a,b] She found that it is possible to classify semiempirical approximations of the MO method by expanding the matrix elements in the overlap integral (S_{ij}) for nearest neighbor atoms in the molecule. This analysis showed that the Hückel method is

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correct to the first order in S_{ij}, while the PPP method is correct to the second order in S_{ij}. This insight was important for the further development of semiempirical methods and led to the reparametrization of the PPP method. Some of Inga's doctoral students, among them the renowned Swedish quantum chemist Björn Roos,[12] determined semiempirical parameters for organic π-electron systems containing various heteroatoms, for example, nitrogen, oxygen, sulfur, and halogens.[11c,d] These parameters were then used to calculate spectroscopic properties of bioorganic molecules such as porphyrins, purines, and pyrimidines.[6]

Another difficulty with biochemical systems is that they often contain ions of transition metals (e.g., copper and iron), which have complicated electronic structures. Inga's research group developed the semiempirical Peel method,[13a] which is a generalization of the PPP method that allows transition metals to be handled. A series of extensive studies of bonding, electronic structure, and spectra of biologically relevant metal complexes were made during the 70s and 80s.[6,13b−d] For this work, Inga Fischer-Hjalmars received the International Society of Quantum Biology Award in 1985.

As if Inga's scientific width already described was not enough, Inga and her husband Stig wrote several papers on solid-state physics. Their focus was the relation between microscopic and macroscopic properties of solids, exploring for instance the validity of the continuum description of discrete systems, such as molecular crystals. One can only speculate that Inga's motivation for this work was to get a better understanding for extended systems in chemistry, such as crystals and solutions, which were then difficult to handle in quantum chemistry.[6,14a,b]

HUMAN RIGHTS

Inga Fischer-Hjalmars was not only a scientist, but also a humanist of great proportions. During the 1970s she became aware of the difficult situation for oppositional and Jewish scientists in the Soviet Union.[15a] These people were not permitted to leave the Soviet Union, even if their application for an exit visa was for temporary reasons (e.g., to visit a relative or to attend a scientific conference) or if it was for permanent emigration to Israel. Not only were many applications for a visa rejected, in many cases the person who applied was dismissed from his or her university position and sometimes even evicted from the official residence bound to the job. In the worst cases, oppositional persons were imprisoned, locked up in mental hospitals, or just disappeared.

Inga's commitment to the rights of these so-called *refuseniks* was manifested in several ways. Some of the scientists who lost their jobs arranged secret meetings of refuseniks and other oppositional scientists. Inga visited these meetings, gave lectures, and supported the refuseniks with scientific equipment and other supplies that were hard to get inside the Soviet Union.[15b,c] She also worked with diplomatic methods through organizations such as the International Council of Scientific Unions (ICSU) and the International Committee of Scientists for Soviet Refuseniks. Inga wrote letters to the editors of several journals, in which she revealed the abuses and urged the international scientific community to act.[15d,e] She wrote admonishing letters to the Soviet administration and on one occasion (a conference held in Canada in the late 1970s) she confronted the representatives of the Soviet Academy of Sciences, by reading out a list of names of scientists who had disappeared without a trace.[15c] Some of these persons were never found again. Clearly, Inga Fischer-Hjalmars was a fearless and courageous person. For this engagement, she was awarded the New York Academy of Science's Heinz R. Pagels Human Rights of Scientists Award in 1990.

Inga Fischer-Hjalmars died in 2008 but her scientific achievements live on in the tradition of applied quantum chemistry in Swedish universities and internationally. In 2009, the Swedish Chemical Society installed an annual award for the best doctoral thesis in theoretical chemistry in the name of Inga Fischer-Hjalmars.

ASSOCIATED CONTENT

Supporting Information

A complete list of Inga Fischer-Hjalmars's peer-reviewed scientific publications, technical reports, and popular scientific writings in English and Swedish. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Lindqvist, K.; Sundling, S. *Xylocain-en uppfinning-ett drama-en industri*; AB Astra PR och information, Stellan Ståls tryckerier AB: Stockholm, 1993. (b) Widmark, G. Xylocain, ett bedövningsmedel från K45. In *K45 Stockholms högskolas/universitets första egna byggnad på Kungstensgatan 45*; Hallberg, R., Ed.; Digaloo AB: Stockholm, 2008. (c) Bernholm, B. Deras jobb har lindrat smärtan för de flesta! *Expressen* (A Swedish news paper), April 7, 1973.

(2) (a) Fischer-Hjalmars, I. Woman Scientists in Sweden. In *Woman Scientists, The Road to Liberation*; Richter, D., Ed.; The Macmillan Press LTD: London; 1982. ISBN 0333324684. (b) Interview with Inga Fischer-Hjalmars made by Udo Anders in 1999. *Early Ideas in the History of Quantum Chemistry*, a Web site by Dr. Udo Anders. http://www.quantum-chemistry-history.com/Fi_Hjal1.htm (accessed Jul 2012). (c) Roos, B. *Theor. Chim. Acta* **1994**, *87*, 243−245.

(3) (a) Löfgren, N. *Studies of Local Anesthetics, Xylocaine—A new synthetic drug*, Doctoral Dissertation, Stockholms Högskola, Ivar Häggströms Boktryckeri AB, Stockholm, 1948. (b) Löfgren, N. M.; Lundquist, B. J. *Alkyl Glycinanilides*. US Patents 2 441 498, May 11, 1948. (c) Private communication between the author and Professor emeritus Gunnar Widmark (1921−2012) in September 2011. (d) Reilly, T. J. Preparation of Lidocaine. *J. Chem. Educ.* **1999**, *76*, 1557.

(4) (a) Ahlström, L.; Euler, H. V.; Fischer, I.; Hahn, L.; Högberg, B. Nukleoproteotide in normalen und cancerösen Zellen. II. Deoxyribonukleinsäuren. *Ark. Kemi Min. Geol.* **1945**, *20A* (15), 1−23. (b) Euler, H. V.; Fischer, I.; Hasselquist, H.; Jaarma, M. Stability of Isolated Cell Nuclei in Different Media. Enzyme Systems in Nuclei.

Ark. Kemi Min. Geol. **1945**, *21A* (12), 1−15. (c) Euler, H. V.; Fischer, I. Nukleoproteotide in normalen und cancerösen Zellen. III. Viskositätsstudien an gelösten Zellkernen und daraus isolierten Nukleoproteiden. *Ark. Kemi Min. Geol.* **1945**, *22A*, 1−23.

(5) (a) Löfgren, N.; Fischer, I. Studies on Local Anestethetics. III. The Inium Ion of Alkaloids and Synthetic Organic Bases as Pharmacodynamic Group. *Sven. Kem. Tid.* **1946**, *58*, 219−231. (b) Fischer, I. The Effect of Ortho-Substitution on the Dipole Moments of Aniline Derivatives. *Acta Chem. Scand.* **1950**, *4*, 1197−1205. (c) Fischer, I.; Löfgren, N. The Dipole Moments and the Ultraviolet Absorption Spectra of Xylocaine and Two Related Compounds. *Acta Chem. Scand.* **1950**, *4*, 1408−1412.

(6) Inga Fischer-Hjalmars's complete list of publications is given as Supporting Information.

(7) *La Liaison Chimique*, Paris, 12−16 April, 1948.

(8) (a) Coulson, C. A.; Fischer, I. Miss. Notes on the Molecular Orbital Treatment of the Hydrogen Molecule. *Phil. Mag.* **1949**, *40*, 386−393. (b) For detailed comparison of the VB and MO methods the author recommends Atkins, P. W. *Molecular Quantum Mechanics*; Oxford University Press: London, 1970, Coulson, C. A. *Valence*; Oxford University Press: London, 1951, or, Hoffmann, R.; Shaik, S.; Hiberty, P. C. A Conversation on VB vs MO Theory: A Never-Ending Rivality? *Acc. Chem. Res.* **2003**, *36*, 750−756. (c) Pople, J. A.; Nesbet, R. K. Self-consistent Orbitals for Radicals. *J. Chem. Phys.* **1954**, *22* (3), 571−572.

(9) (a) Fischer, I. Studies of the hydrogen bond and the *ortho*-effect. Inaugural dissertation for the degree of Doctor of Philosophy, Almquist & Wiksells Boktryckeri AB, Uppsala, 1952. (b) The proposal of the third opponent requires an explanation of the dissertation ceremony in Sweden in the 1950s. In total there were three opponents, of which two had the role of being factual and scientific opponents. The first opponent was appointed by the university, whereas the second opponent was chosen by the doctoral candidate. The role of the third opponent (chosen by the doctoral candidate) was highly informal. He or she was there to lighten up the mood, deliberately misunderstand the thesis, and to be playful. The grade was decided by an evaluation committee.

(10) (a) Fischer-Hjalmars, I. Theoretical Study of the Ozone Molecule. *J. Chem. Phys.* **1955**, *23*, 411. (b) Fischer-Hjalmars, I. Electronic Structure of Ozone. *Tex. J. Sci.* **1956**, *8*, 136−138. (c) Fischer-Hjalmars, I. The Electronic Structure of the Ozone Molecule. *Ark. Fysik* **1957**, *11*, 529−565.

(11) (a) Fischer-Hjalmars, I. Deduction of the Zero Differential Overlap Approximation from an Orthogonal Atomic Orbital Basis. *J. Chem. Phys.* **1965**, *42*, 1962−1972. (b) Fischer-Hjalmars, I. Connections between Current π-Electron Theories. *Theor. Chim. Acta* **1966**, *4*, 332−342. (c) Fischer-Hjalmars, I.; Grabe, B.; Roos, B.; Skancke, P. N.; Sundbom, M. Semiempirical Studies of Metal Complexes of Biological Importance. *Int. J. Quantum Chem.* **1967**, *1*, 233−246. (d) Fischer-Hjalmars, I.; Sundbom, M. Semi-empirical Parameters in π-Electron Systems. III. Heteroatomic Molecules Containing Nitrogen. *Acta Chem. Scand.* **1968**, *22*, 607−627.

(12) Siegbahn, P. E. M; Lind, R. Björn O. Roos: 1937−2010 Mentor, Colleague, Innovator. *Int. J. Quantum Chem.* **2011**, *111*, 3256−3259.

(13) (a) Fischer-Hjalmars, I.; Henriksson-Enflo, A. Peel, a Modified PPP-Method, Applied on the Spectra of Some Nucleic Acid Bases. *Int. J. Quantum Chem.* **1990**, *37*, 517−528. (b) Demouling, D.; Fischer-Hjalmars, I.; Henriksson-Enflo, A.; Pappas, J. A.; Sundbom, M. Quantum Chemical Aspects on Some Problems in Bioinorganic Chemistry. *Int. J. Quantum Chem.* **1977**, *12* (Suppl. 1), 351−369. (c) Fischer-Hjalmars, I.; Henriksson-Enflo, A. Metals in Biology: An Attempt at Classification. *Adv. Quantum Chem.* **1982**, *16*, 1−41. (d) Fischer-Hjalmars, I.; Holmgren, H.; Henriksson-Enflo, A. Oxidation State and the Chemical Bond in Metal-Organic Complexes. *J. Mol. Struct. (Theochem)* **1992**, *261*, 21−36.

(14) (a) Fischer-Hjalmars, I. On the Validity of the Continuum Description of Molecular Crystals. *Int. J. Eng. Sci.* **1981**, *19*, 1765−1773. (b) Brulin, O.; Fischer-Hjalmars, I.; Hjalmars, S. Continuum Equations Derived from an Orthotropic Polar Model of the Micro-Structure. *J. Tech. Phys.* **1988**, *29*, 19−27.

(15) (a) Professorn som kämpar för de glömda. *Judarna i Sovjet* (A Swedish news bulletin by the Swedish Committee for the Jews of the Soviet Union.), **1989**, Vol *4*, pp 1. (b) Fischer-Hjalmars, I.; Lebowitz, J. L. *Sixth International Conference in Collective Phenomena; Reports from the Moscow Refusnik Seminar*; Annals of the New York Academy of Sciences; New York Academy of Sciences: New York, 1985; Vol *452* (c) Personal communication with Dr. Olof G. Tandberg (a former international secretary of the Swedish Royal Academy of Science), 2011. (d) Fischer-Hjalmars, I. Letter to the editor: Freedom to meet—ICSU's stance. *Trends Biochem. Sci.* **1983**, *8*, 82. (e) Fischer-Hjalmars, I. Correspondence: Soviet refusniks. *Nature* **1989**, *337* (5), 10.