

Halogen Bonding: An Odd Chemistry?

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Abstract: Halogen bonding is a flourishing field of research, but has for long been little recognized. The same goes for its scientific hero, Odd Hassel, who laid the foundations for all current developments. The crystallographic observation of halogen–oxygen interatomic distances shorter than the sum of the van der Waals radii of the involved atoms, and the interpretation of this phenomenon as a charge-transfer interaction, have been ground-breaking. Today, charge-transfer to a polarized halogen is not any longer seen as “odd”, but is commonly referred to as halogen bonding, and is widely exploited in chemistry. Despite the recognition of Hassel’s work with a Nobel prize in 1969, surprisingly little appreciation is given to date to the devoted scientist, who established a world-leading laboratory during one of the darkest eras of history. Herein, we wish to revive the legacy and highlight the impact of Odd Hassel’s ground-breaking discoveries.

Keywords: Odd Hassel, charge-transfer, halogen bond, X-ray, halonium

1. Nobel Prize from Kitchen Tables and Test Tubes

The Nobel Prize in chemistry in 1969 was awarded to Sir Derek Barton and Odd Hassel “for their contributions to the development of the concept of conformation and its application in chemistry.”^[1] Whereas Barton remains widely remembered,^[2] Hassel is rather overlooked and is, for instance, barely mentioned in textbooks. He was recognized by the Nobel committee for his early experimental work on the *chair*-like

conformation of cyclohexane, which he published in a Norwegian journal in 1943 during World War II.^[3] Although the importance of conformational analysis in chemistry and related fields is immense, his later work on weak chemical bonds may be seen as even more impactful. In this *essay*, we intend to revive the legacy of Odd Hassel and emphasize the importance of his discoveries, particularly for the field of halogen bonding.

Hassel became the first professor of physical chemistry in Norway in 1934.^[4] He led the newly formed Department of Chemistry at the University of Oslo, a small university at the periphery of Europe, where he initiated his studies and received a B.Sc. in chemistry in 1920. Subsequently, he spent a year in France and Italy studying theoretical physics, but returned to chemistry to work with organic dyes in the laboratory of Kasimir Fajans in Munich for 6 months. Here he discovered an indicator for analytical determination of silver ions which later became widely used (Fajans’ indicator), although his intellectual contribution to the discovery was not much acknowledged by Fajans: “(...) *the assistant wasn’t very bright and had no idea of what happened*”.^[5] Having studied chemistry in Germany for a number of years, most notably at the *Kaiser Wilhelm Institute für Faserstoffchemie* in Berlin-Dahlem, where he worked with X-ray crystallography, Hassel

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was highly skilled. Supported by a Rockefeller Scholarship, he achieved his doctoral degree at the *Friedrich-Wilhelms-Universität* in Berlin in 1924, with the famous Fritz Haber (1918 Nobel Prize) as one of his PhD-opponents. He returned to Oslo in 1925 and became affiliated with the university as a *docent*, initially focusing his work on inorganic chemistry. His interest in the three-dimensional structure of organic molecules was raised around 1930. He visited IG Farben, a German company, in 1930 to learn gas-phase electron diffraction, and would become a major contributor to the application of electron diffraction techniques for structure elucidation of both organic and inorganic compounds.^[7] Covering the costs privately, he purchased his first electron diffraction apparatus in 1934; however, this instrument was unable to hold the vacuum necessary for the planned measurements. Therefore, together with his co-workers he built his own instrument, making use, for instance, of a kitchen table, test tubes and anything that fit the purpose (Figure 1). This allowed him to initiate his ground-breaking experiments in the autumn of 1940. Much of his crucial work was published in Norwegian in a Norwegian journal. The first key publication describing the chair structure of cyclohexane, he published in the Norwegian journal *Tidsskrift for kjemi, bergvesen og metallurgi* ("Journal of chemistry, mining, and metallurgy") in 1943,^[3] which was neither easily accessible nor well-known internationally. Hassel was outspoken and profoundly in opposition



Figure 1. Left: Odd Hassel smoking a pipe at Blindern campus, Oslo. Right: Gas-phase electron diffraction apparatus constructed by Hassel and co-workers. Photographers: *unknown*.^[6]

to the Nazi occupation of Norway, which had begun in April 1940, around the same time his first gas-phase diffraction instrument became operational. His preference for Norwegian instead of the internationally better recognized German journals, despite his language skills and excellent scientific contacts with German scientists, could be interpreted as a way to express his political views. In 1943, shortly after the publication of his famous paper on the conformation of



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Máté Erdélyi graduated at Semmelweis University, and obtained PhD in organic chemistry at Uppsala University. Following postdoctoral research in physical organic chemistry at UCSD, in NMR spectroscopy and structural biology at the Max Planck Institute for Biophysical Chemistry, he initiated his independent research at the University of Gothenburg. Year 2017 he moved to Uppsala University. His research focuses on halogen bonding, NMR method development, natural product and medicinal chemistry.

cyclohexane,^[3] Hassel and a number of other intellectuals were arrested and transferred to the Grini prison camp. It is said that he spent much of his time at Grini teaching chemistry to his fellow inmates. He was released in November 1944 to return to an almost deserted department at the university. Hassel took up the experimental work again and completed the studies of cyclohexane in 1947.

In his Nobel lecture, which one could have expected to be focused on cyclohexane and conformation, Hassel mostly discussed intermolecular interactions.^[1] His discoveries were well ahead of their time and received little to no attention for decades. As the understanding and exploitation of weak chemical forces are becoming crucial aspects of contemporary chemistry, the interest in Hassel's work on the charge-transfer complexes of halogens has grown. This is well-reflected by the number of citations of his famous paper entitled "*Structural aspects of interatomic charge-transfer bonding*" in *Science* (1970)^[8] growing from 0 in 1999 to 84 in 2010, and 356 in 2021. In the past decade, Hassel's contribution to the field has become more evident. His work is fundamental, and we highlight its importance in more detail herein.

2. The Discovery of Charge-Transfer Complexes

Understanding the basic principles of the processes leading to the formation of intermolecular complexes has been a long-standing challenge. Triggered by exciting results of spectroscopic investigations, a general interest in molecular interactions in liquid systems was on the rise in the 1940s. These studies revealed "donor-acceptor" interactions that were explained by the charge-transfer (CT) theory formulated by Mulliken in the 1950s.^[9] This rather general explanation of spectroscopic observations intrigued Hassel, as the reliable detection of atomic arrangements within such charge-transfer complexes remained elusive. The accurate determination of molecular geometries became feasible first when X-ray diffraction methods became available. In the early 1950s, Hassel, who had received training in these techniques during his stay in Berlin, started X-ray crystallographic investigations of charge-transfer complexes.^[8] The structures he obtained and interpreted laid the foundations of our understanding of halogen bonded complexes, and continue to inspire scientists worldwide.

In the early 1900s, charge-transfer was generally accepted to result from the transfer of negative electronic charge from a donor (Lewis base) to an acceptor (Lewis acid). Among the electron donors, those containing lone pairs of electrons, such as oxygen, nitrogen and sulfur, were of high interest. Hassel took a closer look at these types of systems, and investigated intermolecular charge-transfer complexes of molecules capable of donating a non-bonding electron pair and halogens, or

halogen-containing molecules. The architecture of donor-acceptor complexes could not be confidently determined in liquid systems. Therefore, Hassel performed a systematic X-ray crystallographic work to gain understanding of the basic principles of charge-transfer interactions. As the structures of highest interest were comparatively unstable, moisture sensitive or displayed low melting points, he faced significant experimental challenges. Nevertheless, despite the possible uncertainties due to the limitations of the research methods that were available at the time, he hoped that his results could be sufficient to facilitate theoretical investigations of the nature of these interactions, and give new insights into the forces present in the corresponding liquid systems.^[10]

Hassel published a striking crystal structure of an endless chain of alternating 1,4-dioxane and bromine molecules (Figure 2) in the early 1950s.^[11] This is the first ever reported crystal structure of a halogen-bonded complex, and probably the most famous of the structures that have been solved by Hassel.^[12] The observation of bromine molecules bridging electron donor moieties was unexpected as this contradicted the assumption that both halogen atoms of the bridging Br₂ could not simultaneously bind electron donors, as such bonds increase the negative charge. Nevertheless, the observations of the structural features and the general conclusions made by Hassel are still valid and, provide to date an explanation for the existence of halogen bond complexes.

Despite the limitations of accuracy of the X-ray diffraction measurements in the 1950s, the distances and bond angles of Hassel's bromine-dioxane adduct were reported with sufficient accuracy to allow general conclusions to be drawn about the structures of charge-transfer complexes.^[11] The distance between the oxygen and bromine atoms was reported to be 2.71 Å, which is shorter than the sum of the respective van der Waals radii confirming the formation of (halogen) bonds. The

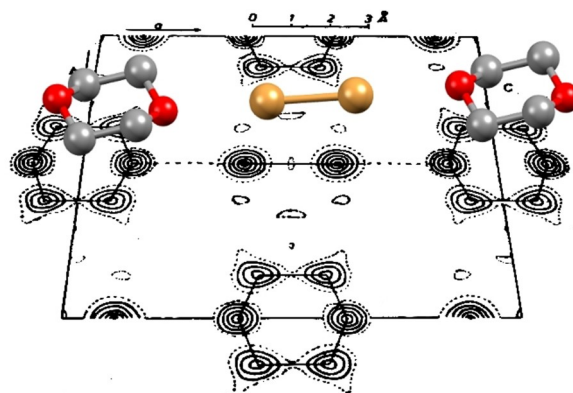


Figure 2. The famous X-ray structure of the 1:1 adduct of 1,4-dioxane and bromine, as reported by Odd Hassel in 1954, overlaid with the corresponding diffraction pattern. Oxygen are shown in red, bromine in yellow and carbons in grey.

noticeable lengthening of the intramolecular bromine–bromine bond, from 2.28 to 2.31 Å, was concluded to result from the charge-transfer interaction of 1,4-dioxane and bromine. Similar structural features were also observed for the corresponding chlorine-1,4-dioxane adduct. The chlorine–oxygen distance (2.76 Å) was reported to be shorter than the sum of the corresponding van der Waals radii, and a small increase, 1.99 Å to 2.02 Å, was observed for the chlorine–chlorine bond.^[13] The O–Cl–Cl bond angle was reported to be 178°. Upon comparison of these structures, Hassel drew some, still valid, general conclusions about the complexes of halogens and Lewis bases: (i) as compared to “free” halogen molecules, the intermolecular halogen–halogen bond increases in the order Cl < Br < I, indicating the strength of the charge-transfer interaction increases with the increase in size of the halogen. He also noted that (ii) the distance between the Lewis base and the halogen increases rather slowly from chlorine to iodine “*indicating a certain degree of compensation of the effect of larger halogen radius by the increase in charge-transfer bond strength*”.^[8] Charge-transfer interactions were from early on presumed to be highly directional, with the bond forming along the axis of the lone pair orbital of the Lewis base. Furthermore, Lewis bases with a donor atom possessing more than one lone pair of electrons were expected to be able to act as multivalent electron donors. This assumption was proven by the crystal structure of the bromine–acetone adduct, showing an infinite chain of alternating acetone and bromine molecules with the oxygen of each acetone binding two neighboring bromine molecules with a bond angle of 110° (Figure 3).^[14] It resembles the structure of the previously reported bromine–dioxane adduct.

Besides the charge-transfer complexes of halogen diatomics and Lewis bases, also those of electron acceptors that contain one or multiple halogen atoms linked to a non-halogen, typically a carbon atom, had caught Hassel’s interest. Based on further crystallographic data, he established the general principles governing the geometries of donor–acceptor complexes.^[15] The most noticeable feature of these systems is the nearly linear carbon–halogen–*n*-donor atom arrangements,

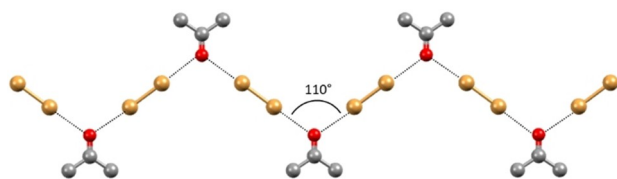


Figure 3. The X-ray structure of the 1:1 adduct of acetone and bromine, showing an infinite chain, as reported by Odd Hassel in 1959. This structure confirmed that a Lewis base capable of donating two non-bonding electron pairs can simultaneously form charge-transfer (halogen) bonds to two electron acceptors (halogen bond donors). Oxygens are shown in red, bromine in yellow and carbons in grey.

which was new at the time. Today it is generally expected and observed for halogen bond complexes.^[12]

3. Halogen Bonding: The Blooming of Hassel’s Chemistry

Upon the rediscovery of the attractive interaction of polarized halogen atoms with Lewis bases in the early 21st century, the research field of halogen bonding started blossoming.^[12] The interaction that intrigued Hassel and that was neglected for three decades has rapidly grown into a widely studied phenomenon and found numerous applications, for instance, in crystal engineering, supramolecular chemistry, organocatalysis, materials chemistry and medicinal chemistry.^[16] In line with Hassel’s observations, in an R–X⋯Y halogen bond complex, where R–X is defined as the halogen bond donor with X being a halogen, and Y as a halogen bond acceptor, the interatomic distance between X and Y is shorter than the sum of the corresponding van der Waals radii. Due to the X⋯Y interaction, the covalent R–X bond is lengthened relative to the not-interacting R–X molecule.^[17] Furthermore, the halogen bond is highly directional, with the R–X⋯Y bond angle being typically close to 180°. These general structural features are in agreement with the conclusions Odd Hassel drew already in the early stages of his research on analogous complexes.

4. The Halogen Bond of Halonium Ions

Another noteworthy crystal structure published by Hassel in 1961 is that of the [bis(pyridine)iodine(I)]⁺ I₃[−] complex,^[18] which confirmed the existence of halogen(I) cations. This structure was initially virtually ignored, but following the discovery of its synthetic applicability,^[19] halogen(I) complexes have drawn increased attention.^[20] Hassel’s route to the crystal structure of [bis(pyridine)iodine(I)]⁺ complex might have been serendipitous, as his initial purpose was to investigate a pyridine·2I₂ complex;^[18,21] nevertheless, he found it to be of “*considerable interest*”.^[18] The high amount of iodine in the sample brought some practical challenges for structural determination, for example, the N–I distances could not be accurately measured. They were estimated to be shorter than the interatomic distances generally observed in iodine–*N*-donor complexes. However, the centrosymmetric arrangement of the N–I–N bond and the nearly planar geometry of the complex were reported with certain confidence. Hassel’s structural observations have been later repeatedly confirmed by [bis(pyridine)halogen(I)]⁺ complexes and their analogues having been found to prefer a symmetric geometry both in solution and in the solid state.^[20] Due to its directionality and

robustness, the [bis(pyridine)halogen(I)]⁺ motif has been applied as a building block in the construction of large supramolecular assemblies, such as capsules, cages and helices (Figure 4).^[20]

Hassel's driving force was to identify the exact atomic arrangements of the donor-acceptor complexes, and to understand the forces keeping them together. The more structural data he collected, the more confident he became about the importance of charge-transfer interactions. Even though the nature of the halogen bonding, and related weak interactions such as chalcogen, pnictogen and tetrel bonding, may remain a matter of discussion, the foundations of our current understanding has without doubt been laid by Odd Hassel. His early interpretation that these interactions possess a charge-transfer character has been supported, for example, by theoretical studies by Shaik and co-workers in 2014 stating "our conclusion is clear-cut, most of the X-bonds are held by charge transfer interactions".^[22] A variety of additional papers corroborate that charge-transfer plays a key role in halogen bonding interactions.^[23]

Hassel was a true scientific giant and a visionary of his time. The determination of the 3D-structure of organic compounds, the development of gas-phase electron diffraction techniques and the early description of halogen bonding are some of the main hallmarks of his scientific contributions. When assessing his achievements, it should also be considered that he performed cutting-edge research with very limited resources at a small and peripheral university, and that his life and work were strongly influenced by World War II. Hassel's spirit and achievements are an inspiration to all scientists.

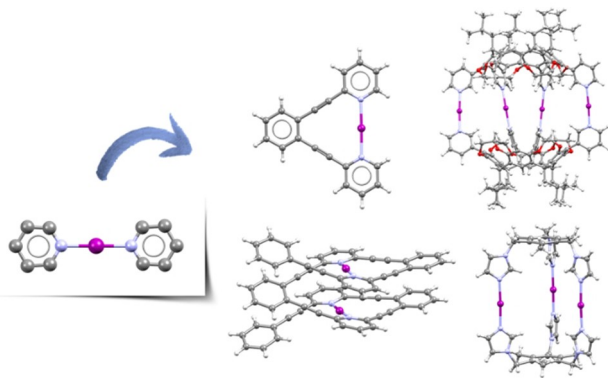


Figure 4. The [bis(pyridine)halogen(I)]⁺ complex, originally described by Odd Hassel in 1962 has turned into a versatile supramolecular synthon that is applicable to the construction of complex capsules, cages and helices.

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