Jacobus Henricus van 't Hoff; Hundred Years of Impact on Stereochemistry in the Netherlands**

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The First Nobel Prize for Chemistry

There is no award in science that can compete with the Nobel Prize; an award announced in a call from Stockholm in the month of October. At this very moment a selected number of eminent and highly respected chemists are hopefully and wishfully waiting to have their name added to the impressive list of previous laureates. All other chemists are eager to know who will be honored for his or her outstanding contributions to chemistry this year. How different it was exactly a hundred years ago, when in October 1901, at the age of 48, the Dutch physical chemist Jacobus Henricus van 't Hoff (Figure 1) was named the first recipient of the Nobel Prize in chemistry in recognition of his discovery of the laws of chemical kinetics and the laws governing the osmotic pressure of solutions. Since awards gain significance in time, and that is certainly the case for the Nobel Prize, the first recipient certainly felt different from the laureate(s) of this year. Unfortunately, the feelings of Van 't Hoff in October of 1901, as compared to those of this years recipient(s), will remain within the realm of imagination.

Jacobus Henricus van 't Hoff,[1] at that time Professor in Berlin, was highly respected within the chemical community for bringing physics and chemistry together (physicam chemiae adiunxit). However, this was only two decades after he was highly criticized for his ideas on stereochemistry and only one decade after his colleagues disagreed with him on the theory of dilute solutions. At the time he introduced the concept of tetrahedral carbon he was a 22-year-old physical chemist at Utrecht, and the major opposition to the three-dimensional arrangements of atoms in a molecule came from organic chemists from Germany. In 1895, he moved from the Netherlands to Germany, initiated by Max Planck. Without doubt every modern chemist agrees that Van 't Hoff fully deserved the Nobel Prize, although many of them will connect Van 't Hoff's name more to stereochemistry than to the awarded science on chemical kinetics or osmotic pressure, despite the existence of the Van 't Hoff factor *i* for the osmotic pressure of electrolytes.

Figure 1. Jacobus Henricus van 't Hoff (1852–1911) (with permission of the Boerhaave Museum, Leiden).

In this essay, a short description of the first chemistry Nobel laureate and his chemistry is given.[2] Although Van 't Hoff is one of those unique scientists who inspired almost all chemists, his impact on the stereochemistry as performed at universities in the Netherlands is unparalleled. Therefore, this essay will also highlight some of the other achievements in stereochemistry following the hundred years after Van 't Hoff's Nobel Prize and will conclude by showing some prospects for future stereochemical research within supramolecular chemistry; an area of intense research in the Netherlands. It is with the deepest respect that I take the liberty of addressing parts of the work of Van 't Hoff and its impact on the stereochemistry in the Netherlands;[3] the more I read about his achievements, the more I am impressed by the brilliance of his ideas and the more I realize the insignificance of our own small contributions in comparison.

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Jacobus Henricus van 't Hoff (1852–1911)

Jacobus Henricus van 't Hoff was born in Rotterdam on August 30, 1852 as the third child of Alida Jacoba Kolff and Jacobus Henricus van 't Hoff. He was one of the first students that attended a new type of high school (HBS: Hoogere Burger School; Figure 2) that was initiated to educate young people to become businessmen of small enterprises. Strangely, he did not go to the Gymnasium, which prepared students for study at a university. His teachers at the HBS stimulated his interest in chemistry, and consequently he started his study of chemical technology in Delft; however, he was much more interested in chemistry than in technology. Therefore, he moved to the University of Leiden for which he needed special permission from the Minister of Domestic Affairs. It is probably fair to say that he received his true training and passion for science in the laboratories of August Kekulé in Germany and Adolphe Wurtz in France. His stay in Paris, where he met Joseph-Achille le Bel and where the ideas of Louis Pasteur on optical activity were all around, should have given him the ideal opportunity to get his creative ideas on stereochemistry and the tetrahedral arrangement of carbon to explain the experiments of Pasteur (Figure 3). The results were disclosed in "*La Chimie dans l'Espace*" in 1875 (Figure 4).[4] The same environment brought le Bel almost simultaneously to similar ideas.

Figure 2. A statute of van 't Hoff in front of his former high school the Hoogere Burger School in Rotterdam, where he received his degree in 1869 (with permission of the KNCV).

Jacobus Henricus van 't Hoff

1852	*born in Rotterdam*
1869–1871	*studied engineering at Technical Highschool of Delft*
1871–1872	*studied chemistry (Bachelor) at the University of Leiden*
1872–1873	*student with August Kekulé in Bonn*
1873	*studied chemistry (Masters) at the University of Utrecht*
1874	*worked with Adolphe Wurtz in Paris* *wrote his essay on stereochemistry* *received his PhD degree at the University of Utrecht*
1874–1876	*private teacher doing laboratory experiments in his free time*
1876–1877	*assistant at the Veterinary College in Utrecht*
1877–1878	*Lecturer at the University of Amsterdam*
1878–1895	*Professor of Chemistry at the University of Amsterdam*
1895–1911	*Professor at the University of Berlin*
1901	*Nobel Prize for Chemistry*
1911	*died of lung tuberculosis*

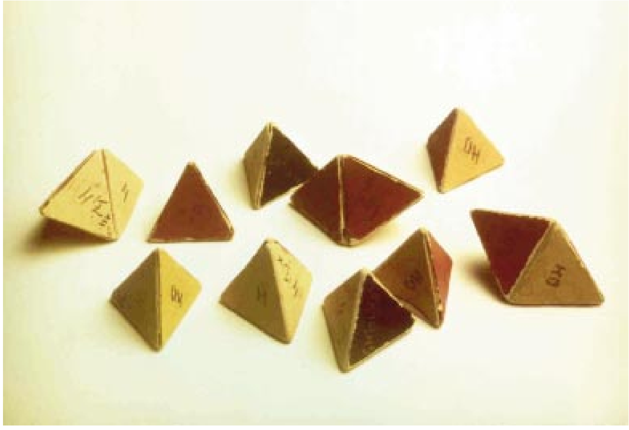


Figure 3. Ten models of asymmetric molecules made by van 't Hoff for his friend G. J. W. Bremer. The latter used these in his thesis in 1875. The original models are at the Boerhaave Museum in Leiden (with permission of the Boerhaave Museum).

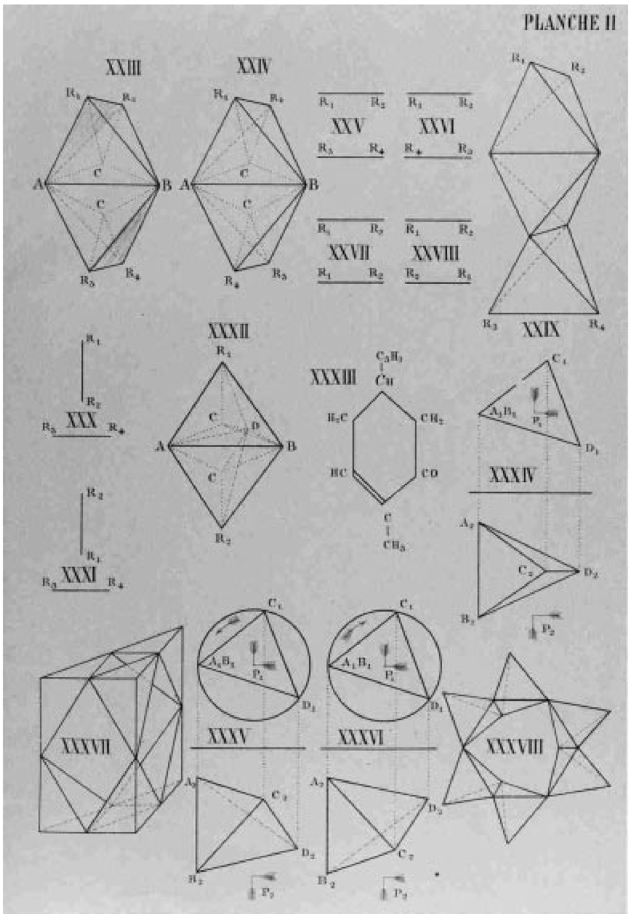


Figure 4. Van 't Hoff's theories as published in *La chimie dans l'éspace* (with permission of the Boerhaave Museum).

Van 't Hoff received his PhD at the University of Utrecht in 1874 for a thesis on cyanoacetic acid and malonic acid. After defending his thesis, he unsuccessfully tried to get a job as a high-school teacher and thus gave lessons on a private basis to earn some money. In 1876 he was appointed as an assistant at the Veterinary College in Utrecht, the place that became famous due to Kolbe's attacks on him (see box).

Young versus Established

The stereochemical ideas about the three-dimensional arrangements of atoms within molecules were made by a 22-year-old Van 't Hoff. With this concept, he could explain the experiments of, the also very young, Pasteur on tartaric acid. Not everyone, and especially the established chemists, agreed with the proposal of Van 't Hoff on stereochemistry, as was expressed by the famous German professor Hermann Kolbe in 1877:[26]

In his opinion the lack of general education and of thorough training in chemistry was one of the causes of the deterioration of chemical research in Germany. He then went on to add that if anyone felt his worries were exaggerated then they should read, if they could, a recent memoir by Van 't Hoff on The Arrangements of Atoms in Space, a document that he felt was crammed to the hilt with the outpourings of a childish fantasy. He went on point out that this dr. J. H. van 't Hoff, who was employed at the Veterinary College at Utrecht, had, it seemed, no taste for accurate chemical research and found it more convenient to mount his Pegasus (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in space.

When in 1877 the Amsterdam Athenaeum became the University of Amsterdam, he was asked by J. W. Gunning to become a lecturer in theoretical and physical chemistry. Not long thereafter, he accepted the full chair of chemistry, mineralogy, and geology at the same university on October 11, 1878 with his inaugural lecture that was entitled: "De Verbeeldingskracht in de Wetenschap", meaning "The imagination in Science", a title that is still relevant today. In this lecture he discussed in detail the many attacks by the German chemist Hermann Kolbe and stressed the importance of imagination together with observation. The Amsterdam period, was by far his most original period in terms of the chemistry, for which he later won the Nobel Prize, and for which he became world famous. An offer from the University of Leipzig in 1887 was rejected, and as a result the city of Amsterdam built a new laboratory for him at the Roetersstraat. The University of Amsterdam later honored their former professor by naming the Physical Chemistry Department the "Van 't Hoff Laboratories". However, at that time Van 't Hoff often mentioned the problem of his many duties as teacher and organizer of the laboratories. In 1895, he was visited by Max Planck and accepted an offer to become a member of the "Königlich Preußische Akademie der Wissenschaften" in Berlin. In 1896 he also became a professor at the University of Berlin. He received his own laboratory and had only one hour of teaching duties a week. He dedicated his time fully to science and in 1901 he received the first Nobel Prize for Chemistry. Van 't Hoff died of lung tuberculosis on March 1, 1911.

Physicam Chemiae Adiunxit

Although science progresses with an ever-increasing speed, some issues are time insensitive and the early introduction of those issues is given to the true masters of science only. Connecting physics and chemistry (Physicam Chemiae Adiunxit) was the inscription on a sculpture given to J. H. van 't Hoff by his (former) students from the University of Amsterdam in 1889. It not only nicely shows their appreciation for his elegant way of bringing physical theories within the realm of chemistry; it also illustrates the scientific time insensitivity. It is less than two years ago that Angewandte Chemie launched successfully the new Journal ChemPhysChem, which has grown to become a highly appreciated forum for publishing science that brings physics and chemistry together. The title "De Verbeeldingskracht in de Wetenschap", meaning "The imagination in Science", of Van 't Hoff's inaugural lecture at the same University, offers another way to learn about the modern ideas from Van 't Hoff at that time. He was arguing, as a defence against the attacks of Kolbe, that next to observations it is useful to use your imagination. The third and last example of time insensitivity based on studying the history of Van 't Hoff, can be found in his struggle with the board of the city of Amsterdam. He was not only asking for more money to get a perfect infrastructure for science, he also argued that there should be places at Universities where scientists could dedicate most of their time to science and where they were not fully occupied by teaching and administrative duties. This passion brought him to Germany in 1895.

The award-winning chemistry (1872–1901)

Although every textbook on organic chemistry will highlight Van 't Hoff's contributions to the understanding of stereochemistry, the Nobel committee honored Van 't Hoff's work in the area of physical chemistry in general. Details of the work for which the award was received can be found in three seminal contributions, from which I would like to highlight only a few aspects. In 1884 the dynamics of chemical reactions were disclosed in a remarkable book entitled "*Etudes de dynamique chimique*", published in Amsterdam.[5] He was interested in linking the chemical constitution of molecules to their properties and in giving organic chemistry a physical and/or mathematical foundation. He describes the notion that molecules with oxygen atoms react faster than molecules without oxygen, for example the oxidation of methanol is faster than that of methane. The serendipitous finding that 2,3-dibromosuccinic acid decomposes at 100 °C into hydrogen bromide and bromomaleic acid was used to follow the formation of hydrogen bromide with time. With these kinetic measurements he found that the reaction was unimolecular. As an example of a bimolecular reaction he studied the hydrolyis of the sodium salt of chloroacetic acid. Based on the temperature dependency of both reactions, he deduced the now well-known thermodynamic relationship between the absolute temperature T and the rate constant k in which A and B are temperature independent factors [Eq. (1)].

$$\mathrm{d}\ln k/\mathrm{d}T = A/T^2 + B \tag{1}$$

A is that which later was denoted to as E_a/R, the quotient from the activation energy and the gas constant. In the second part of his *Etudes*, he discussed the issue of chemical equilibrium and introduced the double arrow to denote an equilibrium. In the last part of the *Etudes*, he discussed the affinity of chemical compounds. All in all, the *Etudes* were fundamental for a completely new field at that time: chemical dynamics.

After the completion of the *Etudes de dynamique chimique*, he studied the theory of dilute solution. As Professor Snelders mentioned in his book on the history of science in the Netherlands,[2] he used his 1884 summer vacation with his wife and three children in Hilversum for performing this study. The results were disclosed in three articles that were published in 1886. The full text can be found in "*Kongliga Svenska Vetenskaps-Akademiens Handlingar*";[6] please remember that at that time there was no reason what so ever to show your qualities as a scientist to the Swedisch Academy. However, again according to Professor Snelders' analysis, he thought that the Norwegian scientists Guldberg and Waage, who did earlier seminal work in the field, were from Sweden and to honor them he submitted its manuscripts to Sweden. It is an interesting question whether this mistake helped him to receive the first Nobel Prize for Chemistry. Anyhow, the major contribution mentioned in the articles relates to the, as it is know now, Van 't Hoff factor i. Since the osmotic pressures of electrolytes were always higher than predicted by the equations used to that time, sometimes with a factor of two or three, he modified the equation as shown in Equation (2).

$$\Pi = icRT \tag{2}$$

With the correction factor i Van 't Hoff was able to get theoretical and experimental results to agree. Using four different techniques, he started to establish the value of the factor; all of the measurements are important ingredients for fundamental studies of osmotic pressures.

Finally, Van 't Hoff was actively involved in explaining the findings made by Arrhenius on the conductivities of electrolytes in water.[7] The anomalies found in Arrhenius' experiments were attributable to electrolytic dissociation. Together with Wilhelm Ostwald he founded the "*Zeitschrift für Physikalische Chemie*" in 1887 and the work describing the reason for the fact that not all species contributed to the conductivity at high concentrations was published there in the first year of issue.[8] Together with the theories of Arrhenius, his work initiated another way of thinking about chemical reactivities. Both theories were in contrast with the general ideas at that time and it took some years before the scientific community accepted them.

Chemistry in the Netherlands (1901–1945)

The move made by Van 't Hoff from Amsterdam to Berlin was logical for that period of time and was illustrative for the leading position of Germany in science. In the Netherlands, chemistry became a subject taken seriously at Universities and in 1903 the Royal Dutch Chemical Society was founded. Most, if not all, of the important work that was performed in the Netherlands was published in the *Recueil des travaux chimiques des Pays-Bas.* Major activities at the time were related to synthetic organic chemistry, primarily due to the industrial relevance of the work, and stereochemistry was not an issue of serious investigation. However, the pioneering work of Professor Jacob Böeseken (1868–1949) in Delft, on what was later called conformational analysis, is worth mentioning in connection with Van 't Hoff's stereochemical interest.[9] Böeseken also studied *cis*- and *trans*-cyclopentanediol; the latter could be resolved in its two enantiomers in contrast to the *cis*-isomer. During World War II the scientific activities slowed down considerably at Dutch universities and for those interested in details, I would like to refer you to an excellent report published 1947.[10]

The Dutch stereochemistry schools (1945–1985)

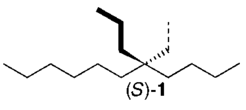
Owing to the high impact of scientific and technological findings for the outcome of World War II, an immense expansion of academic activities was observed throughout the world in the period after 1945. A similar trend was observed within the Netherlands and in addition major Dutch industrial laboratories started fundamental research projects. This was the start of an active collaboration between academia and industry as well as an exchange of scientists; a relationship that remained fruitful through the years and probably was the basis for the current status of Dutch chemistry. The impact of Van 't Hoff for Dutch science is illustrated below with a short description of three selected examples from the period 1945–1985 with stereochemical topics as a lead.

To honor the contributions to science by one of their former students, the University of Utrecht also named their Laboratory for Physical Chemistry after Van 't Hoff. In the period after the war Professor Johannes Martinus Bijvoet (1892–1980) was the director of this laboratory. He performed with his co-workers Peereboom and Van Bommel one of the most critical experiments in the field of stereochemistry.[11] Using anomalous scattering in X-ray diffraction they were able to determine the absolute configuration of sodium rubidium tartrate, and thereby show that M. A. Rosanoff of New York University in 1906 made the correct choice, or better guess, for the assignment of the configuration of (+)-glyceraldehyde. As a result it was not necessary to change the assignments of all stereoisomers published prior to that date. This landmark experiment was published in 1951, exactly 50 years ago, and will be the topic of an upcoming essay in *Angewandte Chemie* by Professor Jack Dunitz.[12] The Van 't Hoff Laboratories still exists at Utrecht.

In Leiden, Professor Egbert Havinga (1909–1988) was appointed as Professor of Organic Chemistry in 1945. He excelled in many aspects of physical organic chemistry, including photochemistry and stereochemistry. He created the Leiden school of Organic Chemistry, and for many reasons it is appropriate to see him as one of the successors in the Van't Hoff tradition. His many contributions have attracted high international recognition. His work started with the conformational analysis of cyclohexane derivatives, and inspired by the photochemical synthesis of vitamin D he explored the many theoretical issues of the stereochemistry of the electrocyclic ring closures of 6π-electron systems. He formed a very successful partnership with Professor L. J. Oosterhoff (1907–1974), a theoretical organic chemist. One of the most intriguing results of their collaboration was published in *Tetrahedron* in 1961.[13] In a study on the specificities of the photochemical and thermal transformations in the vitamin D field, they discussed the difference in pathways observed. In addition to a number of possible causes, they mention the thoughts of Professor Oosterhoff: "*As Prof. Oosterhoff pointed out, another factor that possibly contributes to the stereochemical difference between the thermal and photo induced ring closure may be found in the symmetry characteristics of the highest occupied* π*-orbital of the conjugated hexatriene system. In the photo-excited state, the highest occupied orbital is antisymmetric with regard to the plane that is perpendicular to the bond 6,7 making ”syn“ approach less favourable.*" This conservation of orbital symmetry approach was later followed by the well-known work of Woodward and Hoffmann, who in their first article on this topic in 1965 note the important role of Havinga and Oosterhoff: "*Professor Oosterhoff (Leiden) clearly deserves credit for having first put forward the suggestion that orbital symmetries might play a role in determining the course of the stereochemical phenomena attendant upon triene cyclization (private communication to prof. Havinga). The suggestion was described so succinctly that it has received no currency, and it has been not generalized to include other cases*".[14] Why the Leiden team did not give their initial thoughts more attention remains unclear, although it is argued that Oosterhoff did not like the approximations made in the one-electron model and was pursuing a more general explanation using valence bond theory.

Professor Havinga was able to organize a Fulbright fellowship to get Hans Wynberg back to the Netherlands as a visiting scientist in Leiden in 1959. In 1961 Wynberg was appointed as Professor of Organic Chemistry in Groningen where he established one of the most successful schools of modern stereochemistry in the Netherlands. He continued the Van't Hoff style of combining careful observations with sparkling imagination. Hans Wynberg was the first scientist who used chiral phase-transfer reagents based on quinine to perform catalytic asymmetric synthesis, while he also studied the optical activity in bio- and chemiluminescence in collaboration with students from the Leiden school.

One of Wynberg's benchmark experiments, being part of many textbooks of organic chemistry, concerned the optical inactivity of an enantiomerically pure branched alkane (*S*)-**1**.[15] The lack of optical transitions in the UV/Vis region and the high degree of flexibility of (*S*)-**1** was argued to be the reason for this unconventional behavior. This experiment was obviously connected with the seminal work of Van't Hoff. In recent years, and long-after his formal retirement, Professor Wynberg and his co-workers of his contract research company Syncom introduced the Dutch resolution technique; a methodology in which combinatorial approaches are used to speed up the discovery of successful combinations in the selective crystallization of diastereoisomers, leading to a quick access to enantiomerically pure compounds.[16] Moreover, many students from Hans Wynberg have taken up academic positions and continued his tradition in modern stereochemistry.



(*S*)-**1**

The present and future of Dutch stereochemistry (from 1985)

For a variety of reasons Dutch chemists love to work on issues related to stereochemistry. Obviously, most of these reasons are similar to those well known to all of us, but the tradition set by Van't Hoff and the excellent teachers in stereochemistry in the period after Van't Hoff have provided great inspiration to study stereochemical topics in the Netherlands. In the final section of this Essay, I would like to show some of the many possibilities of stereochemistry in combination with supramolecular chemistry, a topic of great interest at present within the Netherlands. With the increasing complexity of molecular structures and supramolecular assemblies, the intriguing issues of the origin of life and the importance of the interaction of light with matter, it is highly attractive to introduce stereochemical subtleties within supramolecular research topics.

Professor David N. Reinhoudt (University of Twente) initiated activities into Supramolecular chemistry in the Low Countries, these were followed by major activities in Nijmegen, Groningen, and Eindhoven. Directly after the discovery of the crown ethers and their ability to complex cations, David Reinhoudt, at the time at the Royal Shell Laboratories in Amsterdam, started the exploration of this class of new compounds. After his move to Twente, he extended his activities to a large variety of systems, from which building blocks for nanotechnology have now been developed.[17] Recently his group showed that it is possible to make enantiomerically pure supramolecular objects of nanometer dimensions without using chiral molecules using a so-called memory effect.[18] With the successful application of surface chemistry and micro/nano-manipulation techniques, the work from his group is of prime importance for the progress in the area of nanotechnology in general and hopefully that of chiral nanotechnology in particular.

Roeland J. M. Nolte made his entrée in stereochemistry, after obtaining a PhD degree from Utrecht with Professor Wiendelt Drent, with the synthesis and characterization of chiral polyisocyanides.[19] The synthesis of polymers with one handedness, the study of their stability with respect to atropisomerization, and a postdoctoral stay with the late Professor Donald Cram (Los Angeles), inspired Roeland Nolte to start his own group in supramolecular chemistry at the University of Nijmegen. Seminal contributions to supramolecular catalysis, chiral supramolecular assemblies based on phthalocyanines (Figure 5),[20] and more recently chiral superamphiphilic structures have made him one of the leading

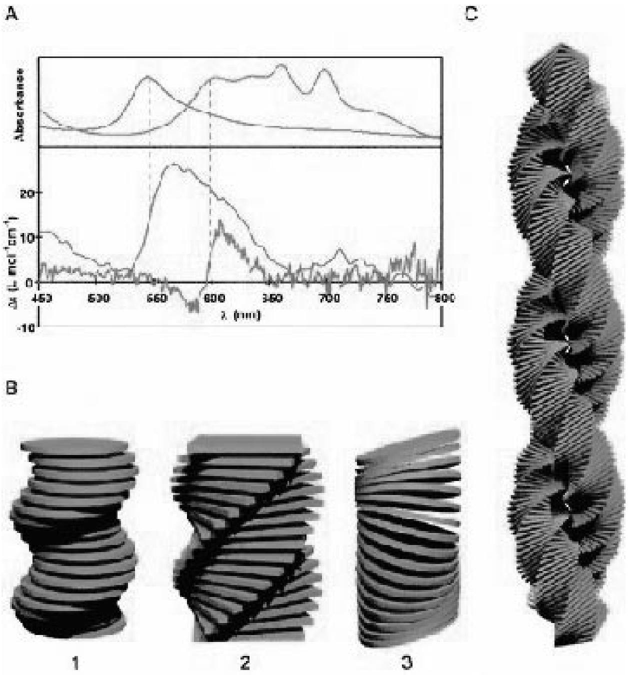


Figure 5. Supramolecular chirality by the self-assembly of chiral phthalocyanines (with permission from ref. [20]).

scientists in the field of supramolecular chemistry.[21] His physical organic background has enabled him to make detailed studies of the aggregation of self-assembling molecules and by using a variety of microscopic techniques the Nolte group have been able to visualize the structures proposed.[22] His recent work is now directed to the incorporation of biomacromolecules in supramolecular systems, leading to an area of hybrid systems with unexplored chemistry.

Ben L. Feringa moved after his PhD with Hans Wynberg to the Royal Shell Laboratories and returned to his alma mater as a professor. As the successor of Wynberg, he not only continued the tradition of stereochemistry in Groningen, but he also broadened the scope of the research significantly. Seminal experiments were performed with chiroptical switches and molecular rotors, based on chiral twisted olefins. As a result of the photochemical isomerization of this twisted double bond, the Feringa group has been able to bias the induced chirality of a liquid crystalline matrix, leading to a molecular switch.[23] The same isomerization, followed by an irreversible ring flip leads to a light-driven monodirectional rotary motion.[24] The group of Feringa is also actively involved in asymmetric synthesis using a variety of new chiral catalytic systems and, therefore, he is successfully combining advanced synthesis with novel stereochemical concepts.[25] In the future developments of molecular motors, switches, and machines, his group will certainly be at the forefront of this discipline.

It is now tempting to end this Essay with a short resume of my own activities in stereochemical issues; an interest that was initiated during my PhD research with Hans Wynberg. However, it is more appropriate to end with the lessons learned from Van't Hoff.

What can we learn from Van't Hoff

It is without doubt that many of the ideas of the current and future generation of chemists in the world are and will be guided by the seminal science of the first Nobel laureate in chemistry, who received this accolade exactly one hundred years ago. Jacobus Henricus van't Hoff was one of the greatest chemical thinkers of his generation and he showed us that imagination is as important in science as observation. It is also not necessary that your scientific community directly agrees with your ideas. This is nicely illustrated with the only other Dutch winner of the Nobel Prize in Chemistry (1995), Professor Paul Crutzen, who likewise was also employed in Germany at the time he received his call from Stockholm. The impact of his research on the chemistry and its effects to the ozone layer was not recognized from the beginning.

Finally, for all of us who believe that it was much easier to establish breakthroughs in chemistry hundred years ago, they should just use their own imagination and focus on the many challenges given to us by the progress in the experimental techniques. In front of us, we can foresee a successful merging of physics, chemistry, and biology leading to a complete understanding of natural processes and to the challenge of the production of artificial systems that can perform complex tasks. If I could have a look in the future for just one second, I would love to see for what scientific breakthrough the Nobel Prizes in sciences were awarded for in the year 2101; a hundred years from now.

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